Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

SUPPLEMENTARY APPENDIX

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Iron Dosing in Treatment Arms

All iron was administered as iron sucrose as a slow bolus injection (or by intravenous infusion) during dialysis sessions in the week following the monthly blood tests (usually the second week of the calendar month).

Proactive, High-Dose Intravenous Iron Arm

Month 1: 600 mg divided equally over three hemodialysis sessions

Month 2 through the end of treatment

- If ferritin ≤700 μg per liter: 200 mg during each of the first two dialysis sessions
- If ferritin >700 μg per liter and/or transferrin saturation ≥40%: the iron dose will be withheld

Reactive, Low-Dose Intravenous Iron Arm

- If ferritin <100 μg per liter and transferrin saturation <40%: 200 mg during each of the first two dialysis sessions
- If ferritin 100 to 200 μg per liter and transferrin saturation <40%: 200 mg during the first dialysis session
- If ferritin 201 to 700 μg per liter and transferrin saturation ≤20%: 100 mg during the first dialysis session
- If ferritin >200 μg per liter and transferrin saturation >20%: no iron
- If ferritin >700 μg per liter and/or transferrin saturation ≥40%: no iron

Statistical Analysis

The method used to analyze the recurrent events data[1] has the advantage, compared with other simpler approaches that have been put forward, of allowing arbitrary dependence structures among recurrent events. The disadvantage of applying this method to an outcome that includes death is that there is the possibility of bias if the impact of treatment on death is substantial (much greater than is likely to be observed in a clinical trial) and quite different from the impact on nonfatal events. Apart from the primary outcome, all other time-to-event end points were analyzed in the intention-to-treat population, with censoring where appropriate, including the dates of death not part of the end point analyzed. Time-to-event curves for the primary outcome and all-cause mortality were constructed using the Kaplan–Meier method. The number of infection episodes was analyzed using a negative binomial model with duration of follow-up as an offset.

Subgroup analyses were carried out for the primary end point and all-cause mortality in the prespecified subgroups by adding the subgroup variables and their interaction with the treatment group to the Cox models and testing for significance of the interaction term.

Cumulative doses of intravenous iron were summarized by study visit and compared between treatment groups at each visit and overall (scaled by duration of follow-up) using stratified Wilcoxon rank sum tests. Approximate confidence intervals were calculated using the Hodges and Lehman pairwise differences approach, succinctly described by Campbell and Gardner.[2] Total ESA dose requirements per month and numbers of units of blood transfused per year were calculated and compared using a Wilcoxon rank-sum test. A 95% confidence interval for the difference in median ESA dose requirements was calculated without stratification. Changes from baseline in quality-of-life outcomes and laboratory values were analyzed over time using a mixed-effects repeated-measures model, with within-group means estimated from least-squares means. Some patients were unwilling/unable to complete quality-of-life outcomes, and these questionnaires were not collected for all participants. No imputation of missing data was carried out. Results for secondary outcomes

are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects within subgroups.

Statistical Assumptions

A number of checks were carried out to assess the assumptions made in the statistical analyses.

Many of the time-to-first-event analyses did not include all-cause death as part of the end point analyzed. All of the time-to-first-event analyses reported in Table 2 of the manuscript are based on cause-specific Cox proportional-hazards models. There is a theoretical possibility that analyses taking into account competing risks models could give different results. To investigate this, we also fitted Fine and Gray competing risks models incorporating causes of death not included in each end point as competing risks. This approach produced results that were almost identical to those generated using cause-specific Cox models.

A second assumption in the Cox models is that of proportionality of hazards. This assumption was assessed by adding and testing the significance of the interaction between treatment group and the natural logarithm of follow-up time to each model as a time-dependent covariate. For the primary outcome, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalization for heart failure, kidney transplant, vascular access thrombosis, hospitalization for any cause, all infection episodes, and hospitalization for infection, there was no evidence of nonproportionality of hazards. For death from any cause, where there was a borderline nonstatistically significant reduction in death in the proactive, high-dose iron group (P=0.054), there was evidence of nonproportionality of hazards (P=0.043), suggesting evidence of a treatment effect evolving with increasing time of follow-up (see Fig. 2B). For the outcome of blood transfusion there was also evidence of nonproportionality (P=0.020), suggesting an early treatment effect that diminished with time. This is illustrated in Supplementary Figure S16.

The assumption of nonproportionality was also assessed for the proportional means model. This was assessed by fitting in turn models censoring follow-up at 6 months, 12 months, and so on in increasing intervals of 6 months until 4 years. The results are given in Supplementary Table S3. The results suggest no evidence of a trend toward treatment benefit in the first 6 months, with a

relatively stable estimated rate ratio thereafter suggesting reasonable compatibility with the proportionality assumption of the model. An interaction between treatment group and the natural logarithm of follow-up time was also added to the model as a time-dependent covariate. This yielded a P value of P=0.23, again indicating no evidence of nonproportionality.

A final assumption of the analyses is that censoring is not informative. As can be seen from Supplementary Figure S1, excluding deaths, the total number of patients censored due to incomplete follow-up was similar in the two treatment arms, with 362 and 346, respectively, in the reactive, low-dose and proactive, high-dose arms, with no evidence of differences in the individual causes of incomplete follow-up.

End Point Definitions

The following information is reproduced (unchanged) from the approved Endpoint Adjudication

Committee (EPAC) Charter

5 Event definitions

For those event-types requiring adjudication, the event will usually be adjudicated on the basis of strict application of the endpoint definitions below. However, the clinical likelihood that a suspected event has occurred will be individually assessed even in the absence of fulfilment of all of the criteria specified in the event-definition, recognizing that information may at times be difficult to interpret (e.g. the exact measurement of ECG changes may be imprecise) or unavailable. The EPAC will discuss such cases at a full EPAC meeting and adjudicate them using their clinical expertise and the totality of the evidence before arriving at a classification decision that is based on full consensus**.**

5.1 Deaths

In cases where a patient experiences an event and later dies due to that event, the event causing death and the death will be considered as separate events *only* if they are separated by a change in calendar day. If the event causing death and the death occur on the same calendar day, death will be the only event classified.

5.1.1 Cardiovascular deaths

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke and death due to other cardiovascular causes as follows:

Death due to Acute Myocardial Infarction refers to a death usually occurring up to 30 days after a documented acute myocardial infarction (verified either by the diagnostic criteria outlined below for acute myocardial infarction, above, or by autopsy findings showing recent myocardial infarction or recent coronary thrombus) due to the myocardial infarction or its immediate consequences (e.g. progressive heart failure) and where there is no conclusive evidence of another cause of death.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and other (e.g. ECG, angiographic, autopsy) evidence.

- NOTE: This category will include sudden unexpected cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.(i.e. myocardial infarction Type 3 – see section 5.2.1, below).

*If ECG tracings are not available for review, the EPAC may adjudicate on the basis of reported new ECG changes that have been clearly documented in the case records or in the case report form.

Death resulting from a procedure to treat an acute myocardial infarction [percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)], or to treat a complication resulting from acute myocardial infarction, should also be considered death due to acute myocardial infarction.

Death resulting from a procedure to treat myocardial ischaemia (angina) or death due to an acute myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation that was not undertaken to treat an acute myocardial infarction or its complications should be considered as a death due to other cardiovascular causes.

Sudden Cardiac Death refers to a death that occurs unexpectedly in a previously stable patient. The cause of death should not be due to another adjudicated cause (e.g. acute myocardial infarction Type 3 – see section 5.2.1 below).

The following deaths should be included.

a. Death witnessed and instantaneous without new or worsening symptoms

b. Death witnessed within 60 minutes of the onset of new or worsening symptoms unless a cause other than cardiac is obvious.

c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor), or unwitnessed but found on implantable cardioverter-defibrillator review.

d. Death in patients resuscitated from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, including acute myocardial infarction, and who die (without identification of a non-cardiac aetiology) within 72 hours or without gaining consciousness; similar patients who died during an attempted resuscitation.

e. Unwitnessed death in a patient known to have been alive and clinically stable within 24 hours of death without any other cause of death identified (information regarding the patient's clinical status in the 24 hours preceding death should be provided, if available)

Death due to Heart Failure refers to a death occurring in the context of new or worsening clinical manifestations of heart failure (see "hospitalisation for heart failure definition – section 5.2.6, below) without evidence of another cause of death (e.g. acute myocardial infarction). In general, the new or worsening clinical manifestations should require the initiation of, or an increase in, treatment directed at heart failure, or occur in a patient already receiving maximal therapy for heart failure. However, if time does not allow for the initiation of, or an increase in, treatment directed at heart failure or if the circumstances were such that doing so would have been inappropriate (e.g. patient refusal), the EPAC will adjudicate based on clinical presentation and, if available, investigative evidence.

Death due to Stroke refers to death after a documented stroke (verified by the diagnostic criteria outlined below for stroke or by typical post mortem findings) that is either a direct consequence of the stroke or a complication of the stroke and where there is no conclusive evidence of another cause of death.

NOTE: In cases of early death where confirmation of the diagnosis cannot be obtained, the EPAC may adjudicate based on clinical presentation alone.

Death due to a stroke reported to occur as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

Death due to subdural or extradural haemorrhages will be classified (based on clinical signs and symptoms as well as neuroimaging and/or autopsy) and categorised separately by the EPAC.

Death due to Other Cardiovascular Causes refers to death due to a documented cardiovascular cause not included in the above categories [e.g. pulmonary embolism, cardiovascular procedure (other than one performed to treat an acute myocardial infarction or a complication of an acute myocardial infarction – see definition of death due to myocardial infarction, above), aortic aneurysm rupture, peripheral arterial disease].

5.1.2 Non-cardiovascular deaths

A non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. There should be unequivocal and documented evidence of a non-cardiovascular cause of death, as in an expected death from a carcinoma.

Further subclassification of non-cardiovascular death will be as follows:

- Infection* (includes sepsis)
- Pulmonary (excluding infection)
- Renal (excluding infection)
- Gastrointestinal (excluding infection)
- Malignancy
- Withdrawal of dialysis
- Non-cardiovascular surgery
- Other non-cardiovascular, specify: ___

*When classifying a death as being due to infection, the adjudication committee will, where possible from the information available, record the site of origin and whether a causative organism was identified.

5.1.3 Undetermined cause of death

This refers to any death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause (e.g. due to a lack of information such as a case where the only information available is "patient died"). It is expected that every effort will be made to provide the adjudicating committee with enough information to attribute deaths to either a cardiovascular or non-cardiovascular cause so that the use of this category is kept to a minimal number of patients.

5.1 Non-fatal cardiovascular events

Date of onset

For purposes of classification, when classifying events that are a cause of hospitalisation, the date of admission will be used as the onset date. In cases where the stated date of admission differs from the date the patient first presented to hospital with the event (e.g. because of a period of observation in an emergency department, medical assessment unit or equivalent), the date of initial presentation to hospital will be used (provided that the patient had not been discharged from hospital in the interim).

For events where an admission date is not applicable (or not available), the date of onset as stated by the investigator will be used.

5.2.1 Acute myocardial infarction

1. General considerations

The term *myocardial infarction* should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.
In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); **and**
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. Myocardial Infarction may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

2. Criteria for Myocardial Infarction

a. Clinical Presentation
The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help
differentiate acute MI from the background disease process.

b. Biomarker Elevations
For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. In general, troponins are preferred. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.

Note: Since chronic kidney disease can be associated with an elevation of cardiac biomarkers, the adjudication committee will interpret results in context and, in particular, with reference to previous values, where available.

c. Electrocardiogram (ECG) Changes
Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be

ischaemic changes and confirmatory information may be new Q waves.

Criteria for acute myocardial infarction

The term *acute myocardial infarction* should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for acute MI:

- Detection of a rise and/or fall of cardiac biomarkers [preferably cardiac Troponin (cTn)] with at least one value above the 99th percentile upper reference limit (*but see note above under "Biomarker elevations", above*) and with at least one of the following:
  - Symptoms of myocardial ischaemia
  - New, or presumed new, significant ST segment-T wave (ST-T) changes (as outlined in Table 1, below) or new left bundle branch block (LBBB)
  - Development of pathological Q waves on the ECG (see Table 2, below)
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

- Percutaneous coronary intervention-related MI is defined by the following criteria:

  1. Elevation of Troponin values > 5 X 99 th percentile URL within 48 hours of the procedure; ***and***

  - Normal baseline Troponin values;

  <u>OR</u>

  - Both of the following must be true:
    - ≥ 20% increase in the Troponin result
    - Evidence that Troponin values were stable/decreasing (e.g. two samples 3-6 hours apart)

  <u>And</u>

  2. In addition, there should be at least one of the following:
     - Evidence of prolonged ischemia (<u>></u> 20 minutes) as demonstrated by prolonged chest pain
     - New ischaemic ST changes or new pathological Q waves (see tables 1 and 2, below)
     - Angiographic findings consistent with a flow-limiting complication such as loss patency of a side branch, persistent slow-flow or no-reflow, embolization
     - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise/and or fall of cardiac biomarker values with at least one value above the 99th percentile URL (*but see note above under "Biomarker elevations", above*).

- Coronary artery bypass grafting (CABG) related MI is defined by the following criteria:

1. Elevation of Troponin values > 10 x 99th percentile URL within 48 hours of the procedure; ***and***

- Normal baseline Troponin values;

OR

- Both of the following must be true:
  - ≥ 20% increase in the cardiac biomarker result
  - Evidence that cardiac biomarker values were stable/decreasing (e.g. two samples 3-6 hours apart)

And

2. In addition, there should be at least one of the following:

- New pathological Q-waves or new left bundle branch block
- Angiographically documented new graft or new native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Clinical classification of different types of myocardial infarction

Universal classification of myocardial infarction:

Type 1: Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to ischaemic imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy.

Type 3: Myocardial infarction resulting in death when biomarkers are unavailable

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolisation, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis that is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

In addition to the clinical classification, above, myocardial infarctions will be further sub-classified as:

1. ST segment elevation myocardial infarction (STEMI).
or
2. Non-ST segment elevation myocardial infarction (NSTEMI).
or
3. Myocardial infarction, type (i.e. STEMI or NSTEMI) unknown.

Table 1: ECG manifestations of acute myocardial ischaemia (in absence of left ventricular hypertrophy and left bundle branch block)

ST elevation
New ST elevation at the J-point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply:≥ 0.2 mV_in men ≥40 years (≥ 0.25 mV in men_< 40 years) or ≥ 0.15 mV in women.

ST depression and T wave changes
New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T wave inversion ≥ 0.1 mV in two contiguous leads with a prominent R wave or R/S ratio >1.

The above ECG criteria illustrate patterns consistent with myocardial ischaemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

Table 2: Pathological Q waves:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, Avl; V1-V6; II, III, and aVF) [a]

The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

*5.2.2 Hospitalisation for unstable angina**

For the diagnosis of hospitalisation due to unstable angina there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfilment of the following criteria:

There should be:

1. Cardiac ischaemic-type symptoms at rest (chest pain or equivalent) or an accelerating pattern of angina (e.g. exercise-related ischaemic-type symptoms increasing in frequency and/or severity, decreasing threshold for onset of exercise related ischaemic type symptoms) but without the fulfilment of the above diagnostic criteria for acute myocardial infarction.

and

2. The need for treatment with parenteral (intravenous, intra-arterial, buccal, transcutaneous or subcutaneous) anti-ischemic/antithrombotic therapy and/or coronary revascularization.

and

3a ECG manifestations of acute myocardial ischaemia (New ST-T changes meeting the criteria for acute myocardial ischaemia - as outlined in Table 1, section 5.2.1).

or

3b Angiographically significant coronary artery disease thought to be responsible for the patient's presentation. [If both invasive and CT angiographic imaging of the coronary arteries were performed, the results of the invasive coronary angiogram should take precedence].

and

4. The EPAC should be satisfied that unstable angina was the primary reason for

hospitalisation.

*5.2.3 Hospitalisation for other angina**

For the diagnosis of hospitalisation for other angina, there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfilment of the following criteria:

There should be:

1 Typical cardiac ischaemic-type symptoms but without the fulfilment of the above diagnostic criteria for acute myocardial infarction or unstable angina

and

2 The need for treatment with new or increased anti-anginal therapy (excluding sublingual nitrate therapy).

and

3a Investigations undertaken in view of the event (e.g. exercise ECG or stress myocardial perfusion scan) showing evidence of reversible myocardial ischemia.

or

3b Coronary angiography showing angiographically significant coronary disease thought to be responsible for the patient's presentation. [If both invasive and CT angiographic imaging of the coronary arteries were performed, the results of the invasive coronary angiogram should take precedence.]

and

4 The EPAC should be satisfied that angina was the primary reason for hospitalisation

*5.2.4 Hospitalisation for other chest pain**

There should be:

1. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay i.e. a date change) due to chest pain but where the definitions (above) of acute myocardial infarction, hospitalisation for unstable angina or hospitalisation for other angina are not met.

2. The EPAC should be satisfied that chest pain was the primary reason for hospitalisation.

*These events are not study endpoints, however the definitions provided for these events will be used by the EPAC to categorise reported myocardial infarction, angina and chest pain events that

do not meet the study definition of acute myocardial infarction.

5.2.5 Stroke

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

A For the diagnosis of stroke, the following 4 criteria should usually be fulfilled:

1. **Rapid onset* of a focal/global neurological deficit with at least one of the following:**
   - Change in level of consciousness
   - Hemiplegia
   - Hemiparesis
   - Numbness or sensory loss affecting one side of the body
   - Dysphasia/aphasia
   - Hemianopia (loss of half of the field of vision of one or both eyes)
   - Complete/partial loss of vision of one eye
   - Other new neurological sign(s)/symptom(s) consistent with stroke

   *If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation.

2. **Duration of a focal/global neurological deficit ≥ 24 hours**
   Or < 24 hours if
   (i) this is because of at least one of the following therapeutic interventions:
   (a) pharmacologic i.e. thrombolytic drug administration.
   (b) non-pharmacologic i.e. neurointerventional procedure (e.g. intracranial angioplasty).
   or
   (ii) brain imaging available clearly documenting a new haemorrhage or infarct.
   or
   (iii) the neurological deficit results in death

3. **No other readily identifiable non-stroke cause for the clinical presentation** (e.g. brain tumour, hypoglycaemia, peripheral lesion).

4. **Confirmation of the diagnosis by at least one of the following****:
a) neurology or neurosurgical specialist.
b) brain imaging procedure (at least one of the following):
   (i) CT scan.
   (ii) MRI scan.
   (iii) cerebral vessel angiography.
c) lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial haemorrhage).

**** If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event may be adjudicated as a stroke if, after discussion, the EPAC is satisfied that the clinical presentation is convincing *and* there is no plausible non-stroke cause for the presentation.

B If the acute neurological deficit represents a worsening of a previous deficit, this worsened deficit must have:

Persisted for more than one week
Or ≤ one week if

(i) this is because of at least one of the following therapeutic interventions:
(a) pharmacologic i.e. thrombolytic drug administration.
(b) non-pharmacologic i.e. neurointerventional procedure (e.g. intracranial angioplasty).

or

(ii) brain imaging available clearly documenting an appropriate new CT/MRI finding.

or

(iii) the neurological deficit results in death

Strokes will be further sub-classified as:

- Ischaemic (non-haemorrhagic) stroke
  (i.e. caused by an infarction of central nervous system tissue)

or

- Haemorrhagic stroke***
  (i.e. caused by nontraumatic intraparenchymal, intraventricular or subarachnoid haemorrhage)

or

- Stroke type (i.e. haemorrhagic or ischaemic) unknown (i.e. when imaging/other investigations are unavailable or inconclusive).

***Subdural and extradural haemorrhages will be adjudicated (based on clinical signs and symptoms as well as neuroimaging and/or autopsy) and classified separately by the EPAC.

5.2.6. Hospitalisation for heart failure

For the diagnosis of hospitalisation for heart failure, there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfilment of the following criteria:

There should be:

1. clinical manifestations of new or worsening heart failure including at least one of the following:
   - New or worsening dyspnoea on exertion
   - New or worsening dyspnoea at rest
   - New or worsening fatigue/decreased exercise tolerance
   - New or worsening orthopnoea
   - New or worsening PND (paroxysmal nocturnal dyspnoea)

- New or worsening lower limb or sacral oedema
- New or worsening pulmonary crackles/crepitations
- New or worsening elevation of JVP (jugular venous pressure)
- New or worsening third heart sound or gallop rhythm

And

2. Investigative evidence of structural or functional heart disease (<u>if available</u>) with at least *one* of the following:

- Radiological evidence of pulmonary oedema/congestion or cardiomegaly.
- Imaging (e.g. echocardiography, cardiac magnetic resonance imaging, radionuclide ventriculography) evidence of an abnormality (e.g. left ventricular systolic dysfunction, significant valvular heart disease, left ventricular hypertrophy).
- Elevation of BNP or NT-proBNP levels.

[Since chronic kidney disease can be associated with an elevation of BNP or NT-proBNP levels, the adjudication committee will interpret results in context and, in particular, with reference to previous values, where available.]

- Other investigative evidence of structural or functional heart disease (e.g. evidence obtained from pulmonary artery catheterisation).

And

3. Need for new/increased therapy *specifically for the treatment of heart failure* including at least one of the following:

- Initiation of intravenous diuretic, inotrope, vasodilator or other recognised intravenous heart failure treatment or up titration of such intravenous therapy if already receiving it.
- Mechanical or surgical intervention (e.g. mechanical or non-invasive ventilation, mechanical circulatory support).
- Alteration to the dialysis schedule to facilitate extra mechanical fluid removal* (this may include extra dialysis sessions or longer dialysis).

*When classifying an event as meeting the definition of "hospitalisation for heart failure, the adjudication committee will record whether or not the treatment administered included extra mechanical fluid removal.

And

4. The EPAC should be satisfied that heart failure was the primary disease process accounting for the clinical presentation.

Figure S1. Trial Flow Chart.

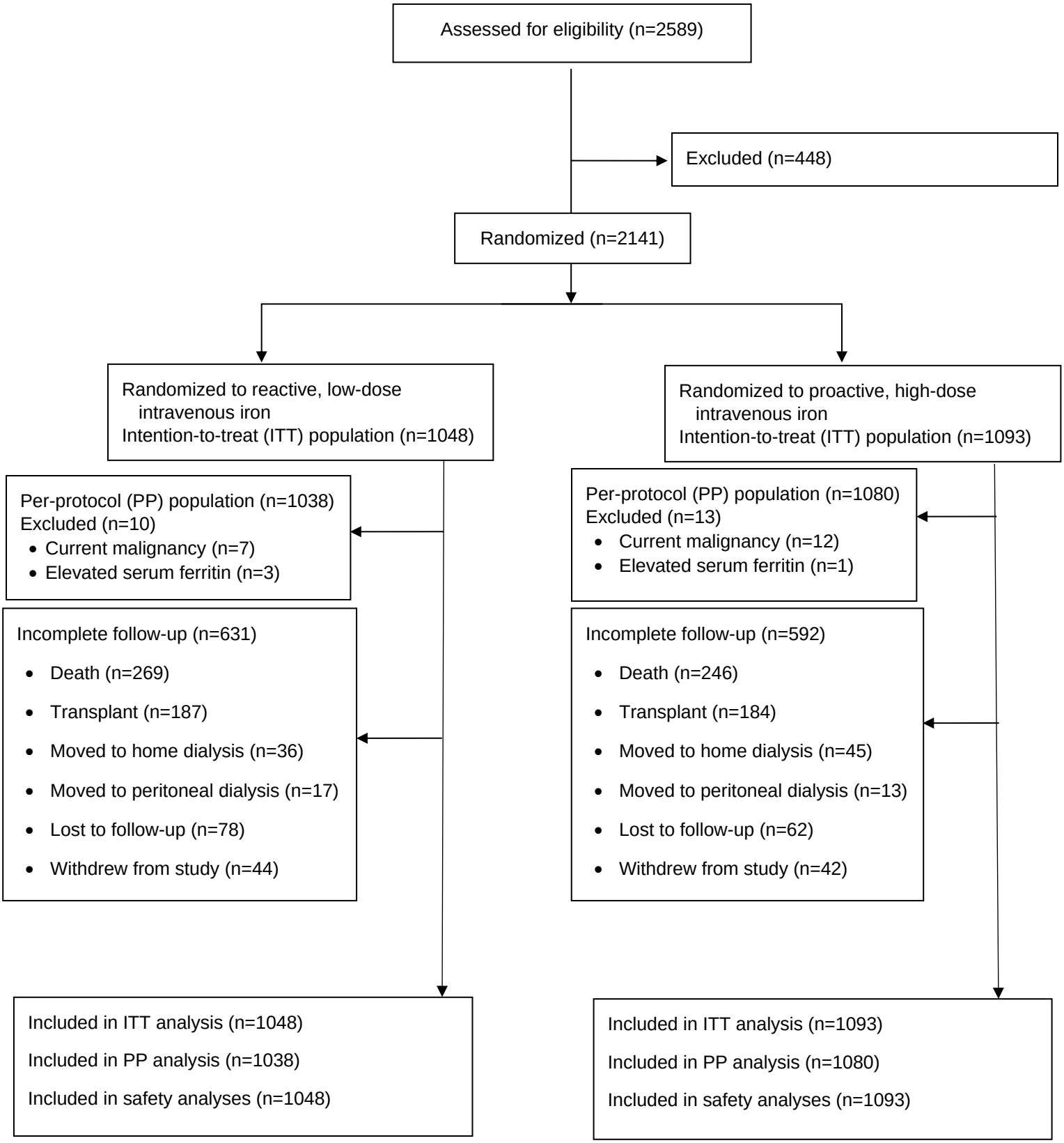
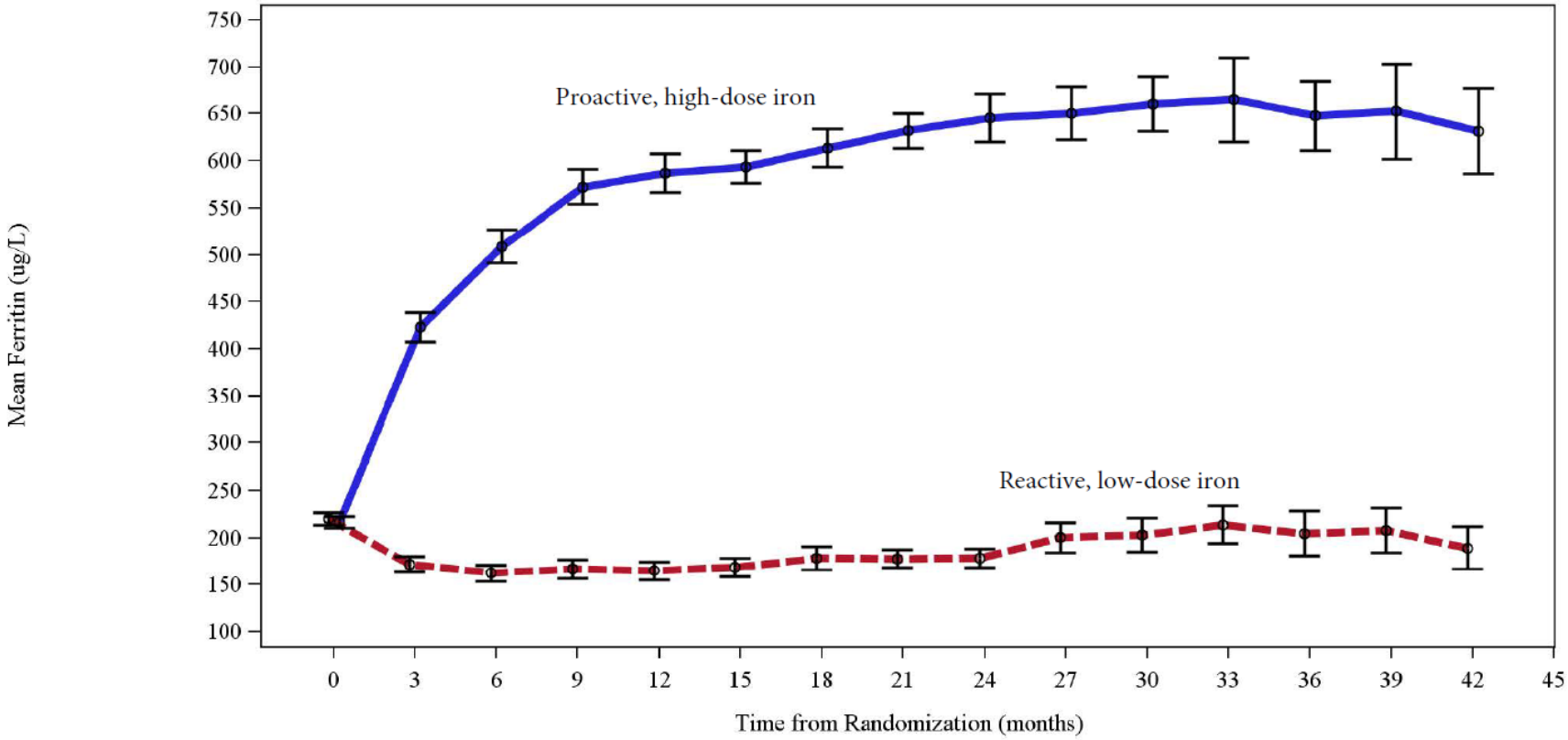


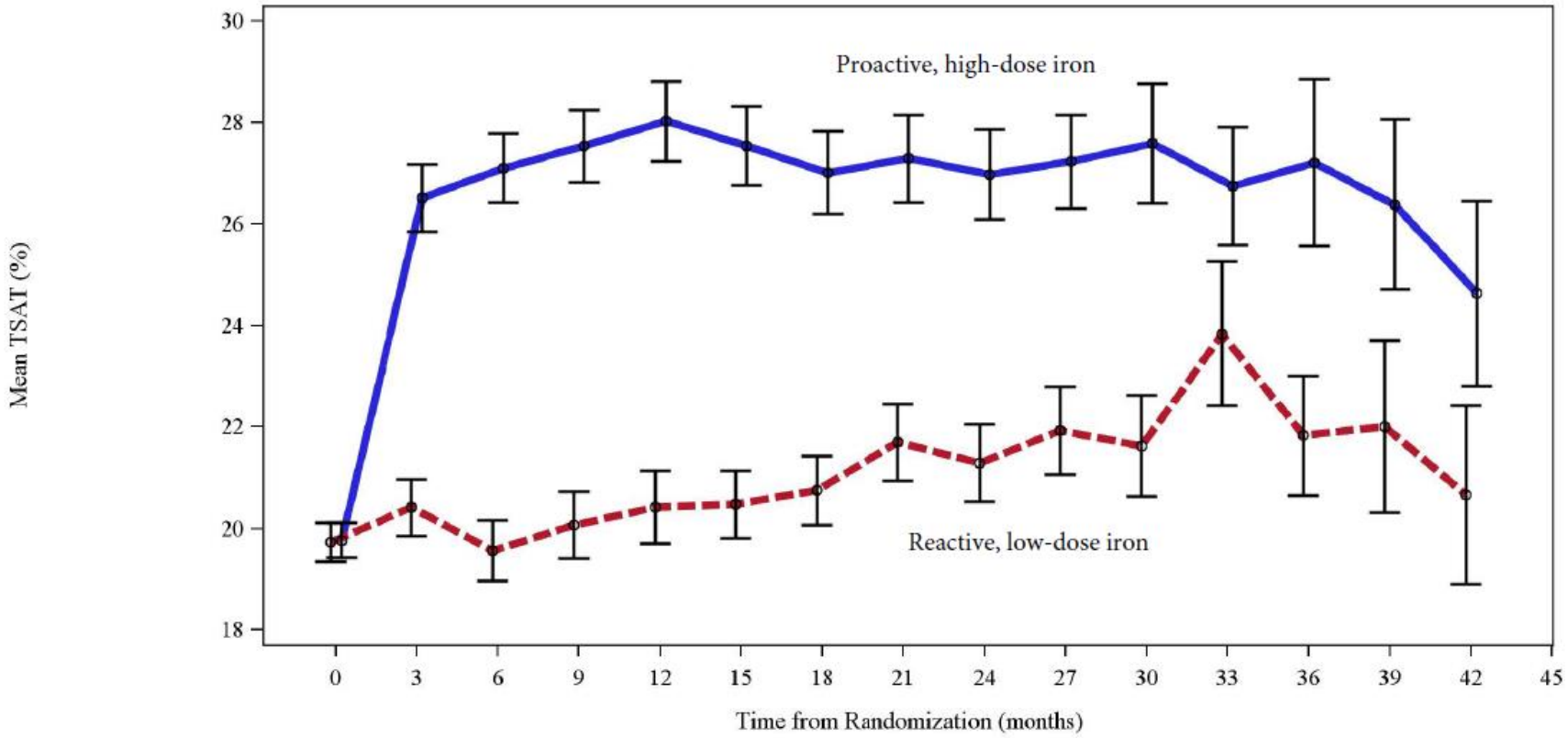
Figure S2. Mean Serum Ferritin Concentration over Time.



Number of patients															
Proactive, high-dose iron	1093	1005	946	887	822	769	715	655	584	481	376	287	206	134	96
Reactive, low-dose iron	1048	972	897	831	766	701	648	603	527	438	365	279	211	135	79

Data presented as mean (95% confidence intervals).

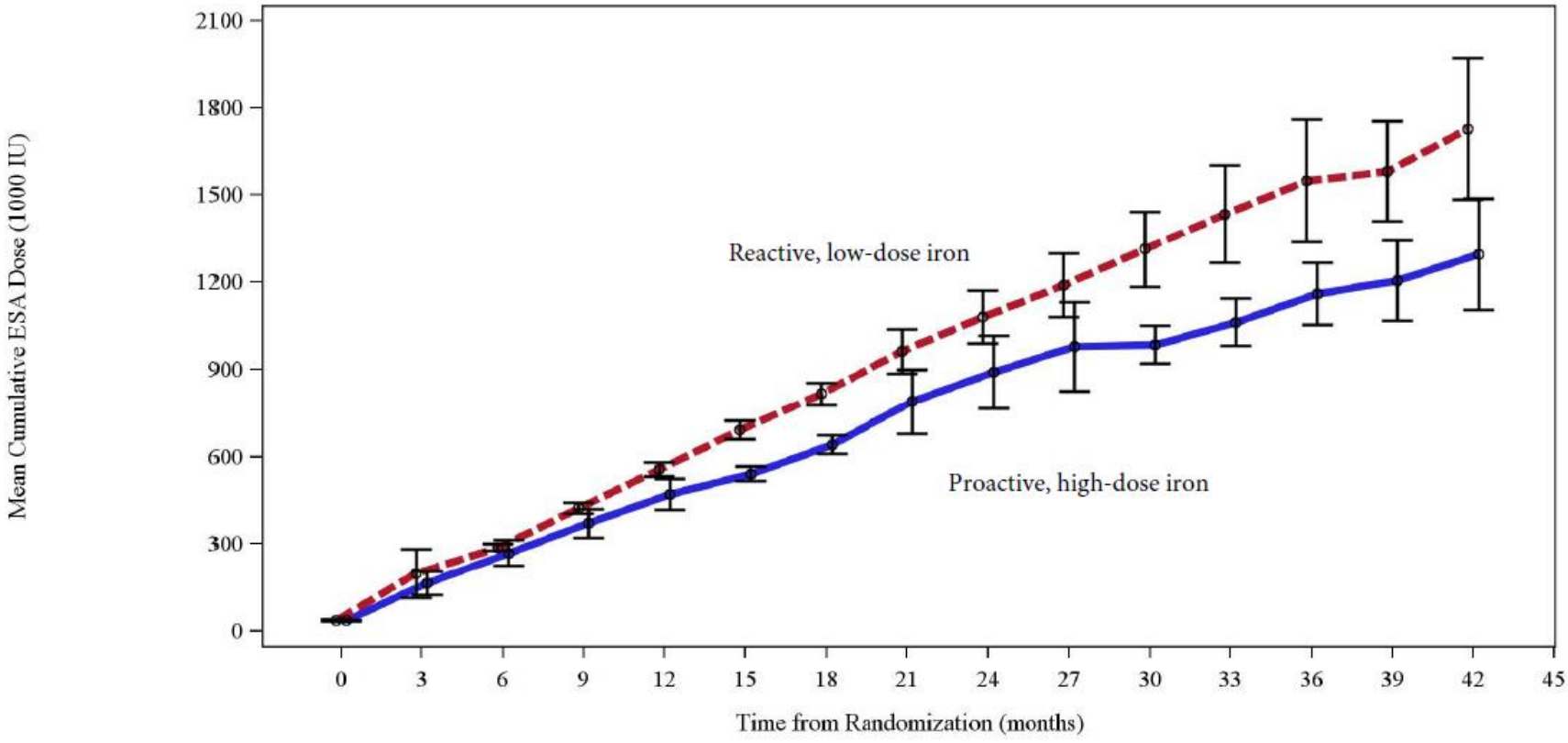
Figure S3. Mean Transferrin Saturation over Time.



Number of patients															
Proactive, high-dose iron	1093	1005	946	887	822	769	715	653	582	480	376	287	206	134	96
Reactive, low-dose iron	1048	972	897	831	766	700	648	603	527	438	364	278	210	135	79

Data presented as mean (95% confidence intervals). TSAT denotes transferrin saturation.

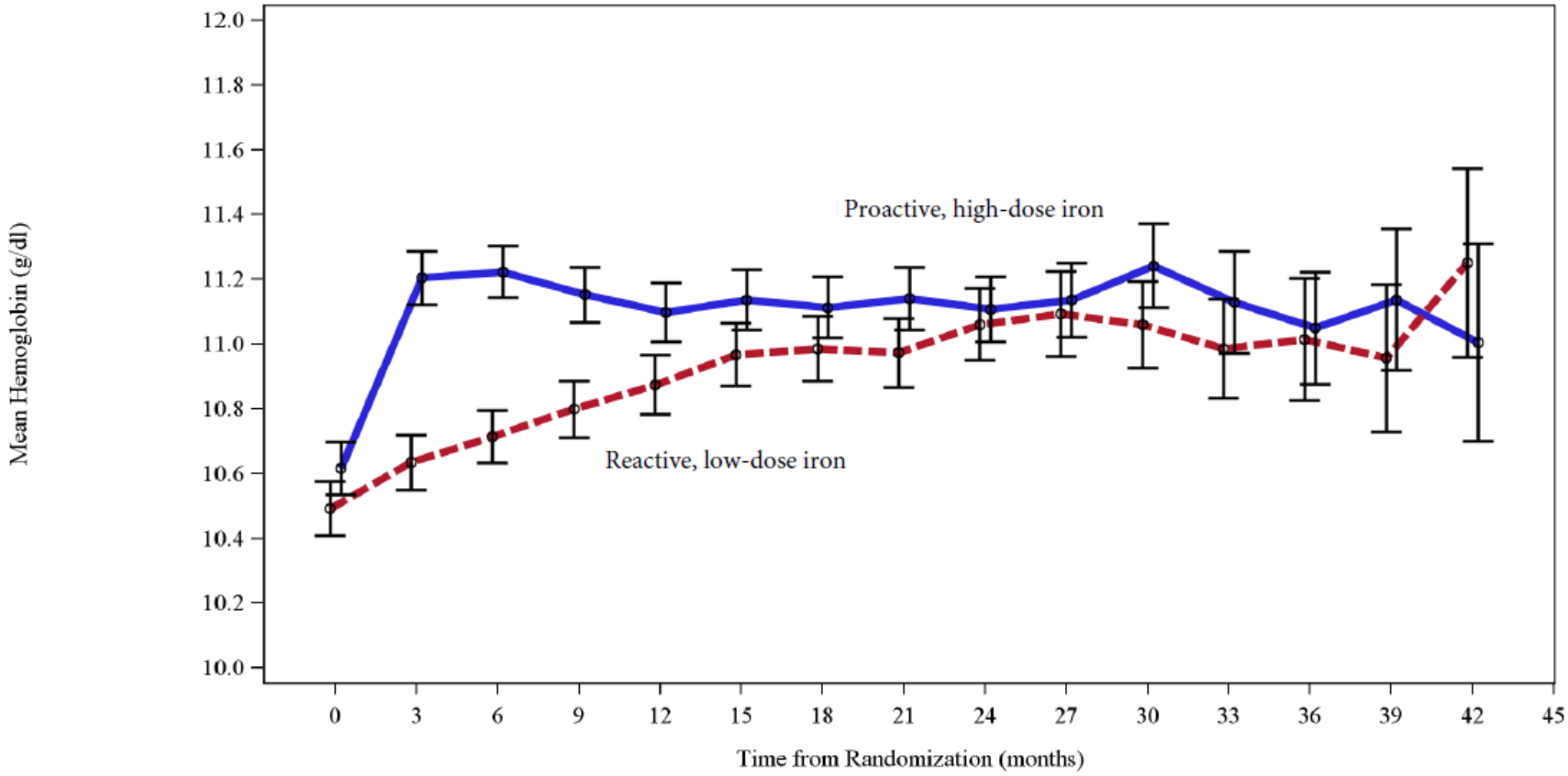
Figure S4. Mean Cumulative ESA Dose over Time.



Number of patients															
Proactive, high-dose iron	1093	1013	953	894	833	776	724	670	594	487	384	293	211	137	97
Reactive, low-dose iron	1048	979	909	842	775	711	656	608	531	440	369	282	213	136	83

Data presented as mean (95% confidence intervals). ESA denotes erythropoiesis-stimulating agent.

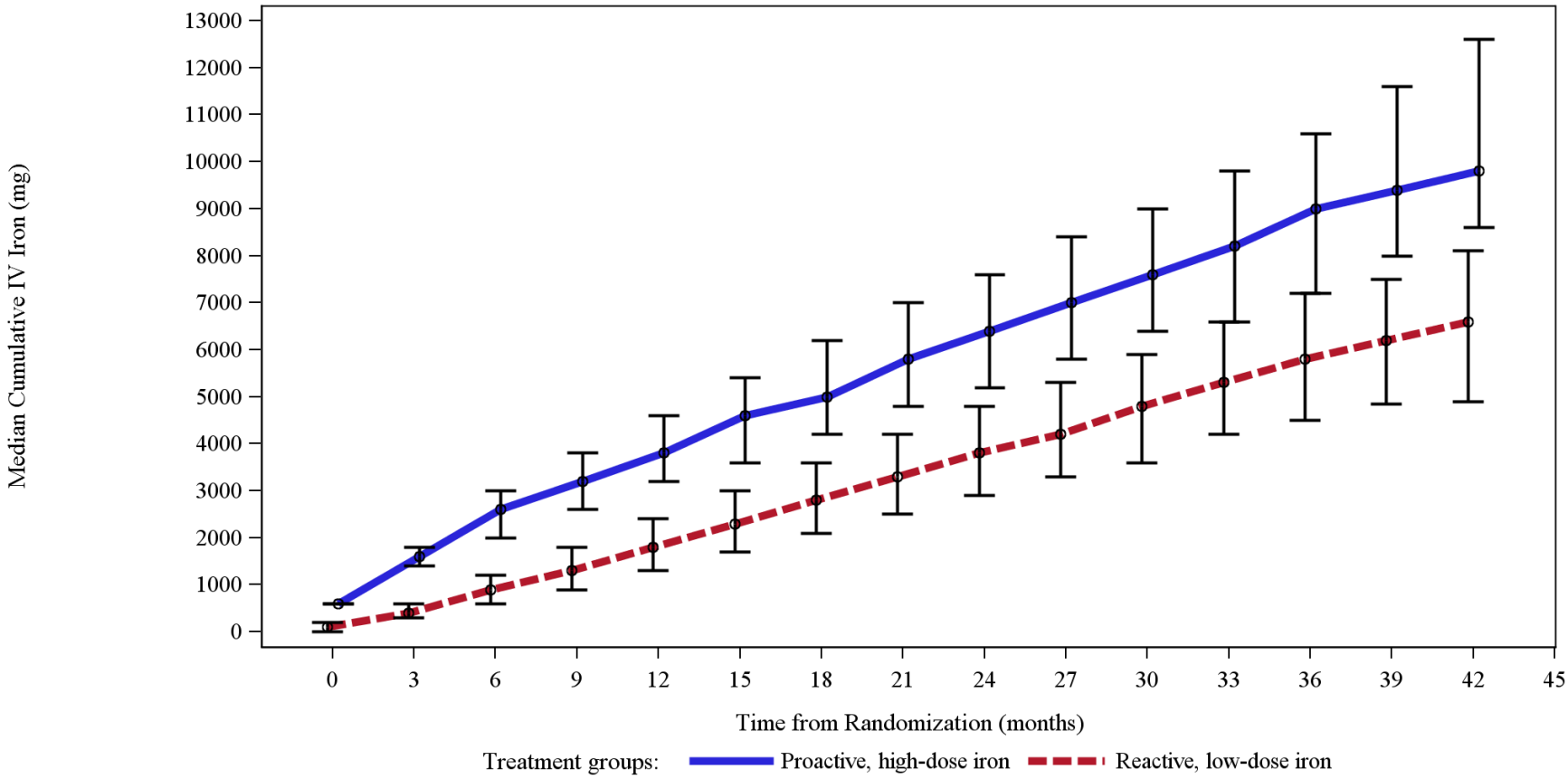
Figure S5. Mean Hemoglobin Concentration over Time.



Number of patients															
Proactive, high-dose iron	1093	1001	945	884	826	770	711	657	584	480	375	286	207	134	95
Reactive, low-dose iron	1047	960	896	832	764	698	646	600	521	436	366	278	211	132	79

Data presented as mean (95% confidence intervals).

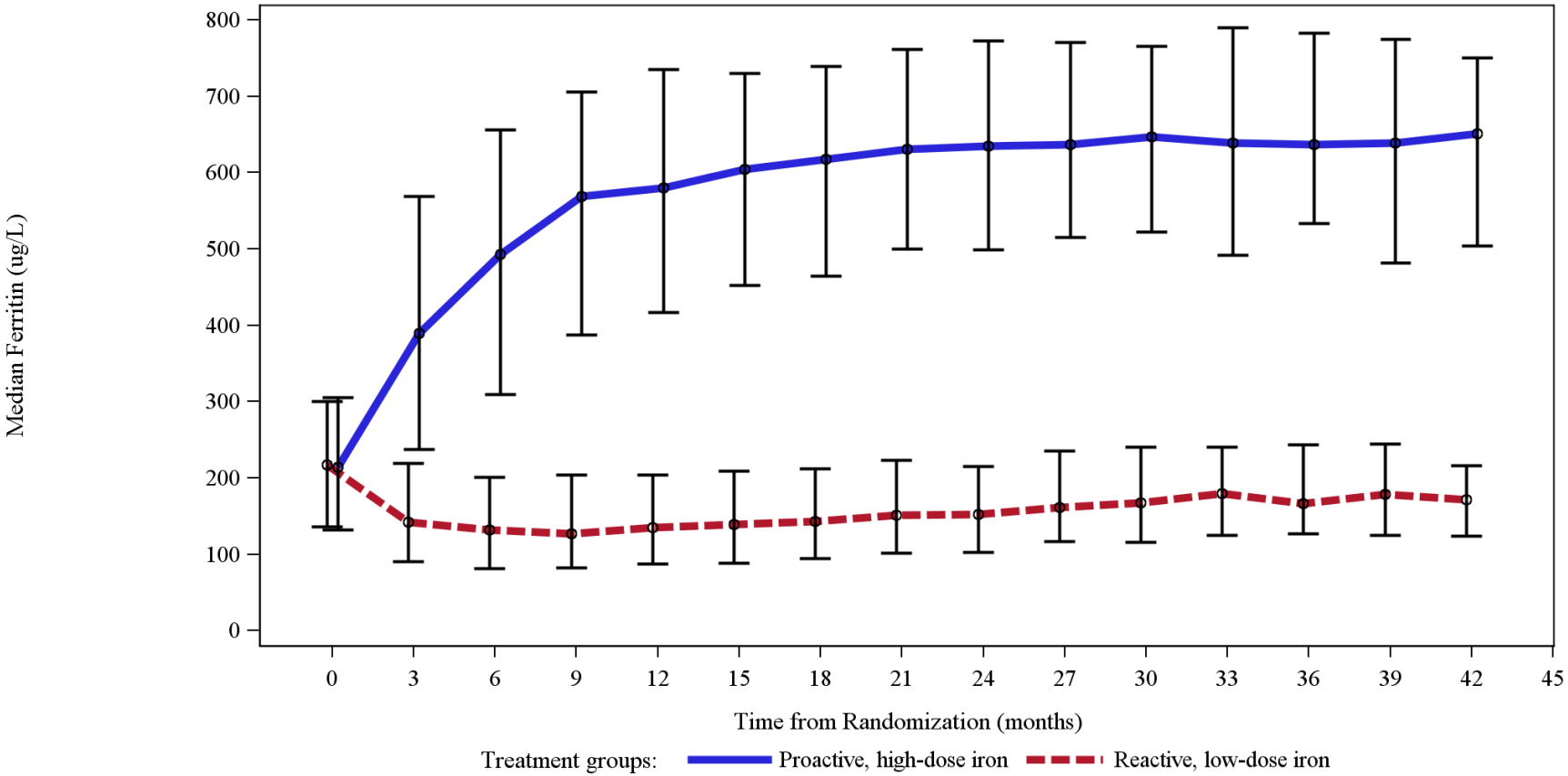
Figure S6. Median Cumulative Intravenous Iron Dose over Time.



Number of patients															
Proactive, high-dose iron	1093	1013	953	894	833	776	724	670	594	487	384	293	211	137	97
Reactive, low-dose iron	1048	979	909	842	775	711	656	608	531	440	369	282	213	136	83

Data presented as median (lower quartile, upper quartile). Data plotted at month 0 represent the first postrandomization iron administration.

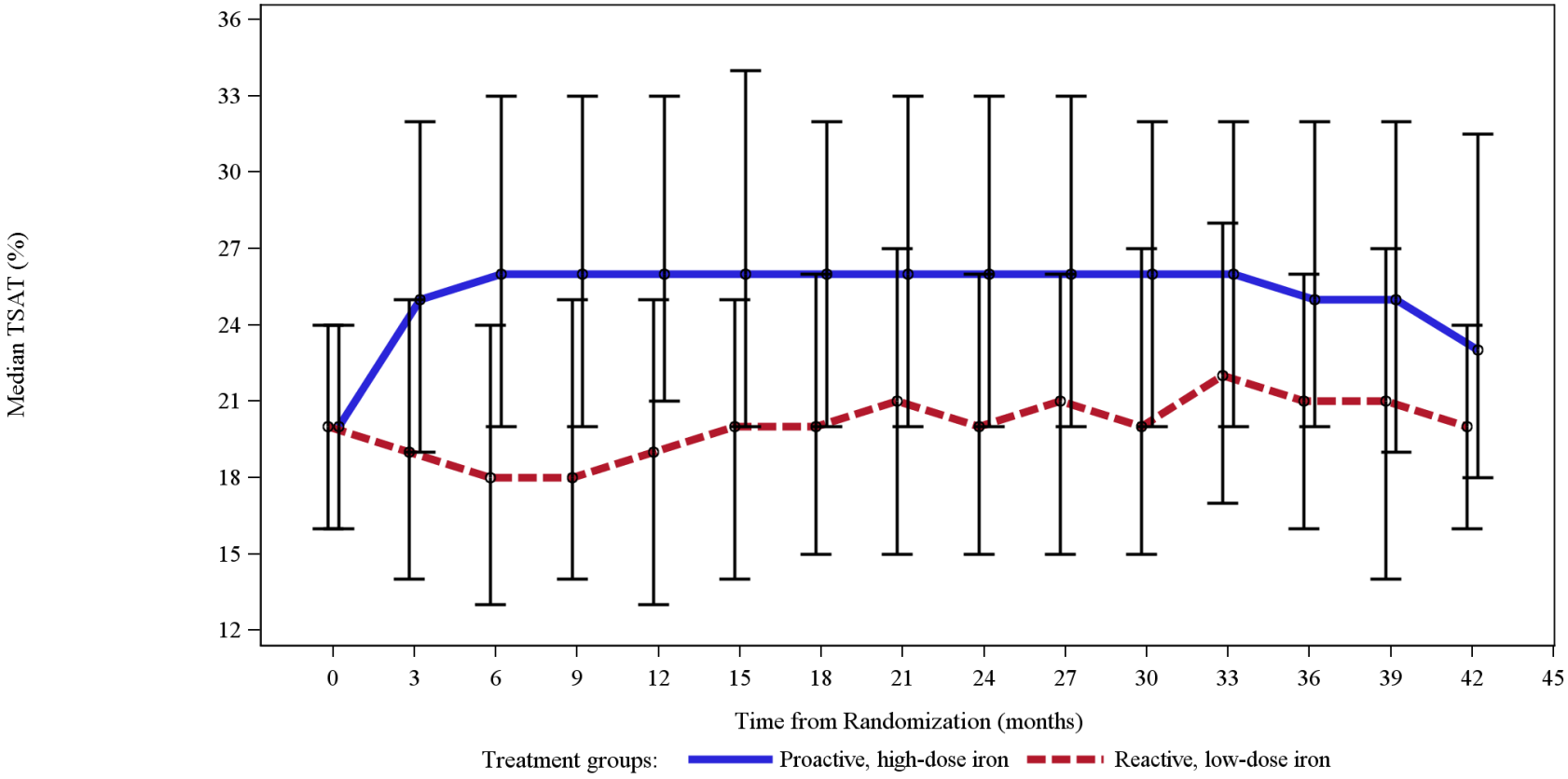
Figure S7. Median Serum Ferritin Concentration over Time.



Number of patients															
Proactive, high-dose iron	1093	1005	946	887	822	769	715	655	584	481	376	287	206	134	96
Reactive, low-dose iron	1048	972	897	831	766	701	648	603	527	438	365	279	211	135	79

Data presented as median (lower quartile, upper quartile).

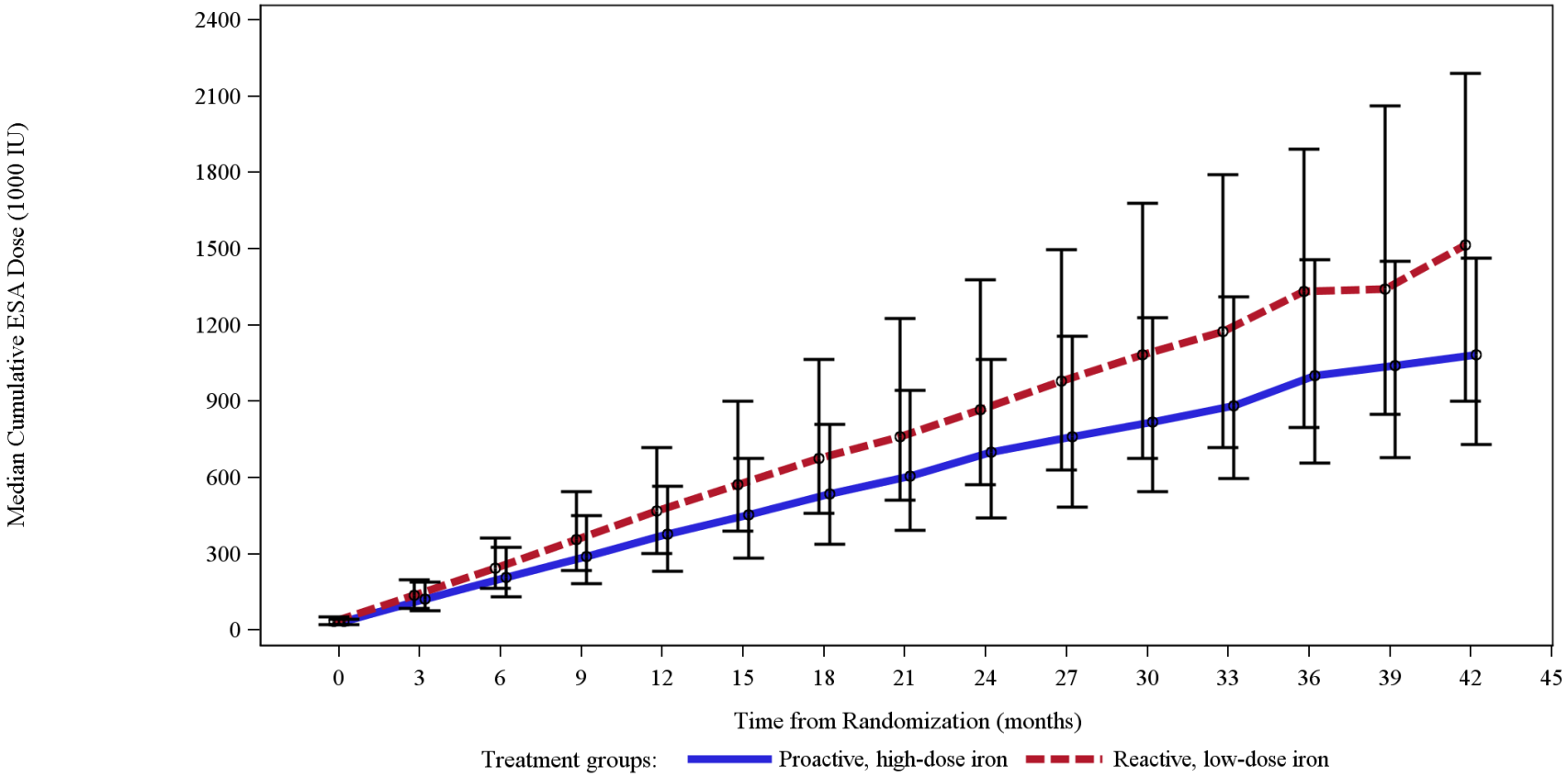
Figure S8. Median Transferrin Saturation over Time.



Number of patients															
Proactive, high-dose iron	1093	1005	946	887	822	769	715	653	582	480	376	287	206	134	96
Reactive, low-dose iron	1048	972	897	831	766	700	648	603	527	438	364	278	210	135	79

Data presented as median (lower quartile, upper quartile). TSAT denotes transferrin saturation.

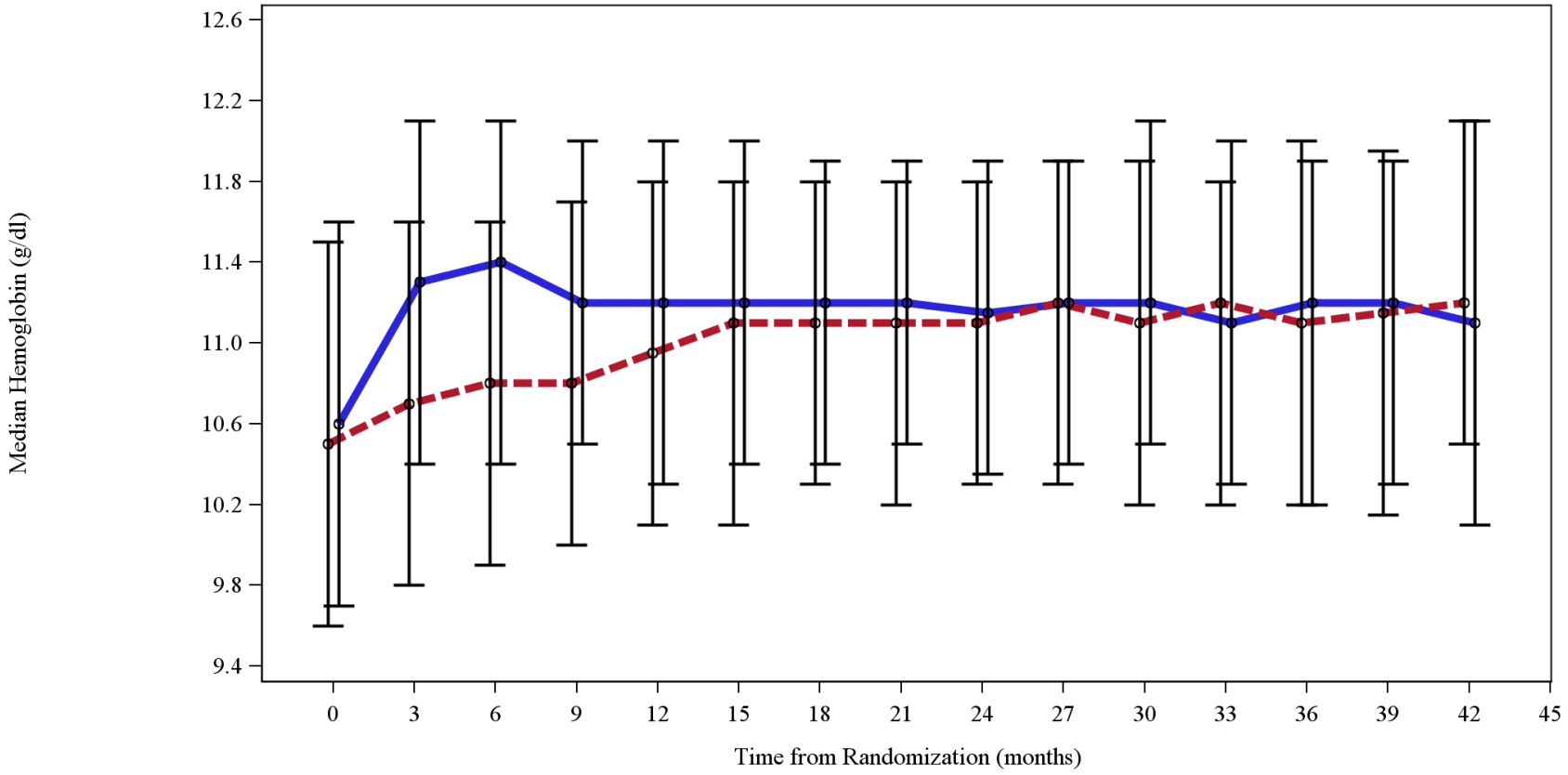
Figure S9. Median Cumulative ESA Dose over Time.



Number of patients															
Proactive, high-dose iron	1093	1013	953	894	833	776	724	670	594	487	384	293	211	137	97
Reactive, low-dose iron	1048	979	909	842	775	711	656	608	531	440	369	282	213	136	83

Data presented as median (lower quartile, upper quartile). ESA denotes erythropoietin-stimulating agent.

Figure S10. Median Hemoglobin Concentration over Time.



Number of patients															
Proactive, high-dose iron	1093	1001	945	884	826	770	711	657	584	480	375	286	207	134	95
Reactive, low-dose iron	1047	960	896	832	764	698	646	600	521	436	366	278	211	132	79

Data presented as median (lower quartile, upper quartile).

Figure S11. Subgroup Analyses — Primary Outcome and Death from Any Cause.

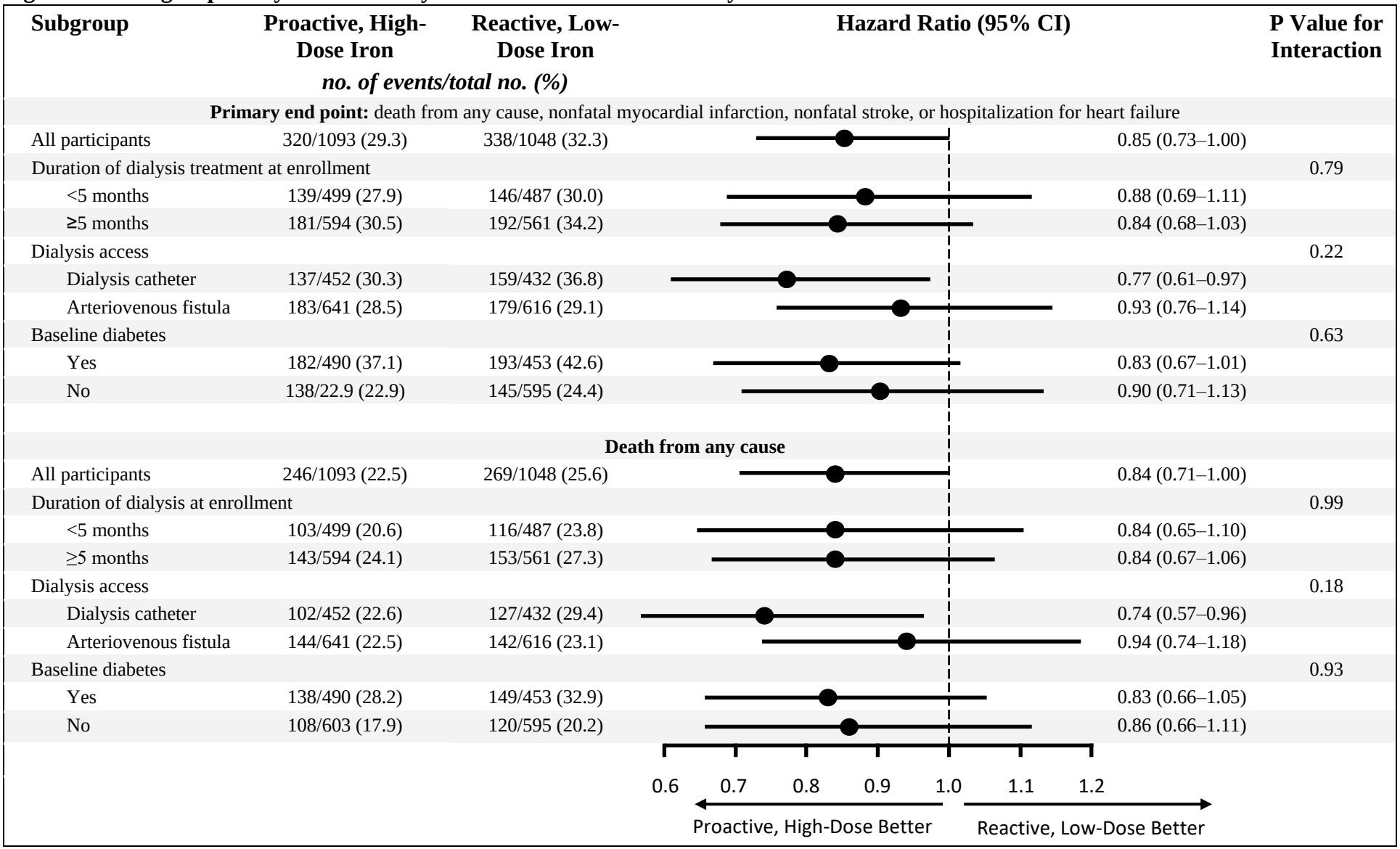
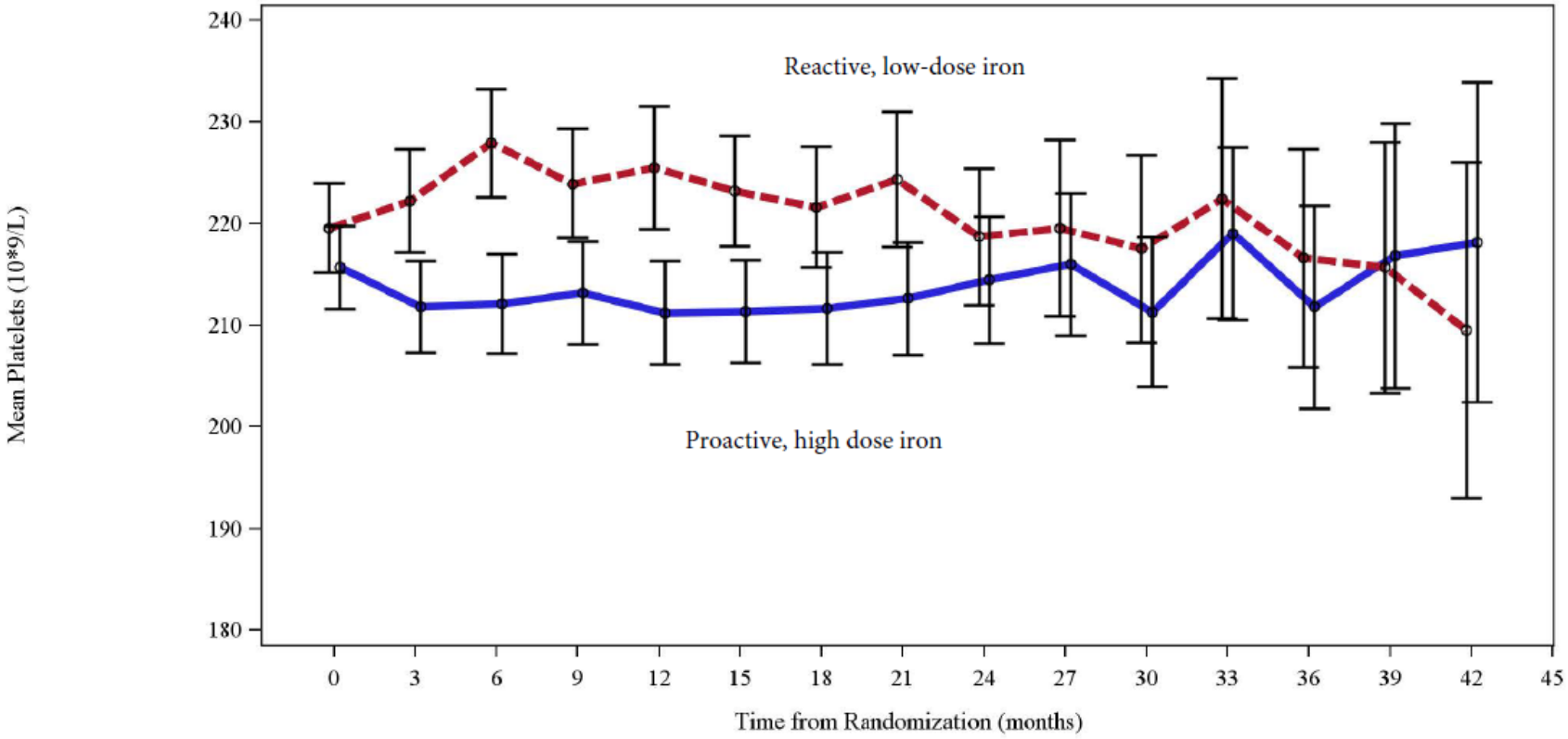


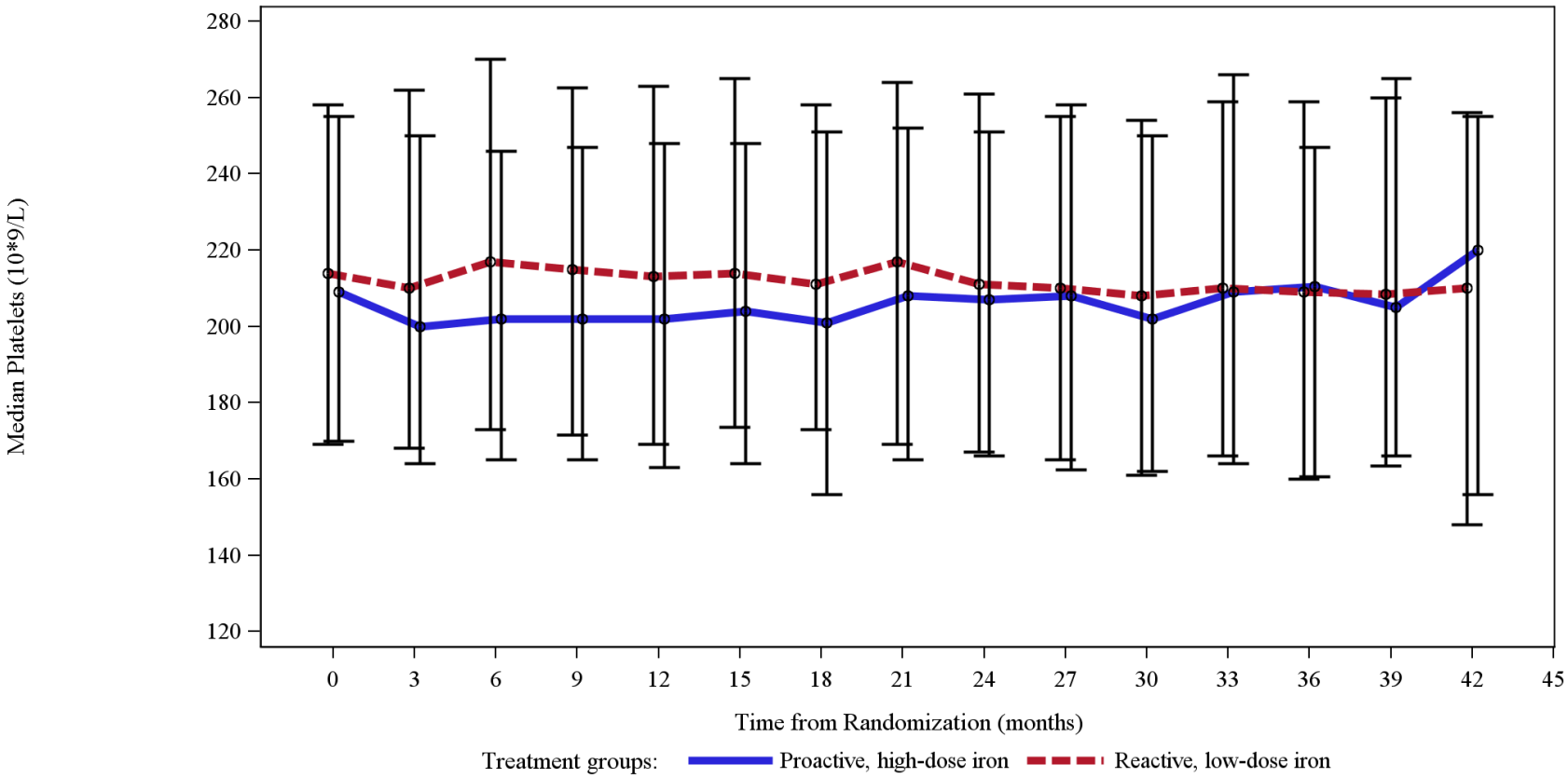
Figure S12. Mean Platelet Count over Time.



Number of patients															
Proactive, high-dose iron	1092	999	941	882	823	769	711	655	583	480	373	284	208	134	95
Reactive, low-dose iron	1046	965	891	828	761	696	645	599	521	433	361	278	210	132	79

Data presented as mean (95% confidence intervals).

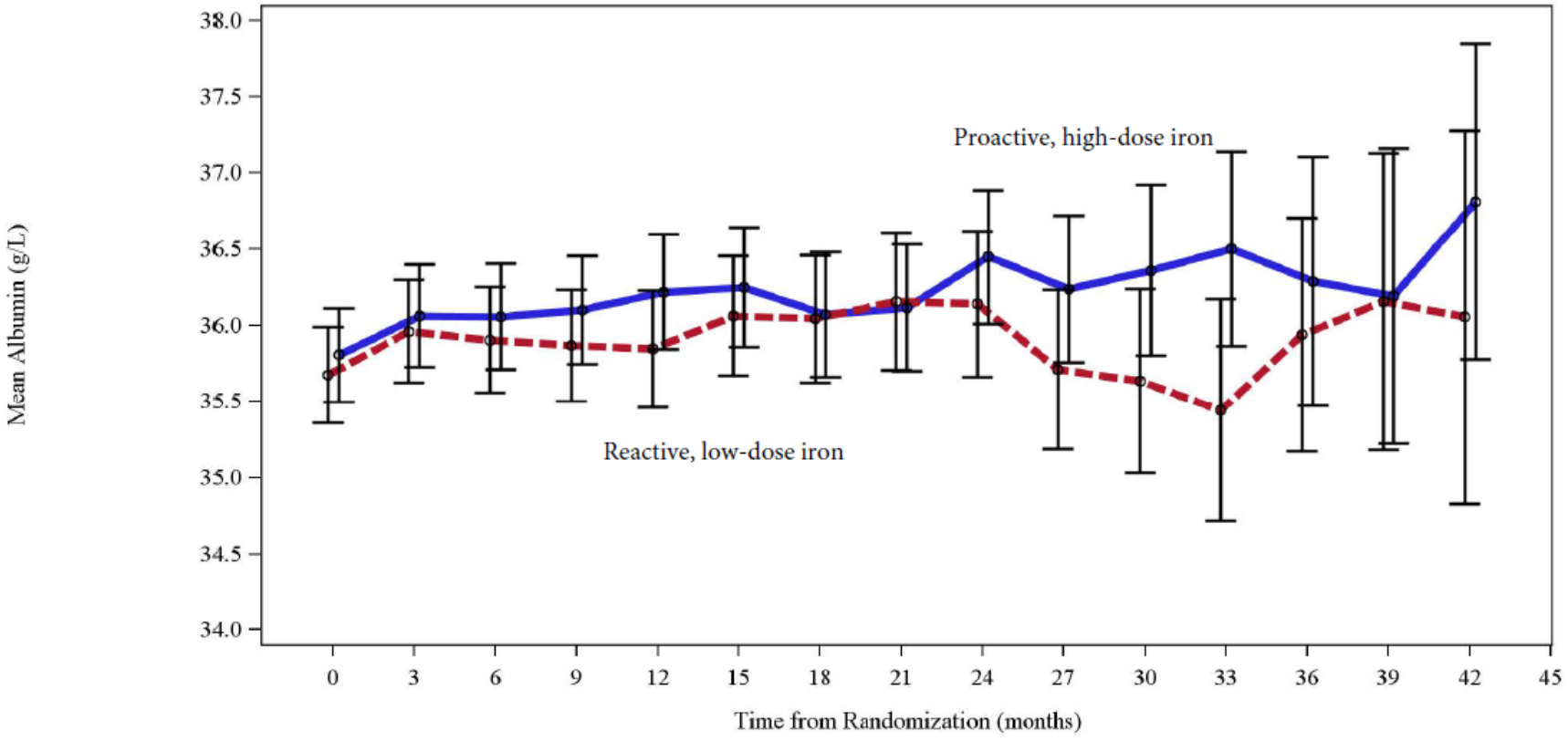
Figure S13. Median Platelet Count over Time.



Number of patients															
Proactive, high-dose iron	1092	999	941	882	823	769	711	655	583	480	373	284	208	134	95
Reactive, low-dose iron	1046	965	891	828	761	696	645	599	521	433	361	278	210	132	79

Data presented as median (lower quartile, upper quartile).

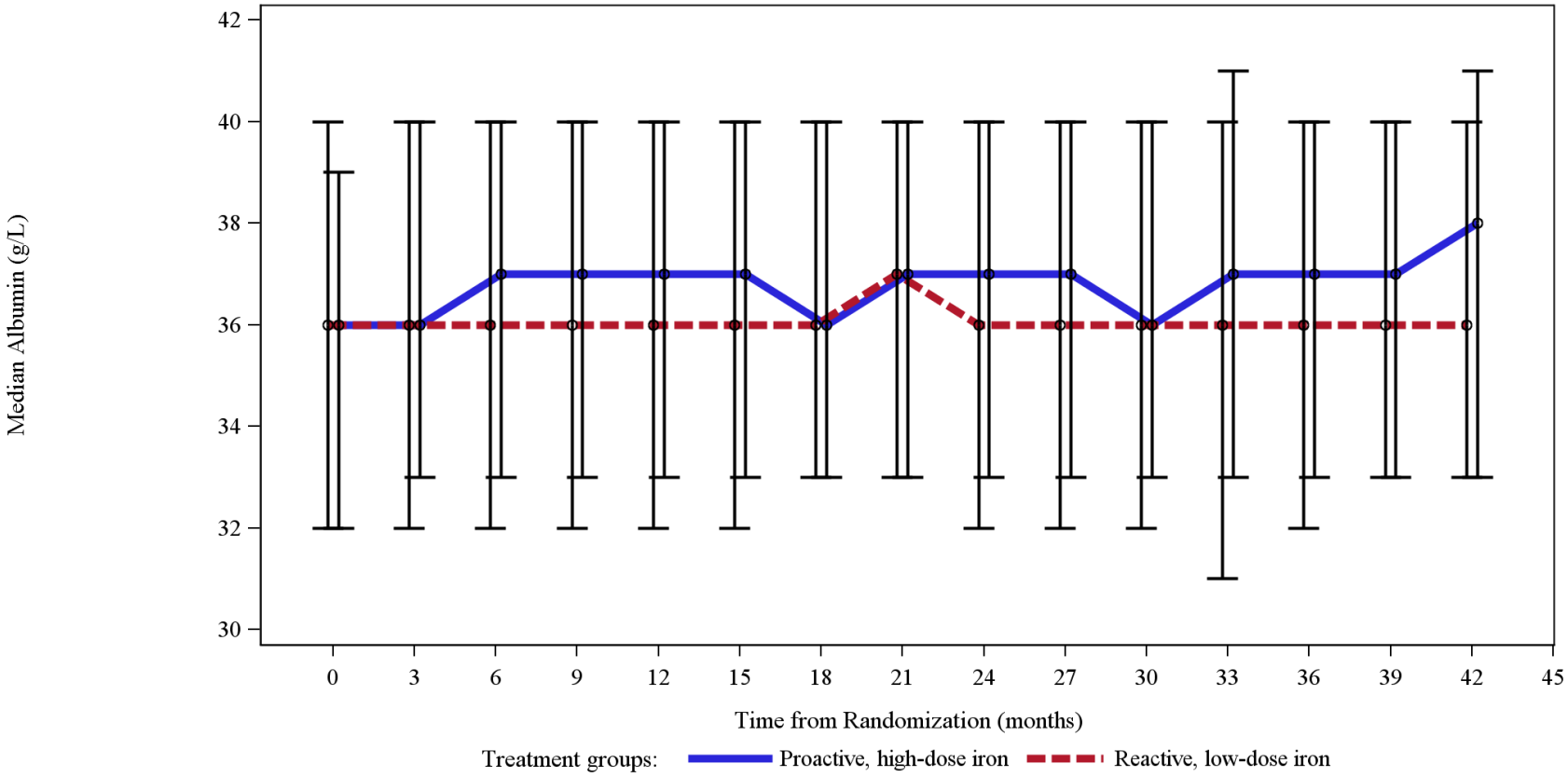
Figure S14. Mean Serum Albumin Concentration over Time.



Number of patients															
Proactive, high-dose iron	1089	989	934	877	806	760	701	649	580	476	367	283	207	132	95
Reactive, low-dose iron	1047	962	987	826	754	695	637	596	520	429	361	276	209	134	78

Data presented as mean (95% confidence intervals).

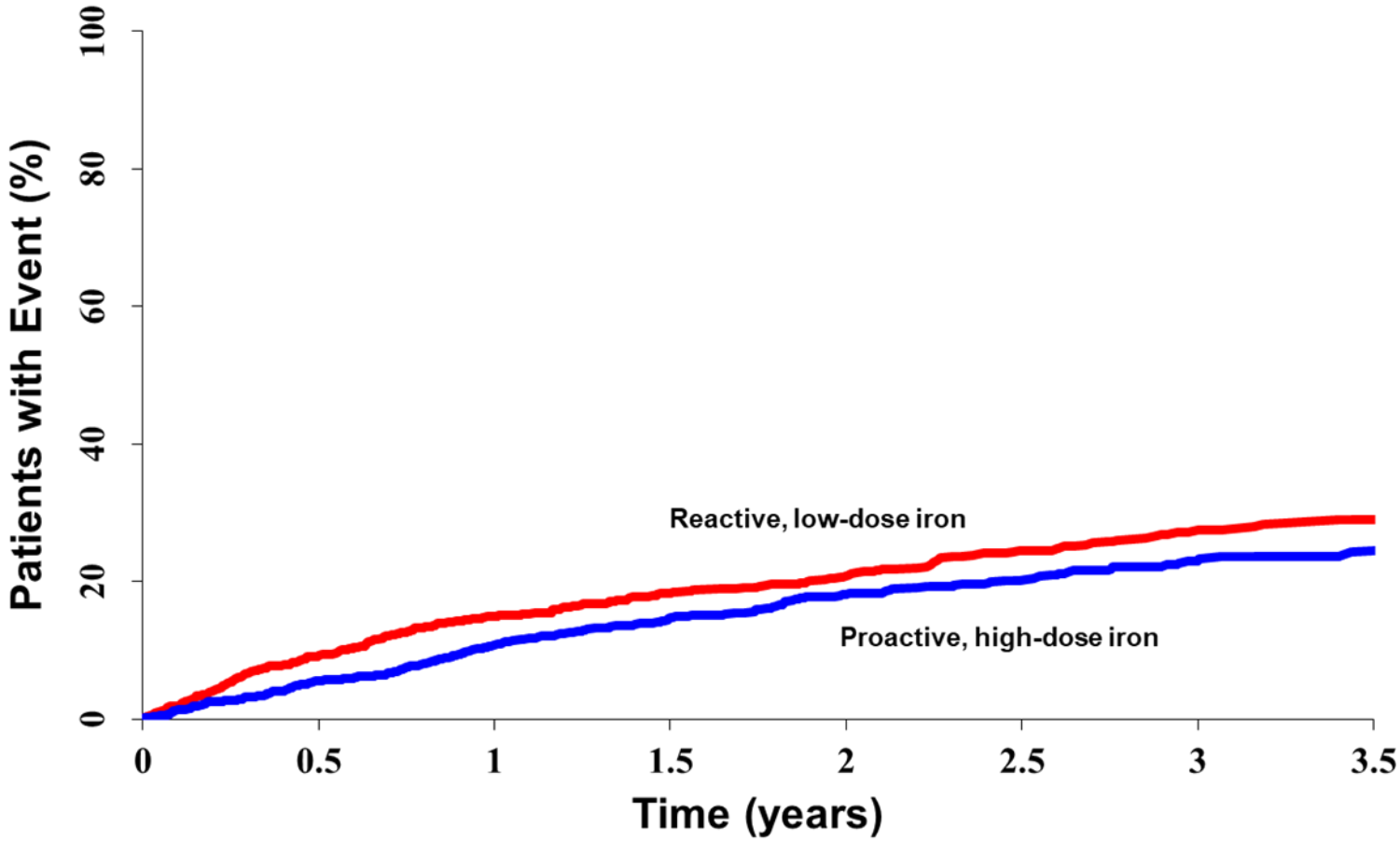
Figure S15. Median Serum Albumin Concentration over Time.



Number of patients															
Proactive, high-dose iron	1089	989	934	877	806	760	701	649	580	476	367	283	207	132	95
Reactive, low-dose iron	1047	962	987	826	754	695	637	596	520	429	361	276	209	134	78

Data presented as median (lower quartile, upper quartile).

Figure S16. Blood Transfusions over Time.



Numbers at risk:

Proactive	1093	752	509	172
Reactive	1048	677	455	163

Table S1. Concomitant Medications at Baseline.*

Medication Class	Proactive, High-Dose Intravenous Iron (N = 1093)	Reactive, Low-Dose Intravenous Iron (N = 1048)
	no. of patients (%)	
Calcium channel-blockers	526 (48.1)	506 (48.3)
ACE inhibitors/ARBs	276 (25.3)	318 (30.3)
Beta-blockers	476 (43.5)	472 (45.0)
Diuretics	466 (42.6)	461 (44.0)
Other BP-lowering drugs	312 (28.5)	310 (29.6)
Antidiabetic drugs	388 (35.5)	338 (32.3)
Anticoagulants	251 (23.0)	239 (22.8)
Antiplatelet drugs	493 (45.1)	479 (45.7)
Lipid-lowering drugs	644 (58.9)	634 (60.5)
Phosphate binders	393 (36.0)	429 (40.9)
Vitamin D supplements	712 (65.1)	684 (65.3)

* There were no statistically significant differences between the two groups except for ACE/ARB drugs (P=0.009) and phosphate binders (P=0.02). ACE denotes angiotensin-converting enzyme, ARBs angiotensin-receptor blockers, BP blood pressure.

Table S2. Adjudicated Causes of Death.*

Primary Cause	Proactive, High-Dose Intravenous Iron (N = 1093)	Reactive, Low-Dose Intravenous Iron (N = 1048)
All deaths	246 (22.5)	269 (25.7)
Cardiovascular death	91 (8.3)	96 (9.2)
Myocardial infarction	16 (1.5)	9 (0.9)
Stroke	12 (1.1)	13 (1.2)
Extra-axial hemorrhage	2 (0.2)	3 (0.3)
Sudden cardiac death	36 (3.3)	40 (3.8)
Heart failure	12 (1.1)	16 (1.5)
Cardiovascular procedure/operation	1 (0.1)	2 (0.2)
Other cardiovascular cause	11 (1.0)	13 (1.2)
Unknown cardiovascular cause	1 (0.1)	0 (0)
Noncardiovascular death	104 (9.5)	120 (11.4)
Infection	47 (4.3)	41 (3.9)
Pulmonary cause (excluding infection)	3 (0.3)	4 (0.4)
Renal cause (excluding infection)	8 (0.7)	4 (0.4)
Gastrointestinal cause (excluding infection)	4 (0.4)	10 (1.0)
Malignancy	16 (1.5)	20 (1.9)
Withdrawal of dialysis	25 (2.3)	36 (3.4)
Noncardiovascular surgery	0 (0)	0 (0)
Other noncardiovascular cause	1 (1.0)	5 (0.5)
Unknown cause	51 (4.7)	53 (5.1)

* Data are numbers and percentages of subjects, with cause of death in each category.

Table S3. Recurrent Events Analysis with Varying Absolute Censoring Times.*

Censoring Time (months)	Rate Ratio	95% Confidence Interval	P Value
6	0.95	(0.65, 1.38)	0.78
12	0.82	(0.62, 1.08)	0.15
18	0.84	(0.67, 1.04)	0.11
24	0.82	(0.67, 0.99)	0.043
30	0.81	(0.67, 0.97)	0.021
36	0.82	(0.69, 0.97)	0.022
42	0.79	(0.67, 0.94)	0.0067

*Analysis examined rates of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

References

1. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. J R Statist Soc B 2000;62:711-30.
2. Campbell MJ, Gardner MJ. Calculating confidence intervals for some non-parametric analyses. Br Med J (Clin Res Ed) 1988;296:1454-6.