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Targeting, monitoring and effect of oral iron therapy on haemoglobin levels in older patients discharged to primary care from inpatient rehabilitation – a cohort study using routinely collected data

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Abstract

Background

Oral iron is commonly prescribed to older patients with suspected or confirmed iron deficiency anaemia, however few studies have examined the effectiveness of oral iron therapy in the real world in this population. We therefore determined the prevalence of iron deficiency in older people prescribed oral iron, examined the response mounted to therapy and ascertained predictors of response to oral iron.

Methods

We analysed a routinely collected, linked dataset from older patients who had undergone inpatient rehabilitation between 1999 and 2011. An initial analysis examined patients within this cohort who were prescribed iron after rehabilitation and derived three groups based upon their ferritin and transferrin indices; probably, possibly and not iron deficient. A second analysis compared pre- and post-treatment haemoglobin to determine the degree of response to iron therapy across each category of deficiency. Finally, patient demographics, linked biochemistry data and comorbid disease based on International Statistical Classification of Disease (ICD-10) codes from previous hospital admissions were used in regression modelling to evaluate factors affecting response to therapy.

Results

490 patients were prescribed oral iron within 90 days of rehabilitation discharge. 413/490 (84%) had iron indices performed; 94 (23%) were possibly deficient, 224 (54%) were probably deficient, and 95 (23%) were not deficient. 360/490 patients had both pre and post treatment haemoglobin data and iron indices; probably deficient patients mounted a slightly greater response to oral iron (17g/L vs 12g/L for not deficient; p<0.05). Only pre-treatment haemoglobin, mean cell volume (MCV) and lower gastrointestinal pathology were significant predictors of a response to oral iron therapy. Notably, acid-suppressant use was not a predictor of response.

Conclusion

We conclude that many older patients are exposed to oral iron without good evidence of either iron deficiency or a significant response to therapy.

Key Points

- Older patients are frequently prescribed oral iron

- Many patients prescribed oral iron lack evidence of iron deficiency and are not monitored for response to therapy

- The increase in haemoglobin seen after oral iron supplementation is very modest

- In multivariable analysis, patients with lower gastrointestinal pathology, low mean cell volume or low pre-treatment haemoglobin mounted a greater response to oral iron supplementation

1. Introduction

Anaemia is common in older populations. The prevalence is approximately 10-15% in those aged 65 to 85, and can be as high as 26% over the age of 85 [1,2]. The prevalence even within the older age group is very variable, given the heterogeneous nature of this cohort and the impact of varying patterns of chronic disease, medication use, nutrition and frailty. Anaemia is not only underdiagnosed but may also be underestimated as a cause of mortality in this population [3,4]. Iron deficiency anaemia is common and may be due to gastrointestinal blood loss, decreased iron absorption [3,5]. Causes of bone marrow failure such as myelodysplasia and myeloma become more common with increasing age and may account for anaemia in some patients [6,7]. Anaemia of chronic disease due to chronic inflammatory disorders [8], and anaemia due to chronic kidney disease are also common [2]. Importantly, these various causes of anaemia may coexist in the same patient, leading to diagnostic difficulty. In a significant proportion, anaemia may remain unexplained despite appropriate investigation [10,11].

Iron deficiency anaemia may be difficult to diagnose in older patients with multiple medical problems [4]. Serum ferritin is the most useful blood test to assess iron stores in the absence of inflammation, with low serum ferritin confirming iron deficiency [5,12,13]. Ferritin is however an acute phase protein, and therefore in patients with concomitant medical problems, a normal ferritin may not fully exclude iron deficiency anaemia [8,12]. Hepcidin, a regulatory protein of iron absorption, is generally higher in inflammatory states, and this may account for lower availability of serum iron in those with anaemia of chronic disease [13] .

Oral iron therapy is prescribed for patients with confirmed iron deficiency or in some cases for unexplained anaemia and response to therapy should be monitored by serial measurements of

haemoglobin [12]. The failure of anaemia to respond to oral iron therapy may be multifactorial. Iron therapy will not be effective for treatment of anaemia if iron stores are replete. If anaemia of chronic disease and iron deficiency coexist, iron utilisation may be suboptimal, and no improvement in haemoglobin seen. Oral iron therapy, commonly prescribed in the form of ferrous sulphate or ferrous fumarate, may cause significant gastrointestinal side effects including diarrhoea, constipation, nausea, anorexia and taste disturbance [14]. These may be intolerable leading to poor compliance with the prescribed medication, and thus no improvement in anaemia.

Few studies to date have examined the effectiveness of oral iron prescribing in older populations [15]. The aims of this study were to ascertain the prevalence of iron prescribing in a cohort of older patients discharged from rehabilitation, to examine the response to oral iron therapy in this cohort, and to ascertain predictors of response.

2. Methods

2.1 Analysis Population

We undertook an analysis of prospectively collected routine clinical data. This analysis used linked datasets held by the Health Informatics Centre (HIC) at the University of Dundee. Data on patients who had undergone inpatient rehabilitation within the NHS Tayside Medicine for the Elderly Service between 1st January 1999 and 31st December 2011 were linked to data on laboratory analyses (haematology and biochemistry), hospitalisation episode data include discharge diagnoses, and dates of death. Information was accessed through the secure Safe Haven run by HIC which anonymized all data prior to hosting on the server for access by the research team. As the analyses used routinely collected clinical data, project-specific ethics approval was not required, but approval for use of the datasets was obtained from the local Data Protection Officer (Caldicott Guardian).

2.2 Variables

Demographic information including sex and age was derived from NHS Tayside records. All haematology and biochemistry results, both from hospital and community samples, are stored within the HIC SafeHaven system. These included mean cell volume (MCV), haemoglobin at baseline, estimated glomerular filtration rate (GFR) (calculated using the MDRD4 equation [16,17]), mean C-reactive protein (CRP), and serum iron, transferrin, ferritin, vitamin B12 and serum folate, where results were available. Baseline haemoglobin was taken as the most recent haemoglobin result available prior to the commencement of oral iron therapy. Iron studies comprising ferritin and transferrin were used to determine iron status, these were also available through the SafeHaven system. Ferritin is primarily used as a marker of iron status in routine UK clinical practice, however some studies have demonstrated that serum transferrin can be used to discriminate between iron deficiency anaemia and anaemia of chronic disease, hence both were included [18]. Post treatment haemoglobin was taken as the highest measurement at any point in the 12 weeks following commencement of iron supplementation; given that all data were retrospectively analysed there was no set point at which follow up tests had been taken. Anaemia was defined by a starting haemoglobin value below the World Health Organisation advised local reference range (120g/L in women and 130g/L in men) (19). Haematology indices were measured using a Sysmex analyser (Wymbush, Milton Keanes, UK); iron and transferrin were measured using a Siemens Advia 2400 analyser, whilst ferritin and folate was measured by a Siemens Dimension Vista analyser (Siemens, Surrey, UK). Vitamin B12 was measured by Siemens Centaur XP (Siemens, Surrey, UK).

Previous hospitalisation with a discharge diagnosis (either as a primary or secondary diagnosis) of chronic obstructive pulmonary disease (COPD), myocardial infarction, stroke, heart failure or hip fracture were derived from International Statistical Classification of Disease (ICD) 9 and 10 codes taken from Scottish Morbidity Record 01 (SMR01) data held by HIC. Any previous cancer diagnosis was derived from Scottish Morbidity Record 06 (cancer registry) data. Previous hospitalisation for lower gastrointestinal (GI) pathology or upper GI bleeding was recorded by matching with ICD-10 codes, which were further categorised in keeping with the work of Button et al.[19]. Previously diagnosed

diabetes mellitus was obtained from the Scottish Care Information – Diabetes Cohort (SCI-DC) data held by HIC; this dataset records all patients in Scotland with a diagnosis of diabetes [20].

Data on prescriptions dispensed by community pharmacies and held by HIC were used as source data for prescribing; this does not include prescriptions used during hospital stays. We extracted prescribing data for aspirin, clopidogrel, anticoagulants, proton pump inhibitors (PPI) and H2 receptor blockers.

2.3 Data Analysis

Analyses were performed using SPSS v21 (IBM, New York, USA). A p value of <0.05 was taken as significant for all analyses. The study subpopulation used for the main analyses comprised all patients commenced on oral iron therapy at the point of discharge from rehabilitation or within 90 days after discharge from rehabilitation. For comparison, the subpopulation who had received iron at any point prior to or after admission were also described. Descriptive statistics were generated for each group of patients. An initial analysis was carried out to determine the prevalence of iron deficiency in accordance with the categorization into three groups. Patients were split into these three groups based upon their ferritin and transferrin indices; not deficient (transferrin <2.0g/L, ferritin >100ug/L), possibly deficient (transferrin 2.0-2.5g/L, ferritin 50-100ug/L) and probably deficient (transferrin >2.5g/L, ferritin <50ug/L) [8]. In each category only transferrin or ferritin was required, given that most patients only had one of these indices measured. Where results from transferrin or ferritin would place patients in different groups, the most iron-deficient group was preferred.

A second analysis examined the response to oral iron therapy mounted by each of the above groups of patients. A significant response was considered to be at least a 20g/L increase in haemoglobin; such a response is typically seen within 3 weeks of commencing iron therapy in younger patients with iron deficiency anaemia [12,21,22]. This cut off was used to divide patients into responders and non-responders. Candidate factors were then tested for their association with response vs non-response

using binary logistic regression model testing (forced entry). A further analysis was conducted using a linear regression model to test the association of baseline factors with the magnitude of response to iron therapy.

Finally, based upon their response to treatment the patient cohort was then split into two groups; responders and non-responders. These groups were then compared in order to determine factors which may influence response to oral iron therapy, including background demographics (age and sex) as well as concurrent disease according to ICD-10. Variables against which analyses were carried out are shown in Table 1.

3. Results

3.1 Patient eligibility and iron status

4382 patients were initially identified for their involvement with the inpatient rehabilitation service. Of this cohort, 490 were prescribed iron within 90 days following of discharge from rehabilitation, and thus were eligible for the main analyses. 360/490 patients (73%) of these patients had at least one follow up haemoglobin measurement within 90 days of initiation of iron therapy, hence were suitable for inclusion in the final analyses of response to treatment. A flowchart demonstrating patient selection for each phase of the analysis is depicted in Figure 1.

413/490 (84%) of patients had recorded iron studies (ferritin and transferrin) to allow for determination of iron status with 94 (23%) possibly deficient, 224 (54%) probably deficient and 95 (23%) not deficient. Of the 360 patients with pre and post treatment haemoglobin data and iron indices, 70 (19%) were possibly deficient, 173 (48%) were probably deficient and 117 (33%) were not iron deficient.

Vitamin B12 and folate deficiency were also considered as part of the analysis, primarily to rule out this as a cause of anaemia. Deficiency was classed as <160ng/L for B12; only 16/490 patients

prescribed iron were vitamin B12 deficient. For folate, deficiency was classed as <3.1ug/L; 23/490 patients had folate deficiency.

3.2 Effect of baseline iron status on response to iron therapy

Haemoglobin results both pre and post iron treatment were available for 360 patients, allowing for investigation of response to therapy. These patients were then subdivided by pre-treatment iron status for further analysis. Table 2 shows the haemoglobin increase mounted by each of the four groups; not deficient, possibly deficient, probably deficient and those without iron studies.

3.3 Predictors of response to iron therapy

A third analysis examined the association between baseline variables and response to iron therapy. For the purpose of this analysis patients were defined as responders (n=116, with haemoglobin increase >20g/L) and non-responders (n=244, with haemoglobin increase <20g/L) based upon biochemical markers within 90 days of treatment starting. Table 3 shows univariate associations between baseline variables and response to iron therapy. A binary logistic regression model was used to determine the significance of factors affecting responders and non-responders to oral iron therapy. This showed that only pre-treatment haemoglobin, MCV and presence of lower GI pathology were significant predictors of a response to oral iron therapy (i.e. >20g/L rise in haemoglobin).

3.4 Predictive value of MCV for response to iron therapy

Given the strength of association between MCV and response to iron therapy, a receiver-operator characteristic curve was constructed; the c-statistic for the ROC curve was 0.71 (95% CI 0.65 to 0.77). MCV had limited utility for identifying a group of patients unlikely to respond to oral iron however; 33/116 (28%) of responders had a baseline MCV of >90fl (normal range 85-95fl). All results were based on the samples tested from the same analyser.

4. Discussion

This study aimed to examine the response to oral iron therapy and determinants of this response. As such, the primary inclusion criteria hinged upon prescription of iron supplementation; hence most, but not all of the included patients were anaemic according to local haematology reference ranges. Our results show that many older patients are prescribed oral iron without evidence of iron deficiency. Not all patients receiving oral iron had iron studies performed, and of those that did have iron studies, a quarter had no evidence of iron deficiency prior to commencing iron therapy. Many patients also lacked follow up haemoglobin measurement to test whether iron therapy was effective; of those with follow-up haemoglobin levels, only a third showed a rise of >20g/L in haemoglobin taken by this study to denote a response.

Many patients in this analysis had only a mildly reduced haemoglobin; baseline haemoglobin and MCV were the most powerful predictors of a successful response to iron therapy. It is perhaps unsurprising that those with a lower initial haemoglobin mount the most significant response to iron; this is in keeping with previous findings [23] that responders to oral iron therapy had a lower baseline haemoglobin (91 vs 98 g/L). Additionally, these patients tended to be younger and had a lower Body Mass Index (BMI) (27.9 vs 31.1kg/m^2). Whilst age was not a determinant of response to iron therapy in our study, it is likely that in older patients age is less of a discriminant than comorbidities or performance status compared to a younger population.

Interestingly, C-reactive protein was not a significant factor in the response patients mounted to oral iron therapy, with no appreciable difference between responders and non-responders. However, this study only took into account conventional CRP measurements, and hence it is possible that chronic low grade inflammation could play a role. High-sensitivity CRP assays would be required to confirm or deny this hypothesis, but as these assays were not used in routine clinical practice, such analyses cannot be undertaken with the current dataset.

Crucially, those who were biochemically iron deficient were more likely to respond to oral iron therapy compared to those who did not show laboratory evidence of iron deficiency. This emphasises the importance of identifying a cause of anaemia, particularly in older patients; iron therapy will not improve anaemia in those who are not iron deficient.

Diagnosing iron deficiency based on widely available measures of iron metabolism, such as serum iron, transferrin and ferritin, is not straightforward. The gold standard test for assessment of iron status is a bone marrow biopsy, however this is invasive and therefore not usually appropriate, especially in elderly patients. Thus, biochemical markers are often relied upon as a surrogate [24]. We used a graded approach to classifying iron status, in part based on published guidance from the British Society for Haematology [22]. Despite the use of this classification, less than half of those in the 'probable iron deficiency' group showed a 20g/L rise in haemoglobin. As previously discussed, there are several possible contributors to this poor response rate including poor compliance with prescribed iron therapy, absence of true iron deficiency and the presence of chronic inflammatory processes.

Previous studies noted that MCV and traditional iron studies are an unreliable test of true iron deficiency anaemia when used in older populations [4,25,26]. One study found that up to 22% of elderly patients without biochemical evidence of iron deficiency would still respond to oral iron therapy [25]; a similar proportion to the response rate in the 'not iron deficient' group in our study. Some of this response may however be due to intermittent gastrointestinal bleeding that resolves and allows Hb to rise, rather than a true response to iron therapy. Of note, in our study, MCV was significant in determining response to iron and hence it may be appropriate to prescribe a therapeutic trial of oral iron on the basis of microcytic anaemia in the absence of iron studies, with monitoring of haemoglobin to determine response.

A systemic review and meta-analysis carried out by Tay & Soiza [27] found similarly that older patients mounted only a weak response to oral iron therapy. Two of the three studies included in their analysis

showed a mean increase in haemoglobin of only 4g/L and 6g/L, neither reaching statistical significance. More importantly, there was no statistically significant improvement in mortality, length of hospital stay or quality of life. Interestingly, the same study hypothesised that poor absorption of iron supplements due to concurrent atrophic gastritis and PPI use maybe a factor in poor response in older patients. Our findings do not support this hypothesis, as there was no significant difference between the responders and non-responders despite 65% and 53% respectively taking PPIs. Conversely, the lack of difference in PPI use rates between the groups does not support PPIs being an effective strategy to ameliorate blood loss and hence improve response to oral iron in this group – this may be because of the wide range of pathologies causing iron deficiency in older people, many of which would not be improved by acid suppression.

A further reason for lack of response to oral iron may be ongoing blood loss, emphasising the need to investigate and treat the underlying cause of the anaemia; patients with recognised lower GI pathology were more likely to respond to iron, suggesting that finding and treating the cause of the anaemia is an important part of ensuring a response to therapy. However, many older, frail patients are either unable or unwilling to undergo invasive investigation for the cause of iron deficiency [28]. Simple tests, such as searching for concomitant vitamin deficiencies can still be performed in the frailest of patients and may improve the response to oral iron; as well as proving or disproving iron deficiency as the principle cause of anaemia. In Tayside a recent addition to the general practice test repertoire is the 'anaemia screen' blood test. On receipt of these samples, a full blood count is first performed and if anaemia is found, further tests, for example blood film and ferritin, or vitamin B12 and folate in the case of macrocytic anaemia are cascaded. This test sequence reduces the need for further blood sampling and provides the GP promptly with increased diagnostic information. This may help reduce iron prescribing for those who are not iron deficient, as information about iron status is readily available. A re-audit of data following the introduction of this test would be useful in order to determine exact outcomes.

Strengths of our study include the use of routinely collected data, which ensures that our results reflect real life practice with minimal selection of patients. The use of linked diagnostic, prescribing and lab data enhanced the range of variables that we were able to consider. A number of weaknesses should also be noted. This study focussed on those admitted to a rehabilitation service in a single health board area and hence investigated at a population of patients with significant burden of disease. Whilst it was possible to correct for several common comorbidities and their effect on response to oral iron, it was impossible to encompass all pathologies and treatments thereof. The heterogeneous nature of this cohort of patients complicates the analysis to a degree, however this heterogeneity reflects 'real-world' clinical practice - older patients rarely present with isolated pathologies.

Once of the major limitations of this study was in the classification of iron deficiency and degrees thereof, given that guidelines vary for the population under study. In the absence of a clear consensus, iron indices were set assuming that chronic inflammation and renal impairment were likely to be common in our population, thus higher thresholds for ferritin were appropriate such as those recommended in other guidelines [11,29,30] . Interpretation of transferrin levels is similarly lacking in consensus, but we selected a level below the normal range (2-4g/L) as indicating that anaemia of chronic disease was a more likely diagnosis than iron-deficiency anaemia; conversely, the higher the transferrin level, the more likely iron-deficiency becomes, and the choice of a 2.5g/L cut off reflects a level consistent with clinical practice by geriatricians.

Our basis for defining a significant response to iron was based on an improvement in haemoglobin; for many patients these follow up data was not available and for others we classified their response as non-significant as their haemoglobin did not rise by 20g/L. However, we could not take account of symptomatic improvement from a small increase in haemoglobin, and we do not of course know whether haemoglobin would have fallen further in the absence of iron therapy. Despite having access to prescribing data, we were unable to ascertain adherence to therapy as the number of times per

day that iron was recommended was not well captured in the datasets that we used. Similarly, the data set limited our ability to exclude all causes of anaemia such as haematuria, poor nutrition or uterine bleeding. The availability of such data as well as previous endoscopy results would have enhanced our analysis; without this we have relied upon ICD-10 codes for upper and lower GI pathologies and bleeds as a surrogate for one of the most common sources of blood loss, as well as influencing possible dietary malabsorption.

5. Conclusion

Oral iron therapy is commonly used in older patients, but in many cases investigation for iron deficiency, accurate diagnosis of iron deficiency, and monitoring of response to therapy are inadequate. These factors may help to explain the poor response rate to oral iron, suggesting that many older people are exposed to potential side effects and harms of oral iron for no symptomatic gain. Better systems are required to improve investigation, diagnosis, and monitoring of anaemia in older people, and consideration should be given to stopping therapy or using alternatives to oral iron if no response to therapy is seen.

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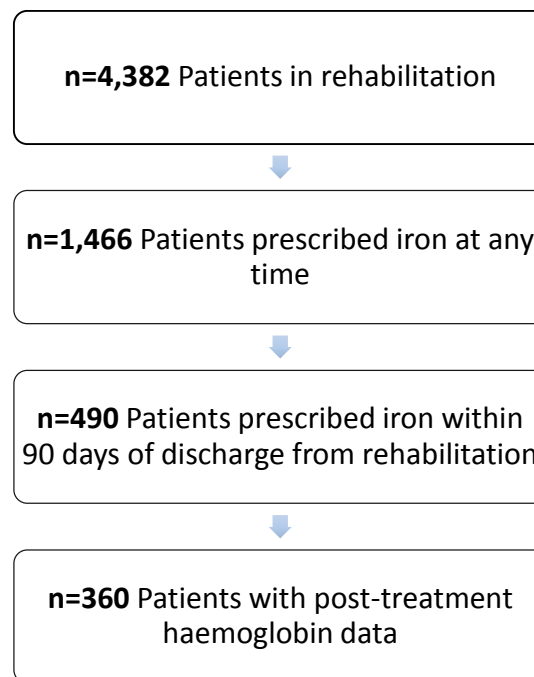**Figure 1** Flow diagram depicting selection of patients

Table 1. Baseline patient details

	Whole cohort (n=4382)	Ever prescribed iron (n=1466)	Prescribed iron within 90 days of rehabilitation discharge (n=490)	Prescribed iron within 90 days of rehabilitation discharge with follow up, haemoglobin results available (n=360)
Mean age (yrs) (SD)	83.9 (7.6)	85.2 (7.0)	85.6 (7.1)	85.2 (6.7)
Male sex (%)	1351 (31)	463 (32)	148 (30)	107 (30)
Congestive heart failure (%)	386 (9)	165 (11)	38 (8)	29 (8)
Previous stroke (%)	312 (7)	110 (8)	32 (7)	28 (8)
Chronic obstructive pulmonary disease (COPD) (%)	635 (15)	198 (14)	65 (13)	49 (14)
Previous myocardial infarction (%)	755 (17)	333 (23)	80 (16)	66 (18)
Diabetes mellitus (%)	753 (17)	282 (19)	83 (17)	59 (16)
Previous cancer diagnosis (%)	564 (13)	193 (13)	56 (11)	43 (12)
Previous hip fracture (%)	491 (12)	180 (12)	51 (10)	34 (9)
Previous admission for upper gastrointestinal bleed (%)	-	26 (2)	26 (5)	19 (5)
Evidence of lower gastrointestinal pathology (%)	-	92 (6)	90 (18)	68 (19)
Died during rehabilitation admission (%)	373 (8.5)	88 (6)	0 (0)	0 (0)
Mean admission Barthel score (SD)	10.3 (3.8)	10.7 (3.7)	11.2 (3.6)	11.3 (3.7)
Mean discharge Barthel score (SD)	14.3 (4.7)	15.0 (4.3)	15.7 (3.6)	15.9 (3.6)
Discharged to own home (%)	3002 (69)	1081 (74)	399 (81)	299 (83)
Mean eGFR (ml/min/1.73m^2) (SD)	63 (27)	50 (12)	50 (12)	50 (12)
eGFR <45ml/min/1.73m^2 (%)	1061 (24)	450 (31)	151 (31)	110 (31)
Mean haemoglobin (g/L) (SD)	120 (19)	105 (15)	105 (15)	109 (13)
Anaemia (female Hb<120; male Hb<130g/L) (%)	2521 (58)	1057 (72)	432 (88)	320 (89)
On proton pump inhibitor (%)	-	268 (18)	265 (58)	204 (57)
On histamine 2 receptor antagonist (%)	-	40 (3)	40 (8)	24 (7)
On aspirin (%)	-	218 (15)	215 (44)	157 (44)
On clopidogrel (%)	-	37 (3)	37 (8)	29 (8)
On oral anticoagulants (%)	-	47 (3)	47 (10)	37 (10)

All values are those at the point of discharge from the first rehabilitation admission

eGFR: estimated Glomerular Filtration Rate

Table 2. Haemoglobin response to iron therapy in relation to iron status (n=360)

Group	No. with haemoglobin measured	Mean baseline haemoglobin (g/L) (SD)	Anaemia at baseline (%)**	Mean baseline mean cell volume (fl) (SD)	No (%) with haemoglobin increase >20g/L	Mean haemoglobin increase (g/L) (SD)	Mean ferritin (ug/L) (SD)
Not iron deficient	59	104 (1.3)	53 (90)	94 (10)	14 (24)	12 (1.5)	347.8
Possibly iron deficient	70	103 (1.4)	62 (89)	91 (7)	17 (24)	13 (1.5)	166.5
Probably iron deficient	173	104 (1.7)	152 (88)	87 (9)	67 (39)*	17 (1.6)*	51.1
No iron studies	58	104 (1.7)	53 (91)	88 (8)	18 (31)	13 (1.5)	-

*p<0.05   ** Hb<120g/L for females or <130g/L for males

Table 3 . Factors associated with response vs non-response to oral iron therapy (n=360)

	Univariate analysis			Binary logistic regression[a]		
	Responders (n=116)	Non-responders (n=244)	p	Odds ratio (95% CI)	β	p
eGFR <45ml/min/1.73m^2 (%)	38 (33)	70 (29)	0.53	-		
Mean mean cell volume (SD)[b]	84.6 (9.5)	90.9 (8.1)	<0.001	0.93 (0.90-0.96)	-0.074	<0.001
Mean start haemoglobin (g/L) (SD)	96 (1.6)	108 (1.4)	<0.001	0.66 (0.54-0.79)	-0.419	<0.001
Vitamin B12 <160ng/L (%)[c]	5 (4)	11 (5)	0.91	-	-	-
Folate <3.1ug/L (%)[c]	3 (3)	9 (4)	0.64	-	-	-
Mean C-reactive protein (mg/L) (SD)[d]	44 (54)	47 (69)	0.71	-	-	-
Aspirin (%)	49 (42)	108 (44)	0.73	-		
Clopidogrel (%)	6 (5)	23 (9)	0.17	0.44 (0.15-1.28)	-0.823	0.13
Oral anticoagulant (%)	12 (10)	25 (10)	0.98	-		
Proton pump inhibitor (%)	75 (65)	129 (53)	0.04	1.47 (0.87-2.48)	0.384	0.15
H2 receptor antagonist (%)	9 (8)	15 (6)	0.57	-		
Upper gastrointestinal bleed admission (%)	9 (8)	10 (4)	0.15	2.24 (0.81-6.16)	0.806	0.12
Lower gastrointestinal pathology (%)	30 (26)	38 (16)	0.02	1.76 (0.94-3.30)	0.568	0.08
Diabetes mellitus (%)	25 (22)	34 (14)	0.07	1.34 (0.97-1.86)	0.293	0.08
COPD (%)	18 (16)	31 (13)	0.47	-	-	-
Previous myocardial infarction (%)	18 (16)	48 (20)	0.34	-	-	-
Previous stroke (%)	6 (5)	22 (9)	0.20	0.48 (0.17-1.41)	-0.729	0.18
Congestive heart failure (%)	7 (6)	22 (9)	0.33	-	-	-
Mean discharge Barthel score (SD)	15.8 (3.5)	16.0 (3.6)	0.63	-	-	-

[a] Variables selected if p ≤ 0.2 on univariate analysis (forced entry model)

[b] Mean cell volume normal range 85-96fl

[c] 92 responders and 191 non-responders had vitamin B12 and folate measurements recorded

[d] C-reactive protein levels were available for 313 patients