**ORIGINAL ARTICLE**

**The incidence and importance of anaemia in patients undergoing cardiac surgery in the UK – the first Association of Cardiothoracic Anaesthetists national audit\***

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Note to typesetters: the 11 collaborators listed in Appendix 1 should be tagged so that they are listed on PubMed under ‘Collaborators’, as for e.g. this article: <http://www.ncbi.nlm.nih.gov/pubmed/25407168>

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\*Presented in part at the joint Annual Scientific Meeting of the Association of Cardiothoracic Anaesthetisits and the Society of Cardiothoracic Surgeons, Manchester, UK, March 2015

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Running title: Impact of anaemia in cardiac surgery

**Abstract**

The importance and variability of pre-operative anaemia in cardiac surgical patients across the UK is not known, and there is debate about its association with patient outcomes. The Association of Cardiothoracic Anaesthetists carried out its first national audit on anaemia and transfusion, and analysed data from 19 033 patients operated on in 12 cardiac surgical centres between 2010 and 2012; 5895 (31%) had pre-operative anaemia. Centre-specific prevalence of anaemia varied from 23% to 45%; anaemia was associated with older patients, diabetes and surgical risk (EuroSCORE). Nevertheless, controlling for these factors, regional variation remained as an independent effect (p<0.001). Multivariable analysis demonstrated an independent association of anaemia with transfusion (OR (95%CI) 2.75 (2.55-2.95), p<0.001), mortality (1.42 (1.18-1.71), p<0.001), and hospital stay (geometric mean ratio (95% CI) 1.15 (1.13-1.17), p<0.001). Haemoglobin concentration per se was also independently associated with worse outcomes; a 10 g.l-1 decrease in haemoglobin was associated with a 43% increase (95% CI 40%-46%) in the odds of transfusion and a 16% increase (95% CI 10%-22%) in the odds of mortality (both p<0.001). This large UK-wide audit has demonstrated marked regional variation in both anaemia and transfusion, but a consistently high incidence of both. The independent association between pre-operative anaemia and worse outcomes in UK practice has also been confirmed, and robust prospective study of anaemia treatment before cardiac surgery is required; these data will assist in designing such trials.

**Introduction**

Anaemia is defined as a haemoglobin concentration (Hb) < 120 g.l-1 for non-pregnant adult women or < 130 g.l-1 for men, with an estimated prevalence of 19% in women and 14% in men in Europe [1]. There is considerable evidence that pre-operative anaemia is associated with poor surgical outcomes [2, 3] in non-cardiac surgery, but the evidence in cardiac surgical patients is more limited [4-9]. Previous cardiac surgical studies have shown anaemia to be much more prevalent than in the general population [9], and also showed a strong association with increased morbidity and mortality, as well as increased costs associated with surgery. There is uncertainty as to the prevalence of anaemia in differing regional populations now presenting for cardiac surgery, and how this relates to differing ages, sex and comorbidities [10]. In data from the United States National Health and Nutrition Examination Survey, the prevalence of anaemia was lowest in men aged 17-49, at 1.5%, but was 12.2% in women of that age. In the elderly, anaemia was more common; affecting 11% of males and 10.2% of females aged >65 years, rising to 26.1% and 20.1% respectively in those >85 years old [11]. Although anaemia appears to be equally prevalent in post-menopausal women and men, the definition of anaemia is 10 g.l-1 apart between the genders. This is important, as women have a higher mortality after cardiac surgery [12]. Anaemia is also more common with increasing frailty, and its prevalence has been reported to be as high as 40% in nursing home residents [13]. Population studies in the UK have shown anaemia to be more common than diabetes, with a similar incidence to cardiovascular disease [14]. However, with respect to surgical patients, the United States’ National Surgery Quality Improvement Program (NSQIP) database showed the prevalence of anaemia in all patients undergoing surgery to be 30% [2], with a 29% prevalence reported from a European study [15].

Patients undergoing cardiac surgery may be particularly susceptible to the consequences of pre-operative anaemia due to their underlying poor cardiac reserve and the high volume of blood loss and haemodilution associated with cardiopulmonary bypass and cardiac surgery [4]. However, anaemia is associated with an increased risk of blood transfusion, which may itself increase morbidity and mortality after cardiac surgery [16]. Moreover, an interaction between anaemia and blood transfusions has been demonstrated, with increased morbidity and mortality in patients who are both anaemic and receive transfusions greater than additive effects of each exposure individually [17].

To date, no multicentre review of the prevalence and consequences of pre-operative anaemia among UK cardiac surgery patients has been undertaken. The Association of Cardiothoracic Anaesthetists (ACTA) therefore decided to form a collaborative group to describe the prevalence of pre-operative anaemia among UK cardiac surgery patients and evaluate the effect of anaemia on outcomes in UK cardiac surgery centres.

**Methods**

This study comprises a national service audit of NHS cardiac surgery centres accredited by ACTA that collected relevant patient data as part of routine institutional practice. The Research and Ethics Committee of the London School of Hygiene and Tropical Medicine approved the study, and individual patient consent was not required. All 35 UK cardiac surgery centres were invited to take part in the study; of these,18 routinely collected the data required and agreed to participate, and 12 centres ultimately provided data (six centres were unable to provide data due to lack of local resources). We collected anonymised routinely collected data on all adult (>/= 18 years) cardiac surgery patients (including elective, urgent and emergency surgery) from 2010 through 2012, inclusive. Data elements collected included patient demographics (age, gender, height, weight), comorbid disease (diabetes, hypertension), pre-operative blood tests (Hb, creatinine), operative details (centre, type of surgery, time on cardiopulmonary bypass), and postoperative outcomes (postoperative Hb, number of units of red cells transfused, ICU length of stay, duration of hospital stay (calculated from day of surgery to day of discharge from hospital), and in-hospital death). In addition, the logistic EuroSCORE, a validated predictive score for operative morality in cardiac surgery [18] was collected.

Patients without a pre-operative Hb measurement were excluded. The association between anaemia and other pre-operative variables was assessed using the Chi-squared test for categorical data, and the t-test for continuous variables. Differences between centres for the prevalence of anaemia were assessed using the Chi-squared test. The association between anaemia and the outcomes of transfusion at any point in the peri-operative period, ICU and hospital length of stay and 30-day mortality were analysed using multivariable logistic regression. Crude estimates of the effect of anaemia on outcomes are reported alongside estimates adjusted for age, gender, logistic EuroSCORE, centre, operation type, previous cardiac surgery, diabetes, body surface area and hypertension. As length of stay was not normally distributed a natural logarithm transformation was carried out and therefore estimates of association are reported as geometric mean ratios. The analysis of length of stay was restricted to patients who were discharged alive. Two centres did not report date of discharge and therefore patients from these centres were not included in the analysis of length of stay. Data was complete for transfusions and mortality but there was some missing data for logistic EuroSCORE (1.7%), hypertension (1.7%) and body surface area (3.7%). Multiple imputation using chained equations was carried out as a sensitivity analysis for each outcome. Sensitivity analyses using multiple imputation did not substantially change the estimates or alter the conclusions.

All data analysis was performed using Stata 14 (StataCorp, College Park, TX, USA).

**Results**

A total of 23 800 adult patients underwent cardiac surgery at one of the 12 centres during the three year study period. Of these, 4754 (20%) patients did not have a pre-operative Hb recorded and were excluded from the descriptive analysis.

 Of the remaining 19 033 patients, 5895 (31%) had pre-operative anaemia (Table 1). Centre-specific prevalence of anaemia varied from 23% to 45% (p< 0.001). Comparing those with anaemia vs. those without, anaemic patients were older, were more likely to be women, had a lower body mass index (BMI), a higher baseline creatinine, a higher proportion of those with hypertension, and a higher proportion of patients with diabetes. In addition, there was strong evidence that the distribution of the type of operations that anaemic patients underwent differed from those without anaemia (p<0.001), with a lower proportion of CABG operations and a higher proportion of combined CABG + valve operations and redo surgery (Table 1). Nevertheless, after adjusting for age, gender, logistic EuroSCORE and type of operation, there was still significant variation (p<0.001) between centres in prevalence of anaemia (Table 2).

At operation, anaemic patients spent longer times on cardiopulmonary bypass, had longer cross-clamp times, and had higher predicted mortality by the logistic EuroSCORE. With respect to patient outcomes, patients with anaemia were more likely to receive a RBC transfusion, and when transfused, received more units of RBCs, compared with those without anaemia (Table 3), although this did vary across the centres (Fig. 1). Marked variation was also observed in centre-specific rates of transfusion, ranging from 31% to 60% (Table 2). Anaemic patients stayed longer in ICU and in hospital, the latter by a median of 2 days (both p < 0.001). Perhaps most importantly, patients with anaemia were twice as likely to die after cardiac surgery, and mortality was linked to severity of pre-operative anaemia and gender (Fig. 2). Severity of anaemia pre-operatively was also related to length of stay, with women again more likely to stay longer in hospital (Fig. 3). However, women with Hb > 150 g.l-1 stayed longer in hospital (Fig. 3).

Multivariable analysis confirmed the independent association between anaemia and transfusion, hospital stay and mortality (Table 4). Haemoglobin concentration per se was also independently associated with worse outcomes with a 10 g.l-1decrease in haemoglobin being associated with increased transfusions (OR (95% CI) 1.43 (1.40-1.46)), higher mortality (OR (95% CI) 1.16 (1.10-1.22)) and longer hospital stay (geometric mean ratio (95% CI) 1.15 (1.13-1.17)). A decrease of only 10 g.l-1 in Hb was associated with a significant increase in transfusion (OR (95% CI) 1.70 (1.54-1.88)), in both men and women. Patients with severe anaemia, Hb < 110 g.l-1 , of which there were 1879 (9.9%), were more likely to be transfused (OR (95% CI) 3.63 (3.18-4.15)) and more likely to die during or after surgery (OR (95% CI) 1.60 (1.21-2.11)) compared with patients in the 130-139 g.l-1 range (Table 4).

**Discussion**

This UK-wide study has shown anaemia to be both common before cardiac surgery and to be independently associated with worse outcomes, including length of stay in ICU and hospital, and mortality. Patients with anaemia had a greatly increased risk of death after cardiac surgery, and this was related to severity of anaemia, and was even higher in women than in men; there was a clear cut-off at 130 g.l-1. Even a mild degree of anaemia was associated with a greatly increased risk of transfusion. This is the first study to show the marked variation of anaemia in the population of cardiac surgical patients across the UK, independent of age, gender and comorbidities, and has also confirmed that transfusion varies greatly in the UK. This variation in transfusion practice is independent of the variation in the prevalence of anaemia.

The prevalence of anaemia is known to vary worldwide due to nutritional/dietary differences and other socio-economic and racial differences [19]. However, the variation we have found from our study in patients presenting for cardiac surgery has not been described before, to our knowledge, and the exact cause is unknown, although socio-economic differences are the most likely cause [20]. Observational studies have shown that the most common cause of anaemia in this population of patients is functional iron deficiency, and that nutritional deficiencies of iron, Vitamin B12 and folate are relatively uncommon (16% in total) [21]. Further studies to elucidate the causes of regional variation are required as they will be important to guide management, especially as we have shown such a strong association between anaemia and worse outcome.

 A number of other studies have examined the prevalence and association with outcomes of pre-operative anaemia. A single-centre UK study by Hung et al. reported the prevalence in East Anglia (54%) to be higher than any centre of the 12 included in the current study [9]. This study included patients from 2008-2009, just before the start date of the current study (2010), so change in practice is unlikely to account for this variation. The higher prevalence may be attributable to patient factors (age, comorbidities, burden of cardiac disease), or be specific to the population in this area of the UK. Another single-centre study, also in the UK, showed an independent association between pre-operative anaemia and a 300% increase in mortality, as well as significant increases in morbidity (stroke, renal dysfunction, atrial fibrillation and hospital length of stay) [22]. One other single-centre study, this time from Italy, also showed an association between pre-operative anaemia and increased mortality, stroke and other major morbidity [23]. Karkouti et al. [8] reported a lower prevalence, but they excluded patients who were either dialysis dependent, undergoing emergency surgery, or were severely anaemic with haemoglobin concentrations <9.5 g.l-1, who were all included in our study*.* Kulier et al*.* [5] studied 4804 patients undergoing elective coronary artery surgery from 72 centres worldwide, and showed that low pre-operative Hb was only an independent predictor for noncardiac (renal>cerebral; p<0.001) outcomes; our much larger study confirmed an association between low Hb and mortality, which they did not show.

Pre-operative anaemia before non-cardiac surgery has a similar incidence (31% in men and 27% in women in 39 000 patients in a multi-centre European study), and is also associated with increased mortality, hospital length of stay, admission to ICU and resource use) [15]. A large US cohort study showed an association between severity of anaemia and increase in mortality and morbidity [2]. Our multi-centre cardiac UK study also showed that haemoglobin concentration per se was associated with outcome, and that the magnitude in the reduction in Hb was related to blood transfusion, length of stay and mortality. We also showed that a decrease in Hb of only 10 g.l-1 was associated with a marked increase in transfusion. This has important implications for the peri-operative management of anemia in women in particular, as the WHO define anaemia in women as being 10 g’l-1 lower than in men. It is possible that if the definition of pre-operative anaemia was raised to 130 g.l-1 in both genders, transfusion and associated risk in women may be altered, and prospective trials are required to determine if this may have an effect on outcome. Another interesting finding seen only in women in our study was the increased length of stay associated with supranormal Hb (> 150 g.l-1). Data were small, but a similar finding has previously been reported in association with increased thrombotic and embolic complications. This finding merits more detailed analysis, which is outside of the scope of this study

We cannot conclude that anaemia per se causes any of the outcomes studied, and have only showed an association. Evidence that treatment of anaemia and/or iron deficiency improves patient outcomes has been shown in patients with conditions such as heart failure [25] and chronic kidney disease [26]. Patients undergoing surgery who are either anaemic or functionally iron deficient represent a large cohort of patients globally. The potential implications of reducing mortality, allogeneic transfusion and hospital length of stay make treatment of pre-operative anaemia an important area of further research. Patient blood management is a new NHS initiative introduced in 2014 [26]. It advises that pre-operative anaemia should be investigated and actively managed before surgery, but currently does not recommend specific treatments for different causes. Treatment of anaemia is one potential pre-operative intervention that requires further study [27]. Our study also showed some variability between centres in terms of mortality, as well as anaemia and transfusion. This is only of interest with regards to the variability between centres in anaemia and transfusion that we have already discussed, as the much larger ACTA study has already shown that variability in mortality is mainly (96%) due to patients’ risk profile, comorbidities and health status [28], which adds to the importance of pre-operative optimisation.

 Advantages of this study are that it demonstrates the willingness of a large number of centres to collaborate with their specialist society to collect data to inform their practice. This was the first time ACTA attempted a national audit of a particular area of cardiothoracic practice, and one-third of the centres in the UK registered with ACTA provided data. The other centres were either not interested in joining the study group or did not collect the required data (16 UK centres did not collect and store data on pre-operative Hb at the time of this study), and this may be a potential but unavoidable source of bias. Other disadvantages of this study include the missing data; 20% of patients were excluded from the analysis due to missing pre-operative Hb. This implies that there was either a failure during pre-operative assessment to measure Hb, or, more likely, a failure to capture data adequately. Other disadvantages of this study include the missing data; 20% of patients were excluded from the analysis due to missing pre-operative Hb. This implies that there was either a failure during pre-operative assessment to measure Hb, or, more likely, a failure to capture data adequately. We attempted to take into account missing data of those included in the analysis by performing multiple imputation. The results from the multiple imputation analysis were consistent with the results from the complete case analysis and did not alter our conclusions, however we cannot rule this out as a source of bias. The other major limitation of this study is, as we have discussed above, its retrospective, observational design. In the field of transfusion medicine, retrospective studies have presented different results to large randomised controlled trials [29], and we therefore urge caution when interpreting the results of our study until prospective randomised trials have been carried out in this area.

 The implications for clinical practice of our study is that identification of pre-operative anaemia has been confirmed to be important, which is consistent with the recent National Health Service Blood and Transfusion national audit [30]. The strong association between pre-operative anaemia in our study and many others with mortality and morbidity makes properly designed trials in this area a priority. These are necessary to determine if treatment of anaemia leads to patient benefit. Further study to determine the causes of regional variation in anaemia are also required, to allow comparison of the prevalence of different causes of anaemia in patients presenting to different centres. Studies to compare elective patients with urgent/emergency surgical patients may also help elucidate whether variation may be due to different patterns of presentation of disease. A number of UK centres have recently introduced anaemia clinics so that patients can be actively managed before cardiac surgery, and we look forward to the presentation of results following such management.

**Acknowledgements**

AK is the Editor-in-Chief of *Anaesthesia* and this article has undergone additional external review as a result. AK,CE and TR have received funding for research from Pharmacosmos and TR has also received funding for research from Vifor Pharma Ltd. This study did not require external funding, and the other authors have no conflicts of interest to declare.

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**Figure legends**

**Figure 1** Transfusion rates in anaemic (red) and non-anaemic (blue) patients at the 12 centres (anonymised A-L) audited between 2010 and 2012. Transusion rates are mean (squares) and 95% CI (horizontal bars).

**Figure 2** Mortality rates in patients with varying pre-operative haemoglobin concentrations in men (blue) and women (red). Mortality is mean (square) and 95% CI (horizontal bars).

**Figure 3** Length of stay in patients with varying heamoglobin concentrations in men (blue) and women (red). Length of stay is geometric mean (square) and 95% CI (horizontal bars).

|  |  |  |  |
| --- | --- | --- | --- |
|  | All Patients(n = 19 033) | Anaemic(n = 5895)31.0% | Not Anaemic(n = 13 138)69.0% |
| Age; yrs | 67.0 (12.0) | 69.5 (12.0) | 65.9 (11.9) |
| Gender; men | 13669(71.8%) | 4157(70.5%) | 9512(72.4%) |
| Body mass index; kg.m-2 | 28.3 (5.1) | 27.7 (5.1) | 28.5 (5.0) |
| Pre-operativehaemoglobin. g.l-1 | 13.4(12.1-14.4 [3.8-22.0]) | 11.5(10.6-12.2 [3.8-12.9]) | 14.0(13.3-14.9[12.0-22.0]) |
| Creatinine; μmol.l-1 | 89.3 (76.0-106.1 [6.2-1551.4]) | 94.6(77.8-122.0 [7.1-1551.4]) | 86.6(75.1-100.8 [6.2-1448.0]) |
| Diabetes | 3687(22.0%) | 1534(29.6%) | 2153(18.6%) |
| Hypertension | 12 971(69.5%) | 4101(70.8%) | 8870(68.9%) |
| Operation typeCABGValveCABG + valveDouble valveSurgery on aortaOther | 9688(50.9%)4182(22.0%)2250(11.8%)290(1.5%)375(2.0%)2239(11.8%) | 2673(45.4%)1367(23.2%)839(14.2%)111(1.9%)148(2.5%)756(12.8%) | 7015(53.4%)2815(21.4%)1411(10.7%)179(1.4%)227(1.7%)1483(11.3%) |
| Previous cardiac surgery | 315(1.7%) | 142(2.4%) | 173(1.3%) |
| CPB used | 15 503(81.5%) | 4757(80.7%) | 10 746(81.8%) |
| Time on bypass; min | 96(75-125 [1-1945]) | 100(76-132 [1-1000]) | 94(74-122 [2-1945]) |
| Cross-clamp time; min |

|  |  |
| --- | --- |
| 63 |  |
| (46-86) |  |
| [2-1420] |  |

 |

|  |
| --- |
| 66 |
| (48-91) |
| [3-1420] |

 |

|  |
| --- |
| 61 |
| (45-84) |
| [2-1413] |

 |
| Logistic EuroSCORE(% predicted mortality) |

|  |
| --- |
| 4.18 |
| (2.08-8.49) [0.44-97.92] |
|  |

 |

|  |
| --- |
| 6.53 |
| (3.29-13.29) |
| [0.44-96.22] |

 |

|  |
| --- |
| 3.37 |
| (1.82-6.75) |
| [0.44-97.92] |

 |

**Table 1.** Patient demographics, pre-operative investigations and operative characteristics for all patients and stratified by anaemia status. Values are mean (SD), number (proportion) or median (IQR [range]).

CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass

**Table 2** Outcomes by centre over three-year study period (2010-2012). Values are number (proportion) or mean (95%CI).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **n** | **EuroSCORE (%)** | **Anaemic** | **Transfused** | **Observed mortality** | **Risk adjusted mortality** |
| **A** | 1995 | 7.4 (10.2) | 490 (25%) | 622 (31%) | 3.1 (2.4-3.9)  | 2.4 (1.8-3.1) |
| **B** | 732 | 9.2 (13.2) | 207 (28%) | 307 (42%) | 1.4 (0.4-2.1) | 0.7 (0.2-1.2) |
| **C** | 3005 | 10.5 (12.6) | 1336 (45%) | 1268 (42%) | 4.4 (3.7-5.2) | 2.7 (2.2-3.3) |
| **D** | 2201 | 8.2 (11.3) | 709 (32%) | 934 (42%) | 3.8 (3.0-4.6) | 2.8(2.1-3.4) |
| **E** | 265 | 3.0 (3.5) | 83 (31%) | 114 (43%) | 3.4 (1.2-5.6) | 4.4 (1.6-7.1) |
| **F** | 1052 | 6.6 (8.7) | 291 (28%) | 465 (44%) | 4.9 (3.6-6.2 | 4.5 (3.2-5.7) |
| **G** | 1510 | 6.9 (9.4) | 501 (33%) | 673 (45%) | 3.3 (2.4-4.2) | 2.8 (2.0-3.6) |
| **H** | 2369 | 6.7 (8.5) | 618 (26%) | 1136 (48%) | 3.4 (2.7-4.2) | 3.3 (2.6-4.1) |
| **I** | 1984 | 7.2 (10.8) | 637 (32%) | 956 (48%) | 3.8 (2.9-4.6) | 2.9 (2.2-3.7) |
| **J** | 2242 | 6.7 (9.1) | 524 (23%) | 1136 (51%) | 1.9 (1.4-2.5) | 1.6 (1.1-2.1) |
| **K** | 951 | 7.2 (9.9) | 280 (29%) | 535 (56%) | 1.7 (0.9-2.5) | 1.3 (0.6-1.9) |
| **L** | 727 | 5.5 (7.3) | 219 (30%) | 433 (60%) | 2.1 (1.0-3.1) | 2.1 (1.0-3.1) |
| **All Centres** | **19033** | **7.7 (10.5)** | **5895 (31%)** | **8579 (45%)** | **3.3 (3.1-3.6)** | **2.6 (2.4-2.8)** |

**Table 3** Patient outcomes stratified by anaemia status. Values are number (proportion) or median (IQR [range]).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | All Patients(n=19 033) | Anaemic(n=5895)31.0% | Not Anaemic(n=13 138)69.0% | p value |
| Transfused red blood cells | 8579(45.1%) | 3764(63.9%) | 4815(36.6%) | <0.001 |
| Units of red blood cells transfused† | 2 (2-4 [1-78]) | 3 (2-5 [1-77]) | 2 (1-4 [1-78]) | <0.001 |
| Massive transfusion (5 or more units) | 1933 (10.2%) | 1025 (17.4%) | 908 (6.9%) | <0.001 |
| ICU length of stay; days | 2 (1-3[0-373]) | 2 (1-4 [0-373]) | 2 (0-4 [0-368]) | <0.001 |
| Hospital length of stay; days | 7(5-10[0-370]) | 8 (6-14[0-190]) | 6 (5-9[0-370) | <0.001 |
| In-hospital mortality | 628 (3.3%) | 327 (5.6%) | 301 (2.3%) | <0.001 |

†restricted to those who received a transfusion

**Table 4** Association of anaemia and haemoglobin concentration (Hb) with outcome, adjusted for age, sex, logistic EuroSCORE, centre, operation type and body surface area; length of stay additionally adjusted for hypertension.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Transfusion** | **Death** | **Length of stay** |
|  | **Adjusted OR [95% CI]** | **p value** | **Adjusted OR [95% CI]** | **p value** | **Adjusted GMR [95% CI]** | **p value** |
| **Anaemia** | 2.75 [2.55-2.95] | <0.001 | 1.42 [1.18-1.71] | <0.001 | 1.15 [1.13-1.17] | <0.001 |
| **Hb** (per 10 g.l-1 decrease) | 1.43 [1.40-1.46] | <0.001 | 1.16 [1.10-1.22] | <0.001 | 1.04 [1.04-1.05] | <0.001 |
| **Hb** (g.l-1) |  |
| <110 | 3.63 [3.18-4.15] | <0.001 | 1.60 [1.21-2.11] | <0.001 | 1.23 [1.19-1.27] | <0.001 |
| 110 – 119 | 2.49 [2.20-2.82] | 1.01 [0.74-1.38] | 1.15 [1.11-1.18] |
| 120 – 129 | 1.70 [1.54-1.88] | 1.07 [0.82-1.40] | 1.05 [1.03-1.08] |
| 130 – 139 | Ref  | Ref | Ref |
| 140 – 149 | 0.80 [0.73-0.88] | 0.64 [0.46-0.88] | 0.97 [0.94-0.99] |
| 150+ | 0.51 [0.45-0.57] | 0.76 [0.54-1.09] | 0.97 [0.94-0.99] |

OR, odds ratio; GMR, geometric mean ratio

**Appendix 1** Contributors

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*Note to typesetter: these 11 names to be tagged to appear in PubMed as ‘Collaborators’*