

SUPPLEMENTARY MATERIAL

A SYSTEMATIC REVIEW, META-ANALYSIS, AND INDIRECT COMPARISON OF BLINDLY-ADJUDICATED CARDIOVASCULAR EVENT INCIDENCE WITH FERRIC DERISOMALTOSE, FERRIC CARBOXYMALTOSE, AND IRON SUCROSE

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Supplementary Table 1 Components of the adjudicated composite cardiovascular endpoint as reported by Szychzech et al. in the REPAIR-IDA study design report

1. Death due to any cause: Will be adjudicated as the date the subject is pronounced dead.
2. MI: A MI will be defined as the presence of the characteristic changes in cardiac enzyme markers in the setting of either temporally related symptoms of an acute coronary syndrome or ECG changes consistent with either ischemia or infarction. Cardiac enzyme markers indicative of an MI will include:
• An appropriate rise and fall in serum troponin (I or T) or CKMB where at least one value is $\geq 2 \times$ ULN. Where only one value has been measured, if it is $> 2 \times$ ULN, an event may be adjudicated based on the totality of the clinical evidence. • Where only total CPK is measured, serial changes (i.e. at least two values) need to be $> 2 \times$ ULN.
<i>Symptoms indicative of ischemia</i> will need to have been present for ≥ 10 min and may include chest pain, chest pressure or chest tightness. Dyspnea, diaphoresis or nausea may be considered symptoms of ischemia and will be judged based on the totality of the clinical evidence. ECG changes will be defined as:
• New Q waves in two or more contiguous leads • Evolving ST segment to T wave changes in two or more contiguous leads (such as ≥ 0.5 mm transient ST segment depression) • New left bundle branch block (LBBB) • 1-mm ST segment elevation in two or more contiguous leads
3. Stroke
A stroke is defined as a focal neurological deficit of sudden onset that is not reversible within 24 h that results from a vascular cause involving the central nervous system (CNS) and is not due to another readily identifiable cause (i.e. brain tumor or trauma).
Strokes will be sub-classified as hemorrhagic, ischemic or unknown.
4. Unstable angina requiring hospitalization
Unstable angina requiring hospitalization will be defined as ischemic symptoms meeting the following criteria:
1. Lasting ≥ 10 min and considered to be myocardial ischemia on final diagnosis
AND
2. Requiring unscheduled visit to a healthcare facility and overnight admission (does not include chest pain observation units)
AND
3. At least one of the following:
• New dynamic ECG changes • Ischemia evidence on stress testing with or without cardiac imaging • Angiographic evidence of $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery
5. CHF requiring hospitalization or medical intervention
CHF events will meet the following criteria:
1. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-h stay (or a date change if the time of admission/discharge is not available).
AND
2. Clinical manifestation of CHF including at least one of the following: New or worsening: dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, pulmonary basilar crackles, jugular venous distension or radiological evidence of worsening heart failure.

AND
3. Additional/increased therapy
a. IV treatment with diuretic, inotrope or vasodilator therapy OR
b. Mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function) or the use of ultrafiltration, hemofiltration or dialysis that is specifically directed at treatment of heart failure.
6. Arrhythmia will be defined as any symptomatic deviation from normal sinus rhythm experienced by the subject that results in an evaluation by a healthcare provider. The evaluation may include a physical exam during an outpatient visit, an ECG or a hospital admission. Arrhythmias may include any conduction abnormality, atrioventricular heart block, prolongation of QTc interval, supraventricular/nodal arrhythmia, vasovagal episode, ventricular arrhythmia or other cardiovascular arrhythmia.
7. Hypertension
• During the observation period immediately following study drug administration, hypertension will be defined as an increase in systolic blood pressure >20 mmHg that results in a value >180 mmHg or an increase in diastolic blood pressure >15 mmHg that results in a value >105 mmHg • Following the release of a subject from the study visit during which they are receiving medication, hypertension will be defined as requiring an unscheduled outpatient healthcare visit, a hospital admission or a change in medical therapy (e.g. administration of antihypertensives) in conjunction with the objective criteria a rise in blood pressure (an increase in systolic blood pressure >20 mmHg that results in a value >180 mmHg or an increase in diastolic blood pressure >15 mmHg that results in a value >105 mmHg).
8. Hypotension
• During the observation period immediately following study drug administration, hypotension will be defined as a decrease in systolic blood pressure >20 mmHg that results in a value <90 mmHg or a decrease in diastolic blood pressure >15 mmHg that results in a value <50 mmHg. • Following the release of a subject from the study visit during which they are receiving medication, hypotension will be defined as requiring an unscheduled outpatient healthcare visit, a hospital admission or a change in medical therapy (e.g. fluid/volume repletion, holding of antihypertensives) in conjunction with the objective criteria a decrement in blood pressure (a decrease in systolic blood pressure >20 mmHg that results in a value <90 mmHg or a decrease in diastolic blood pressure >15 mmHg that results in a value <50 mmHg)

**Supplementary Table 2 Systematic literature review search terms expressed
using PubMed syntax**

PICO	#	Term
Population	1	"Anemia, Iron-Deficiency"[MeSH]
	2	"iron deficiency"[tiab]
	3	anemia[tiab] OR anaemia[tiab]
	4	#2 AND #3
	5	#1 OR #4
Intervention/ Comparator	6	iron[tiab]
	7	Iron Compounds[MeSH]
	8	#6 OR #7
	9	intravenous[tiab]
	10	parenteral[tiab]
	11	Infusions, Intravenous[MeSH]
	12	#9 OR #10 OR #11
	13	#8 AND #12
	14	cardiovascular[tiab]
	15	Cardiovascular Diseases[MeSH]
Outcomes	16	"all-cause mortality"[tiab]
	17	"myocardial infarction"[tiab]
	18	"Myocardial Infarction"[MeSH]
	19	"stroke"[tiab]
	20	Stroke[MeSH]
	21	"unstable angina"[tiab]
	22	"Angina Pectoris"[MeSH]
	23	"heart failure"[tiab]
	24	Heart Failure[MeSH]
	25	arrhythmias[tiab]
	26	"Arrhythmias, Cardiac"[MeSH]
	27	hypertensi*[tiab]
	28	Hypertension[MeSH]

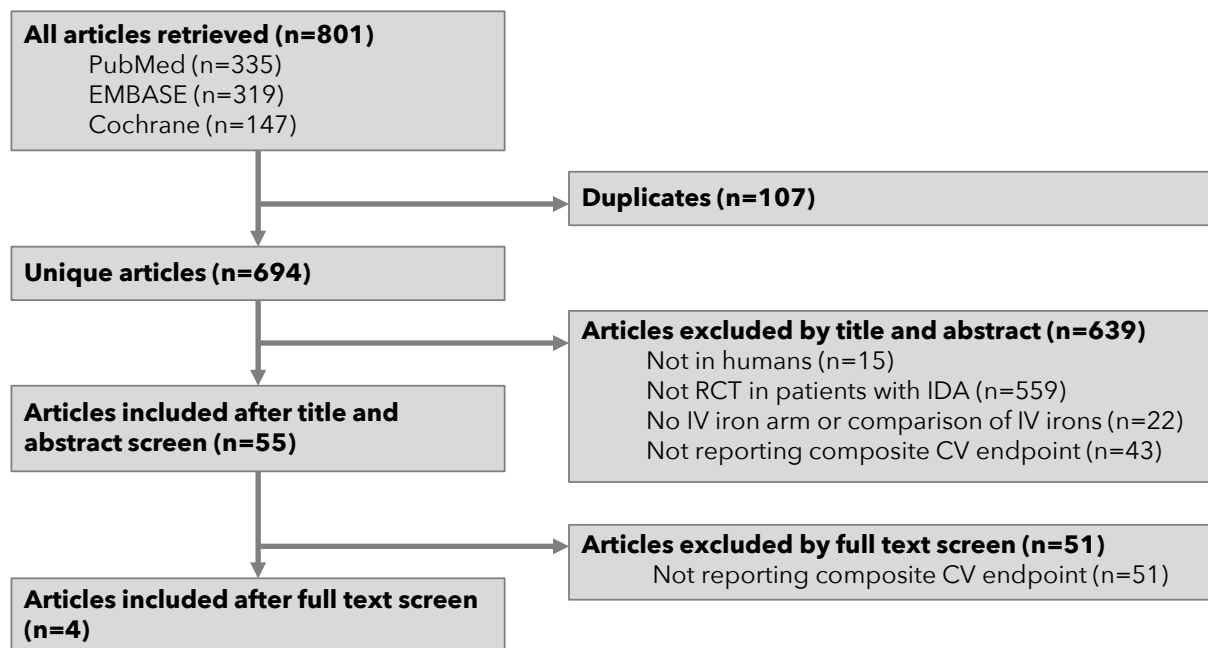
PICO	#	Term
	29	hypotensi*[tiab]
	30	Hypotension[MeSH]
	31	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
Complete search	32	#5 AND #13 AND #31

Supplementary Table 3 Study exclusion criteria

Exclusion criterion	Description of studies meeting criterion for exclusion	Description of study meeting criterion for inclusion
Not in adult humans	Study conducted either in animals or exclusively in human subjects aged under 18 years of age	Study conducted exclusively in human subjects aged 18 years or above
Not prospective RCT in patients with IDA	Study not designed prospectively and/or not conducted by randomly assigning patients with IDA to treatment arms, e.g. observational studies, case reports, or retrospective database analyses	Study designed prospectively and conducted by randomly assigning patients with IDA to treatment arms
No IV iron treatment arm or comparison of IV iron formulations	Study did not include an arm in which patients received IV iron, or studies in which all patients received the same IV iron formulation (i.e. those studies in which other aspects of treatment were under investigation)	Studies including (at least) two study arms in which different IV iron formulations were administered
Not reporting the pre-specified composite cardiovascular endpoint	Studies reporting the incidence of the composite cardiovascular endpoint defined in Supplementary Materials Table 1	Studies reporting the incidence of the composite cardiovascular endpoint defined in Supplementary Materials Table 1

IDA, iron deficiency anemia; RCT, randomized controlled trial.

Supplementary Figure 1 Literature review flow diagram



Supplementary Figure 2 Cochrane Risk of Bias 2 assessment results from the four included randomized controlled trials

Clinicaltrials.gov ID	Study ID	Experimental	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall	
NCT00981045	REPAIR-IDA	Ferric carboxymaltose	Iron sucrose	+	+	+	+	+	+	Low risk
NCT00982007	1VIT09031	Ferric carboxymaltose	Iron sucrose	?	+	+	+	+	+	Some concerns
NCT02940886	FERWON _{IDA}	Ferric derisomaltose	Iron sucrose	+	+	+	+	+	+	High risk
NCT02940860	FERWON _{NEPHRO}	Ferric derisomaltose	Iron sucrose	+	+	+	+	+	+	