Original Article

Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study

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Abstract

Background

Pre-operative anaemia affects a third of patients undergoing cardiac surgery and is associated with increased mortality and morbidity. The National Institute for Health and Care Excellence (NICE) in the UK recommended in 2016 that perioperative teams should identify and treat patients with pre-operative anaemia before surgery. However, introducing new treatment protocols can be challenging in surgical pathways. The aim of this study was to assess the feasibility and effectiveness of introducing a pre-operative intravenous iron service as a national initiative in cardiac surgery.

Methods

We performed a multicentre, stepped, observational study using the UK Association of Cardiothoracic Anaesthesia Research Network. The primary feasibility outcome was the ability to set up an anaemia and intravenous iron clinic at each site. The primary efficacy outcome was change in haemoglobin (Hb) concentration between intervention and operation. Secondary outcomes included blood transfusion and hospital stay. Patients with anaemia were compared to those without anaemia and additionally to those who received intravenous iron as part of their routine treatment protocol.

Results

Seven out of eleven NHS hospitals successfully set up iron clinics over two years and 228 patients were recruited into this study; 92 were not anaemic, 72 anaemic but not treated and 64 who were anaemic received intravenous iron pre-operatively. Patients with anaemia who received intravenous iron were at higher surgical risk, were more likely to have a known previous history of iron deficiency or anaemia, had a higher rate of chronic kidney disease and were slightly more anaemic than the non-treated group. Intravenous iron was administered a median (IQR [range]) of 33 (15 - 53 [4 - 303]) days before surgery. Primary efficacy endpoint showed pre-operative intravenous iron increased [Hb] from baseline to pre-surgery; mean (95% CI) change was +8.4 (5.0 to 11.8) g/l ($p<0.001$). Overall, anaemic compared with non anaemic patients were more likely to be transfused than (49% (59/136) vs 27%

(22/92), p=0.001), and stayed longer in hospital (median days (IQR) 9 (7-15) vs. 8 (6-11), p=0.014). The number of days alive and at home was lower in the anaemic group (median days (IQR) 20 (14-22) vs. 21 (17-23), p= 0.033) There was no difference between treated and non-treated anaemic patients. No adverse events were reported in association with intravenous iron administration.

Conclusion

The development of an intravenous iron pathway is feasible but appears limited to selected high-risk cardiac patients in routine NHS practice. Whilst intravenous iron increased [Hb], there is a need for an appropriately powered clinical trial to assess the clinical effect of intravenous iron on patient-centred outcomes.

Introduction

In a large UK- wide study conducted by the Association of Cardiothoracic Anaesthetists (ACTA) in 2016, anaemia was found to be common before cardiac surgery and independently associated with worse outcomes, including length of stay in ICU and hospital, and mortality. Patients with anaemia had an increased risk of death following cardiac surgery[1]. Anaemia in the general population is common, with a global prevalence in excess of 30%[2]. This prevalence increases with age, affecting half the geriatric population across the UK[3]. An expanding body of evidence continually links pre-operative anaemia to increased surgical mortality, higher rates of transfusion, length of hospital stay and surgical complications[4–6]. This is particularly relevant in cardiac surgery where comorbidities are common, blood loss is greater and transfusion requirements higher[7–9].

Patient blood management (PBM) is a patient-centred, multidisciplinary approach to reducing blood transfusion and consists of a raft of preventative and reactive measures that highlight best practice and quality in blood transfusion. Introduction of PBM is associated with improved outcomes and reduction in cost.[10] The first pillar of PBM has focused on early detection and correction of anaemia. However, these recommendations for the timely of diagnosis of anaemia, with appropriate and early treatment present significant healthcare organisational challenges in an often busy setting before operation.[11,12]

The commonest cause of anaemia is iron deficiency, whether absolute or functional; Folate and Vitamin B12 deficiency are less frequent.[13] Treating iron deficiency anaemia effectively in the time available prior to most cardiac procedures is not possible with oral iron. Intravenous iron is an ideal alternative given newer preparations that can be administered rapidly and with less side-effects and a good safety profile.[14] The use of intravenous iron is more effective in increasing haemoglobin than oral iron[15] and has been observed to reduce transfusion in many surgical specialties.[16]

In 2016, NICE reviewed transfusion practice and recommended the timely identification of anaemia before surgery and to consider alternatives to transfusion.[17] However, sequential audits on PBM practices across National Health Service (NHS) organisations show management of preoperative anaemia is frequently inadequate.[18,19] Similarly, the implementation of PBM in Europe is limited, and

considerable variations exist in the assessment and treatment of preoperative anaemia.[20]

Previously, with the Association of Cardiothoracic Anaesthetists (ACTA), we developed a network of enthusiastic and knowledgeable consultants interested to develop PBM in cardiac surgery [1] We wished to assess the feasibility of the introduction of a pre-operative intravenous iron pathway into routine clinical practice, in line with NICE guidance. The aim of the CAVIAR study was to assess the introduction and efficacy of a pre-operative intravenous iron pathway to treat anaemia in patients before cardiac surgery.

Methods

Design

The UK Cardiac and Vascular Surgery Interventional Anaemia Response (CAVIAR) Study was a multicentre, stepped, observational pilot and feasibility study in patients undergoing cardiac and vascular surgery, the protocol for which has already been published.[21] From a network developed with ACTA, we invited 11 UK cardiac surgical centres (from a total of 19 in the UK) who had expressed an interest in setting up anaemia treatment clinics to take part in this study. Educational support was provided by a core team of experts in PBM, intravenous iron and cardiac surgery. National UK Ethics Committee approval (ref 15/LO/1569, IRAS 188848) was granted and each centre obtained local approval to set up their anaemia pathway following UK NHS procedures, which included proformas, business plans and formulary application approval. Site visits were performed to every unit with advice and educational briefings, literature and protocols for anaemia management were shared between centres once developed. Three annual meetings were held to exchange feedback and support, regular newsletters were sent to all those involved.

The study was designed as a stepped, prospective, observational platform comprising three groups of patients awaiting cardiac surgery: non-anaemic patients (control); anaemic patients of any cause who were not treated with IV Iron for any reason; and anaemic patients treated with intravenous iron before surgery. The trial design was published in advance.[21]

Anaemia was defined according to the World Health Organization definition (Hb <130 $g.L^{-1}$ in men and <120 $g.L^{-1}$ in women). Inclusion criteria were any patient greater than 18 years of age undergoing elective cardiac surgery (coronary bypass, valve surgery or both). Exclusion criteria included: pregnant or lactating women; patients on renal dialysis; prisoners and patients who lacked the capacity or were unwilling to consent to the study.

Recruitment

Centres recruited patients consecutively, between April 2016 until March 2018, but over different time periods depending on the centre's progress in setting up pre-operative anaemia services and availability of study teams. All patients provided full written informed consent and were recruited as controls (non-anaemic) or those with anaemia. Those with anaemia and able to receive intravenous iron were recruited if

they fulfilled local criteria for diagnosis and treatment of Iron-deficiency anaemia (generally Ferritin <100 and TSAT <20%) and could attend pre-operative clinic at least 10 days before surgery. Those who were anaemic and qualified for IV iron treatment, but did not receive IV iron, for any reason, formed the anaemic non-treated group. Largely, this was for logistical or geographical reasons. Following consent, collection of baseline data and blood samples, they were treated with a single dose intravenous iron infusion. This comprised either iron isomaltoside 1000 (Monofer®, Pharmacosmos A/S) at a total dose calculated at 20mg/kg or ferric carboxymaltose (Ferinject®, Vifor Pharma UK), to a maximum of 1000mg, both by infusion over at least 15-30 minutes according to local policy. Patients were observed during and for 30 minutes after infusion (non-invasive blood pressure, ECG and oxygen saturations). Anaemic patients who had received intravenous iron were reassessed on the day of surgery and further laboratory data and blood samples collected.

Outcomes

he primary feasibility outcome was success in setting up an anaemia clinic in the NHS, and the primary efficacy outcome was the ability to increase Hb concentration between treatment and immediately before surgery with intravenous iron. Secondary outcomes were: blood transfusion (proportion of patients transfused, and number of units transfused, excluding patients who received a large transfusion defined as four or more units of red cells); intensive care unit and hospital length of stay; renal function; change in Hb from before treatment to after surgery and mortality. Patients were followed up for 30 days postoperatively and asked about re-admission to hospital so that days-alive-and-at-home (DAH-30)[22] could be calculated. DAH-30 is a composite measure that combines hospital length of stay and mortality, though we included all three outcomes measures for reference.

Analysis

For descriptive statistics, mean and standard deviation (SD) or median and interquartile range (IQR) and range were used for continuous variables as appropriate. Frequencies and percentages were used for categorical variables. Baseline characteristics were compared across the three groups of patients using chi-square tests for categorical variables and F-tests (if normally distributed) or

Kruskal-Wallis rank test (if not normally distributed) for continuous variables. For the primary efficacy outcome, a one sample t-test was used to estimate the mean change in Hb along with its 95% confidence interval and p-value. Multiple logistic regression models adjusting for important baseline predictors were used for the secondary outcome blood transfusion. The Wilcoxon rank sum test was used to compare length of stay (excluding patients who had died) and for days alive and out of hospital. One sample t-tests were used to estimate the mean pre-post-surgery change in Hb and its 95% CI in each group of patients. The proportion of deaths and hospital readmissions were compared using a chi squared test.

Sample size was calculated based upon change in Hb from baseline to pre-surgery in patients who received intravenous iron. Assuming the standard deviation for Hb would be 12 $g.L^{-1}$ based on national audit data[1], we calculated that 72 patients would provide 90% power at a 5% significance level and 62 would provide 80% power (allowing for up to 10% loss to follow-up) to demonstrate a difference in the change from baseline in Hb of 10 $g.L^{-1}$. The report was prepared according to the Strengthening The Reporting of OBservational studies in Epidaemiology (STROBE) framework.

Results

Feasibility

Seven of the eleven (64%) NHS hospitals successfully set up anaemia pathways or clinics as part of their pre-operative cardiac surgical service over the study period. Two centres had difficulties getting approvals for intravenous iron onto their pharmacy formulary; and two had the business plans refused by the hospital Trust or commissioners (funders).

Two-hundred and twenty-eight patients were recruited over 2 years in 11 UK cardiac centres (Supplementary figure 1). The commonest reasons for failure to recruit patients were; administrative and lack of research staff, no date for surgery, date of surgical procedure outside of study treatment window (within 10 days) and 19% of patients approached to take part refused to give consent.

Of the 228 patients recruited before cardiac surgery; 92 (40%) patients were not anaemic, 72 (32%) were anaemic but not treated, and 64 (28%) were anaemic and received intravenous iron pre-operatively. Of the anaemic patients, who would ideally receive IV iron pre-treatment, only 47% (64/136) were treated, due to various logistical barriers. Individual TSAT/Ferritin results for all participants have not been included as the data were not complete at time of analysis.

Patients treated with intravenous iron were more likely to have a history of anaemia and iron deficiency and have chronic kidney disease (Table1). Those treated were slightly more anaemic than the non-treated group, mean (95% CI) difference in [Hb] -2.5 (Table 2).

Intravenous iron was administered a median (IQR [range]) of 33 (15 - 53 [4 - 303]) days before surgery. Mean (SD) dose of intravenous iron was 1293 (303) mg with 60 patients receiving iron isomaltoside at a mean dose of 1314 (303) mg and 4 receiving 1000mg of iron carboxymaltose. No adverse event was reported.

Efficacy

Intravenous iron was efficacious and increased average Hb in anaemic patients before surgery compared to those without treatment; mean (95% CI) change in Hb in patients treated with intravenous iron was +8.4 (5.0 to 11.8) g/L between treatment and surgery, $p<0.001$ (Table 2). Overall, transfusion rates varied from 30% to 65% across the study centres. Twenty-three (10%) patients received a large blood transfusion with greater than four units of red cells and were excluded (9 from the

non-anaemic group, 5 from the non-treated anaemic group and 9 from the treated anaemic group). Non-anaemic patients were less likely to be transfused than anaemic patients, 22/92 (27%) vs 59/136 (42%), adjusted OR 2.53 (1.38-4.63, p=0.003 (Table 3). Non-anaemic patients were also transfused fewer units of red cells and stayed less time in hospital and days alive at home (DAH) was higher (Table 3). There was no difference in transfusion rate, quantity of blood transfused or other outcomes between untreated anaemic patients and anaemic patients treated with intravenous iron (Table 4). Postoperatively, Hb was similar in all three groups. The greatest drop in Hb was in the non-anaemic group, 42.8 (-45.7 to -39.9) g/L, p<0.001 (Table 2).

Discussion

Although feasible, it has proven difficult to detect, diagnose and treat anaemia in cardiac surgical patients within the timeframe before surgery. Only a minority of potential patients undergoing cardiac surgery in the UK were entered into a pathway involving intravenous iron in a timely manner before operation. Hurdles for care were institutional (set up) and local (pathways). Implementation of anaemia identification and management in line with NICE guidance appears to have changed little in the last decade.[20] Our study to develop and intravenous iron service preoperatively was in keeping with the Frankfurt PBM program results where only 57 of 1830 patients scheduled for surgery received intravenous iron.[23] In order to set up anaemia detection and treatment pathways, organisational change is required and this must be multifactorial and cross boundaries. Expertise and buy in are essential from surgery, anaesthesia, haematology, pharmacy, nursing and finance departments.

Although as a non-randomised observational study it is difficult to draw firm conclusions regarding efficacy, treating anaemic patients with intravenous iron before cardiac surgery appears to be efficacious, with a statistically and clinically significant increase in haemoglobin concentration, which is consistent with a meta-analysis on the effect of intravenous iron.[15] Our work also supports the findings of the ACTA audit data that anaemic patients are more likely to be transfused and have worse outcomes than non-anaemic patients.[1] Whilst we did not show any effect of treating anaemia with intravenous iron on transfusion rate or other patient outcomes, this study was not powered to demonstrate such a difference and not dissimilar to results seen in a small pilot RCT.[24]

As is often the case with observational research, the baseline characteristics of the study groups varied significantly. In this study population, anaemic patients who received intravenous iron had a significantly higher rate of pre-existing renal impairment. Renal impairment has a major influence on transfusion requirement as demonstrated in many predictive scores for transfusion risk in cardiac surgery. For example, if we were to calculate the risk of transfusion in a patient at intermediate risk of transfusion prior to cardiac using the ACTA-PORT score,[25] the presence of a pre-operative creatinine > 177 μmol/L would shift the predicted transfusion rate from 45% up to 60%. The higher rates of previously diagnosed anaemia (55% vs 30%), previous iron deficiency (39% vs 13%), and symptomatic angina (63% vs 39%) in

our treatment group, compared with the non-treated anaemic patients, may have contributed to the outcome results.

The complex nature of cardiac surgery and multifactorial causes for coagulopathy with need for significant use of blood resources[26] may override the positive effects of intravenous iron in the preoperative setting. Successful treatment of anaemia before cardiac surgery is possible, but there is currently no strong evidence it can improve cardiac surgical outcomes. In a more general context, it appears that intravenous iron has the ability to significantly improve Hb concentration and reduce risk of transfusion.[27] This has been translated into expert consensus[28] and practice guidelines.[17] Trials examining preoperative cardiac surgical patients have been encouraging, though not definitive. One large retrospective cohort trial showed an improvement in mortality, transfusion rate, renal failure and admission length[29] and a smaller RCT suggested that an increase in [Hb] and a reduction in transfusion rates is possible.[30] However, another small RCT failed to demonstrate that IV iron can improve [Hb],[31] making the evidence rather inconclusive and inadequate to firmly validate the wide spread use of IV iron in this population. To date, this study is the largest of its kind that demonstrates intravenous iron is effective in treating anaemic cardiac surgical patients, within the time constraints of the pre-operative period. CAVIAR-UK was not designed to be the definitive study of the effect of intravenous iron on improving clinical outcomes in this patient group, but rather designed to provide information to guide design and implementation of a subsequent randomised controlled trial, which is now underway.

These results suggest that further research is both possible and necessary to demonstrate that by effectively treating anaemia pre-operatively, we may be able to reverse, or improve some of the associated adverse outcomes. The study also demonstrates that, in the UK centres studied, there were significant deficits in infrastructure and process to allow timely diagnosis and treatment to achieve a meaningful clinical result in an appropriate timeframe. CAVIAR was designed to treat patients at least 10 day pre-operatively as it appears that 7-9 days is required for IV iron to have it peak effect on ferritin levels[32] and it appears that [Hb] increase begins to plateau between 5-14 days.[33] A recent RCT showed that giving IV Iron and EPO immediately before surgery showed a reduction in transfusion, but no demonstrable patient benefit.[34] Greater access to anaemia treatment centres, such as

multidisciplinary pre-operative anaemia clinics, should facilitate prompt and effective treatment for those patients identified at risk.

By nature of its design, this study had significant limitations. As an observational study, the likelihood of significant differences in baseline data is high, and the presence of bias and confounders is common. There were significant differences in baseline characteristics between the groups that could plausibly lead to changes in the treatment effect and measured outcomes. The study was designed to detect an increase in Hb concentration and therefore underpowered to detect outcome changes. Many of our investigators are now involved in the ITACS trial (NCT02632760), a larger RCT that is currently underway, which aims to demonstrate that IV iron, by increasing [Hb] prior to cardiac surgery, can improve patient outcomes.

Acknowledgements

Funded by a grant from the Association of Cardiothoracic Anaesthesia and Critical Care (ACTACC), the Vascular Anaesthesia Society of Great Britain and Ireland and the British Journal of Anaesthesia, via the National Institute of Academic Anaesthesia. Additional funding for staff resources was provided by Pharmacosmos. The study was included in the NIHR Portfolio and the NIHR provided additional funds to the study centres for assistance with patient recruitment. None of the funders had any influence on study design, trial management, analysis of the data, preparation of the manuscript or decision to submit.

Conflicts of Interest

AK or his institution has received educational grant funding, honoraria or travel expenses from Pharmacosmos, Vifor Pharma, Massimo, Hemonetics, Hemosonics and Fisher and Paykel. MC's salary is supported by Pharmacosmos. CE has done consulting work for Pharmacosmos. SA has received research funding and honoraria from Pharmacosmos. TR reports grants, personal fees and non-financial support from Pharmacosmos; grants, personal fees and non-financial support from Vifor Pharma; grants, personal fees and non-financial support from Acelity; grants, personal fees and non-financial support from Stroke Association; grants from Mason Medical Research Foundation; grants from UCH league of Friends; grants and non-financial support from Libresse/Bodyform.

Table 1 Baseline characteristics. Values are mean (SD) or number (proportion).

	Non-anaemic n=92	Anaemic non-treated n=72	Anaemic treated n=64	p-value
Age; years	67.0 (9.7)	69.3 (11.8)	70.2 (10.9)	0.158
Sex; men	66 (72%)	55 (76%)	46 (72%)	0.767
Weight; kg	85.8 (17.9)	83.2 (18.0)	81.6 (17.9)	0.120
Height; cm	170.0 (10.0)	168.9 (10.6)	167.6 (8.9)	0.340
BMI; kg.m^{-2}	29.3 (5.3)	29.2 (5.9)	29.0 (5.4)	0.929
EuroSCORE-2	1.3 (0.9-2.7 [0.5-19.8])	1.7(0.9-3.3 [0.6-15.0])	2.2 (1.0-3.4 [0.5-16.9])	0.072
Cardiac function				
Good	66 (73%)	55 (76%)	48 (75%)	
Moderate	24 (26%)	15 (21%)	15 (23%)	
Poor	1 (1%)	2 (3%)	1 (2%)	0.866
NYHA				
1	28 (31%)	23 (32%)	12 (19%)	
2	43 (47%)	26 (37%)	32 (50%)	
3	20 (22%)	17 (24%)	19 (30%)	
4	0	5 (7%)	1 (2%)	0.042
Creatinine; umol.l^{-1}	84 (73-96 [56- 205])	85 (72-113 [47-311])	104 (75-120 [46-192])	0.008
Medical history				
Iron deficiency	4 (4%)	9 (13%)	25 (39%)	<0.001
Anaemia	10 (11%)	21 (29%)	35 (55%)	<0.001
Operation				
CABG	44 (48%)	29 (40%)	24 (38%)	
Single Valve	29 (32%)	33 (46%)	22 (34%)	
CABG+Valve	12 (13%)	4 (6%)	9 (14%)	

Other	7 (8%)	6 (8%)	9	(14%)	0.229

Table 2: Haemoglobin concentration by group and time

	Non-anaemic	Anaemic not-treated	Anaemic treated
	n=92	**n=72**	**n=64**
Mean (SD) Hb; g/L			
Pre-treatment	NA	NA	114.2 (9.3)
Pre-surgery	141.1 (10.4)	116.7 (10.2)	122.7 (13.3)
Postoperative	98.3 (13.6)	93.2 (10.5)	93.7 (11.9)
Mean (95% CI) change in Hb-g/L			
Pre/post treatment	NA	NA	8.4 (5.0, 11.8)
Pre/post surgery	-42.8 (-45.7 to -39.9)	-23.4 (-26.5 to -20.3)	-29.0 (-32.4 to -25.6)

Table 3 Study outcomes, anaemic versus non-anaemic patients, excluding 23 patients who were transfused > 4 units red cells. Adj OR: odds ratio for blood transfusion adjusted for sex, BMI, diabetes and operation type

	Non-anaemic (N=92)		**Anaemic (N=136)**		**p-value**
Number (%) transfused	22	(26.5)	59	(48.8)	0.001
Adj OR (95% CI)			3.18	(1.60-6.31)	0.001
Units transfused; n(%)					
1-2	15	(16%)	43	(32%)	
3-4	7	(8%)	16	(12%)	0.016
Median (IQR)	0	(0-1)	1	(0-2)	0.005
Died, n (%)	3	(3.3)	5	(3.7)	0.867
Readmissions; n(%)	15	(16.3)	16	(11.8)	0.327
ITU length of stay-days					
Median (IQR)	2	(1-4)	2	(1-5)	0.571
Hospital stay; days					
Median (IQR)	8	(6-11)	9	(7-14.5)	0.014
DAOH-30; days					
Median (IQR)	21	(17-23)	20	(14-22)	0.033

Table 4: Study outcomes, anaemic non-treated versus anaemic treated after exclusion of 14 patients transfused > 4 units of blood. Adj OR, odds ratio adjusted for baseline haemoglobin, sex, BMI, diabetes, iron tablets, hypertension and operation type.

	Anaemic non-treated n=72		Anaemic treated n=64		p-value
Number (%) transfused	28	(42%)	31	(56%)	0.127
Adj OR (95% CI)			1.33	(0.52-3.40)	0.553
Units transfused; n(%)					
1-2	18	(25.4)	25	(39.1)	
3-4	10	(14.1)	6	(9.4)	0.107
Median (IQR)	0	(0-2)	1	(0-2)	0.082
Died; n(%)	3	(4%)	2	(3%)	0.747
Readmissions; n(%)	5	(7%)	11	(17%)	0.064
ITU length of stay; days					
Median (IQR)	2	(1-4)	3	(1-5)	0.158
Hospital stay; days					
Median (IQR)	9	(7-14)	10.5	(7-15)	0.492
DAOH-30; days					
Median (IQR)	21	(14-22)	19	(15-23)	0.768

Table 5: Distribution of patient groups across centres.

Centre	Non-anaemic n=92		Anaemic non-treated n=72		Anaemic treated n=64	
Blackpool	5	(5%)	5	(7%)	0	
Cardiff	19	(21%)	4	(6%)	21	(33%)
Castle Hill	13	(14%)	10	(14%)	4	(6%)
Derriford	13	(14%)	2	(3%)	2	(3%)
Essex	3	(3%)	18	(25%)	0	
James Cook	0		2	(3%)	14	(22%)
Kings College	0		1	(1%)	2	(3%)
Liverpool	18	(20%)	12	(17%)	12	(19%)
Manchester RI	0		1	(1%)	0	
Papworth	10	(11%)	5	(7%)	9	(14%)
RI Edinburgh	11	(12%)	12	(17%)	0	

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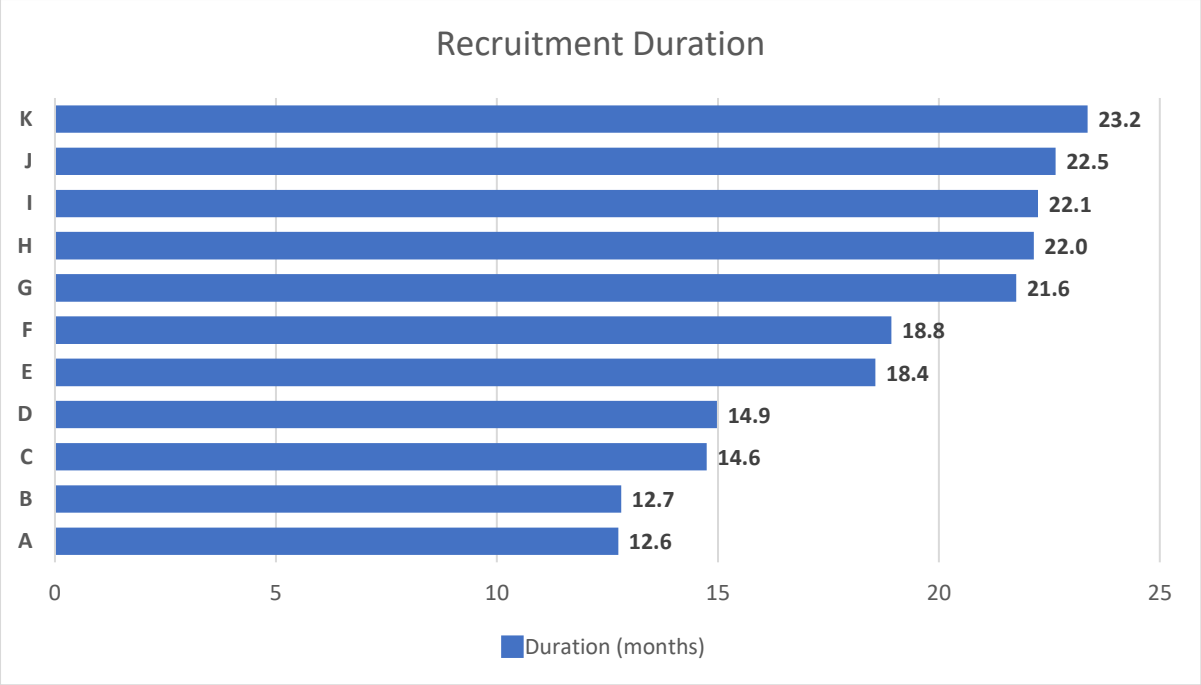
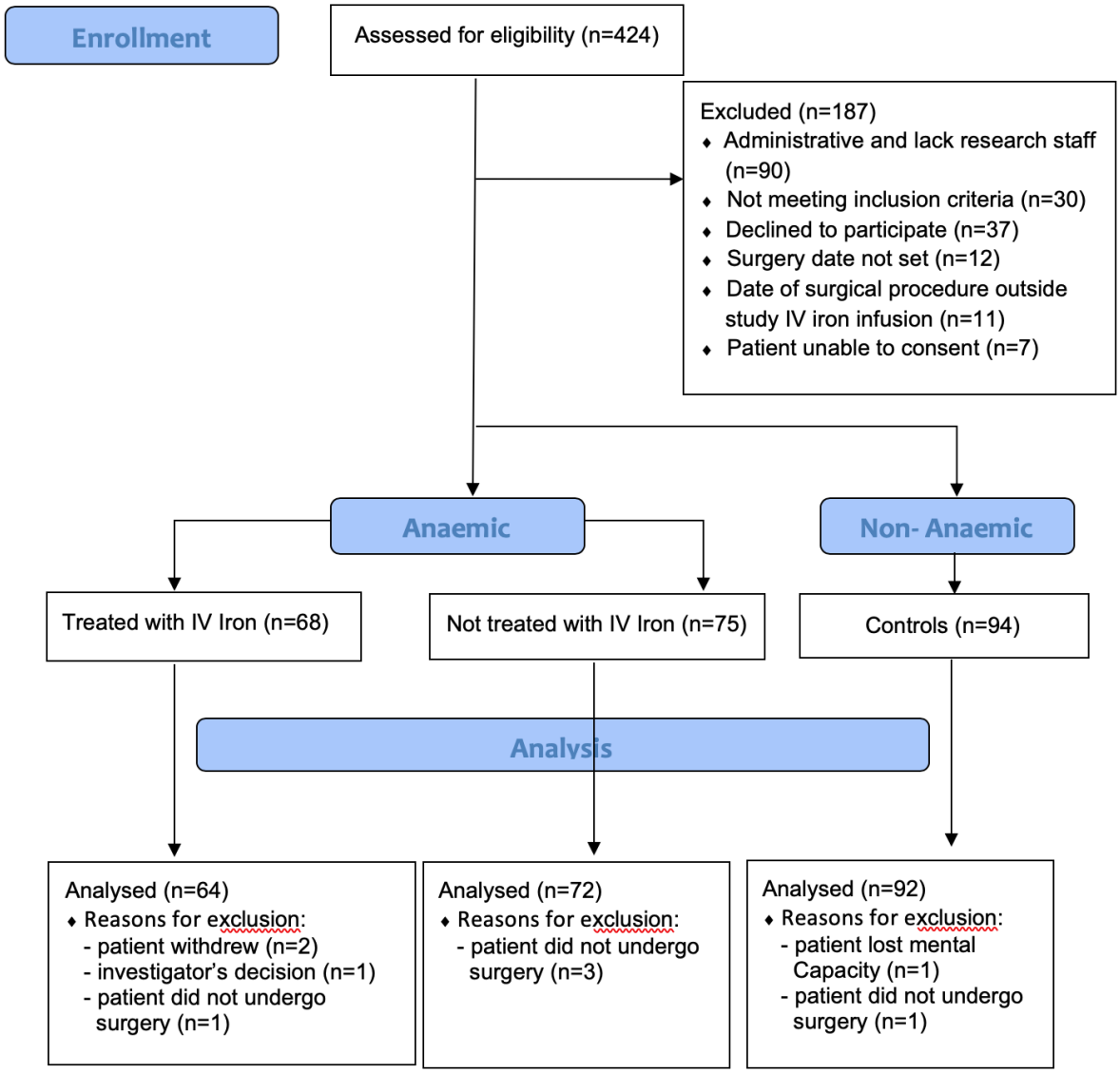


Supplement Figure 1

Duration of screening period for 11 cardiac units in the UK during the time course of the CAVIAR study



Supplement figure 2. Flow chart

Appendix 1: CAVIAR Investigators by site

Royal Free Hospital: Daniel Martin
Papworth Hospital: Andrew Klein(PI) & James Yeates
Cardiff (University Hospital of Wales): Caroline Evans
Liverpool Hospital: Seema Agarwal
Freeman Hospital: Michael Clarke
Royal Infirmary of Edinburgh: Peter Alston
Castle Hill Hospital: Ajith Vijayan
Manchester Royal Infirmary: Akbar Vohra
Essex Cardiothoracic Centre: Anirudda Pai
Brighton & Sussex University Hospitals: Anita Sugavanam
Guy's & St. Thomas Hospital: Jugdeep Dhesi
Royal Oldham Hospital: Damian Kelleher
Royal Cornwall Hospital: Harvey Chant
Royal Blackpool Hospital: Palanikumar Saravanan
Royal Bournemouth Hospital: Richard Green
University Hospitals of Leicester: Matthew Bown
Derriford Hospital: Mark Bennett
King's College Hospital: Gudrun Kunst
James Cook University Hospital: Adrian Mellor