Journal of the American Heart Association

ORIGINAL RESEARCH

Iron Deficiency Is Associated With Impaired Myocardial Reperfusion in ST-Segment–Elevation Myocardial Infarction: Influence of the Definition Used

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BACKGROUND: The role of iron deficiency (ID) in ST-segment–elevation myocardial infarction (STEMI) remains unclear. This study aimed to assess whether ID is associated with impaired myocardial reperfusion in STEMI and whether this association is affected by ID definition.

METHODS: We included 942 consecutive patients with STEMI successfully treated with primary percutaneous coronary intervention. ID was defined either as recommended by international guidelines or, alternatively, as ferritin <100 ng/mL, transferrin saturation <20%, or serum iron ≤13 μmol/L. In 595 patients, serum soluble transferrin receptor levels were measured. Impaired myocardial reperfusion was defined as lack of ST-segment resolution ≥50% 60 to 90 minutes after percutaneous coronary intervention.

RESULTS: ID prevalence varied across these definitions. Impaired reperfusion was present in 12.7% of patients without ID and 41.0% of those with ID defined by transferrin saturation <20% (P<0.001). This association was less pronounced for serum iron ≤13 μmol/L, weaker for guideline criteria, and absent for high (≥1.59 mg/L) soluble transferrin receptor levels or low ferritin. Transferrin saturation <20%, but not ferritin-based criteria, was associated with poorer clinical course and left ventricular function and higher in-hospital mortality and remained an independent predictor of impaired reperfusion after adjusting for baseline predictors and anemia.

CONCLUSIONS: ID defined by transferrin saturation <20% is strongly related to impaired ST resolution and predicts a worse in-hospital outcome in patients with STEMI treated with primary percutaneous coronary intervention. The association of other ID criteria with myocardial reperfusion or with the clinical course is weaker or absent. The potential preventive or therapeutic strategies targeting ID in STEMI warrant further investigation.

Key Words: acute myocardial infarction ■ iron deficiency ■ ischemia ■ reperfusion ■ soluble transferrin receptor

Iron deficiency (ID) is associated with adverse prognostic implications in patients with chronic heart failure (CHF), and the effects of iron supplementation have been extensively studied in this population.[1–4] The potential impact of iron metabolism in patients with acute coronary syndromes (ACS) has received

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This article was sent to Yen-Hung Lin, MD, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.040845

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Iron deficiency is associated with impaired myocardial reperfusion and with worse in-hospital outcomes in patients with ST-segment–elevation myocardial infarction treated with primary percutaneous coronary intervention.
- This association is significantly affected by the definition of iron deficiency, being very robust for low transferrin saturation and absent for low ferritin levels; soluble transferrin receptor levels are poorly discriminative of myocardial reperfusion status.

What Are the Clinical Implications?

- Iron deficiency should possibly be avoided in individuals at high risk of experiencing an acute coronary event; whether iron supplementation can improve prognosis in these patients or once the event has occurred warrants investigation in appropriately designed trials.
- The results support the recently proposed redefinition of iron deficiency in patients with heart failure based on low transferrin saturation and not on ferritin levels and suggest that the former may identify high-risk patients in a wide range of cardiovascular diseases.

Nonstandard Abbreviations and Acronyms

GRACE	Global Registry of Acute Coronary Events
ID	iron deficiency
sTR	soluble transferrin receptor
TIMI	Thrombolysis in Myocardial Infarction
TSAT	transferrin saturation

less attention,[5–12] and most studies have included the whole spectrum of ACS or have been focused only on long-term events.[5–9,12] Because both iron excess and ID can influence cardiomyocyte survival after ischemia and reperfusion,[11,13,14] analyzing the short-term effects of ID in patients with ST-segment–elevation myocardial infarction (STEMI) is of special interest. Myocardial reperfusion status is a major prognostic determinant in STEMI,[15,16] but whether ID is associated with impaired myocardial reperfusion after primary percutaneous coronary intervention (PCI) in patients with STEMI is unknown.

On the other hand, the criteria for diagnosing ID in patients with cardiovascular disease are under discussion. International heart failure guidelines[17,18] adopted a definition based on low levels of ferritin or low transferrin saturation (TSAT). However, this definition has been challenged by studies showing that low TSAT is superior to low ferritin in identifying patients with CHF who have bone marrow iron depletion,[19] a worse prognosis,[19–21] or are more responsive to iron supplementation.[22] Based on these findings, it has recently been proposed that the definition of ID in CHF should be based solely on low TSAT.[23] Because ferritin is an acute-phase reactant,[24] its prognostic usefulness in patients with ACS may be especially hampered, and low TSAT or other ID criteria have shown superiority over low ferritin in predicting long-term mortality in these patients.[7,9] Finally, soluble transferrin receptor (sTR) levels are increased when iron stores are depleted[25]; however, their prognostic usefulness in patients with ACS is unclear.

Accordingly, this study aimed to investigate whether ID is associated with impaired myocardial reperfusion and worse in-hospital outcomes in patients with STEMI treated with primary PCI. To assess whether the distinct implications of the different ID definitions in patients with CHF are also present in the setting of STEMI, we also explored whether this association is affected by the ID definition, and evaluated the value of sTR levels for this purpose. Finally, we performed a secondary analysis of a previous study showing that ID is associated with infarct size and with adverse left ventricular (LV) remodeling in patients with a first anterior STEMI[11] to examine the impact of the ID definition on this association.

METHODS

The protocol for the current study was approved by the ethics committee on Clinical Research of University Hospital Vall d'Hebron (JAB-HIE-2017-01). The requirement of written informed consent was waived. Study data and analytic methods are available on reasonable request.

Patients

The study included all patients with STEMI admitted to our acute cardiac care unit after a primary PCI between December 1, 2016, and February 28, 2023, who had data on iron metabolism and available ECGs before and after PCI to evaluate myocardial reperfusion. STEMI was diagnosed in the presence of prolonged anginal symptoms associated with significant ST-segment elevation in contiguous leads—or ST-segment depression in leads V1 to V3 indicative of posterior infarction—and with troponin elevation. Of

2058 patients with STEMI admitted in this period, 1116 were excluded for several reasons and 942 were ultimately included (Figure 1). The most common cause of exclusion was, by large, the unavailability of iron metabolism study, mostly attributable to the rapid transfer of patients to their community hospitals after primary PCI before they could be sampled or to an international shortage of transferrin reagents occurring during part of the study period. Patients' management was in accordance with practice guidelines.

Clinical, Laboratory, and ECG Variables

Demographic data, cardiovascular risk factors and comorbidities, previous medications, characteristics of the clinical presentation, and data on the in-hospital course including complications and therapies were prospectively collected. Anterograde flow in the culprit vessel was characterized before and after PCI using the TIMI (Thrombolysis In Myocardial Infarction) scale. The extent of coronary artery disease was assessed as the number of vessels with lesions ≥50%. Revascularization of significant distant lesions was often performed in a staged procedure. Blood levels of troponin I were determined, with different assays used throughout the study period, on admission and serially during the first 48 hours. LV function was evaluated before discharge by 2-dimensional echocardiography or cardiac magnetic resonance (CMR) imaging. Standard hematological and biochemical determinations were made on arrival, a fasting blood sample was obtained the first working morning after admission, and serum concentrations of free iron, ferritin, and transferrin were measured using a colorimetric and turbidimetric method with an automated analyzer (AU5800 Beckman Coulter). TSAT was calculated using the formula:

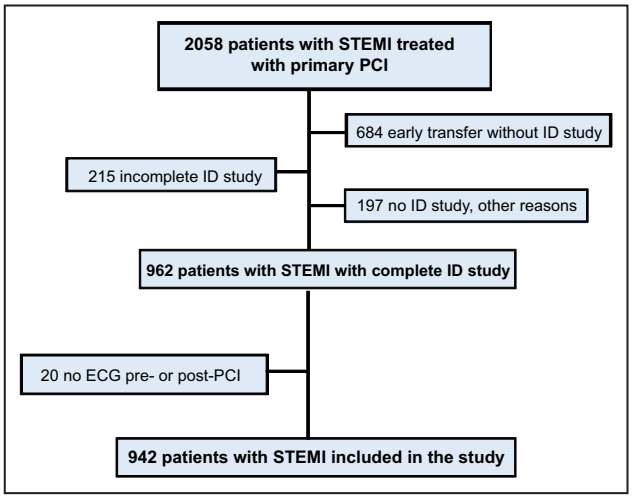

Figure 1. Study flowchart.
ID indicates iron deficiency; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

TSAT=free iron (μg/dL)/[transferrin (mg/dL)×1.25].[5,26] Anemia was defined as a hemoglobin value <13 g/dL in men or <12 g/dL in women.[27] In 595 patients, sTR levels were also measured using a fully automated nephelometric analyzer (BN II Siemens Healthineers). The index ECG establishing the indication of primary PCI and an ECG performed 60 to 90 minutes after restoration of flow at the culprit lesion were analyzed by one investigator (J.A.B.), blinded to iron metabolism data. The magnitude of ST-segment elevation was measured at the J-point. Impaired myocardial reperfusion was defined as the absence of ≥50% resolution of ST-segment elevation after PCI in the lead with maximal ST elevation before PCI.[15,28] Optimal myocardial reperfusion was defined as ST-segment resolution ≥70% after PCI.

Criteria for ID

ID was defined either as recommended by international guidelines (serum ferritin <100 ng/mL, or, when 100–299 ng/mL, TSAT <20%),[17,18] or alternatively as serum ferritin <100 ng/mL, TSAT <20%, or serum iron ≤13 μmol/L. The cutoff for serum iron was selected because it showed the best performance in selecting patients with ID in a previous study using bone marrow iron staining as a gold standard.[19] For sTR levels, a cutoff of ≥1.59 mg/L, the 95th percentile in healthy people reported in a previous study,[29] was selected to define ID.

Impact of ID Definition on Its Association With Infarct Size and LV Remodeling in Patients With STEMI

Our previous study was performed in 125 patients (aged 60±12 years, 89% men) with a first anterior STEMI treated with primary PCI who underwent a CMR imaging study in the acute phase and at 6 months (109 patients had the 6-month study).[11] All patients gave written informed consent. Data on patient characteristics and CMR protocols were reported in the original publication.[11] The results showed that ID, as defined by guidelines, was associated with larger infarcts and more extensive microvascular obstruction in the acute phase and with a higher frequency of adverse LV remodeling (increase in LV end-diastolic volume ≥20%) at 6 months. Here, we have examined these associations with other ID definitions.

Statistical Analysis

Data analysis was performed using SPSS software version 27 (IBM). Continuous variables are described as means±SDs or medians with 25th and 75th percentiles. Categorical variables are described as counts (percentages). Group comparisons were performed using Student *t* tests or Mann–Whitney *U* tests, as appropriate, for

continuous variables and by χ^2 or Fisher exact tests for categorical variables. Two sensitivity analyses were planned in which the association between ID criteria and myocardial reperfusion status was reassessed in the subgroups of patients with a symptom onset-to-balloon time ≤6 hours and in those in whom iron metabolism study was performed within 24 hours after onset of symptoms. Multivariable logistic regression analyses using backward stepwise elimination were performed to assess the association of TSAT <20% (the definition of ID most closely associated with impaired myocardial reperfusion in univariate analysis) and this outcome, as well as the lack of optimal reperfusion, after controlling for baseline predictors and anemia. Variables in the adjustment were age, sex, anemia, and other factors associated (P<0.2) with lack of ST-segment resolution ≥50% (active smoking, diabetes, previous use of diuretics, symptom onset-to-balloon time, and admission glomerular filtration rate) or ≥70% (these variables plus hypertension and previous use of β-blockers, angiotensin antagonists, and statins), respectively, in univariate analyses. The goodness of fit of the models was assessed with the Hosmer-Lemeshow test. Logistic regression was also used to evaluate possible interactions between some relevant variables (age, sex, anemia, diabetes, active smoking, and ischemic time) and the association between ID and impaired myocardial reperfusion. P values <0.05 were considered statistically significant.

RESULTS

Association of ID With Impaired Myocardial Reperfusion and Influence of the Definition Used

Baseline data and characteristics of patients at presentation are summarized in Table S1. ID, as defined by guideline criteria, was identified in 462 patients (49.0%), 228 (24.2%) had serum ferritin <100 ng/mL, 541 (57.4%) had TSAT <20%, and 716 (76.0%) had serum iron ≤13 µmol/L. Of the 942 patients, 273 (29.0%) showed impaired myocardial reperfusion, as defined by absence of ST-segment resolution ≥50%, after primary PCI. Optimal myocardial reperfusion was achieved in 417 patients (44.3%).

ID was associated with impaired myocardial reperfusion. However, this association was significantly affected by ID criteria, being stronger for TSAT <20% (12.7% of patients with TSAT ≥20% and 41.0% of those with TSAT <20% lacked ST-segment resolution ≥50% after PCI, P<0.001), less pronounced for serum iron ≤13 µmol/L, weaker for guideline criteria, and absent for serum ferritin <100 ng/mL (Table 1). The same associations were observed for the ≥70% ST-segment resolution cutoff. Furthermore, these results were confirmed in the subset of patients who underwent reperfusion within 6 hours after symptom onset (Table S2) and in those in whom iron metabolism study was performed in the first 24 hours after symptom onset (Table S3). Multivariable logistic regression analyses retained TSAT <20% as a strong, independent predictor of both impaired myocardial reperfusion (odds ratio [OR], 3.82 [95% CI, 2.62–5.56]; P<0.001) and lack of optimal reperfusion (OR, 2.45 [95% CI, 1.83–3.28]; P<0.001). Other variables associated with these outcomes were absence of smoking, diabetes, and ischemic time (Table 2). The association between ID and impaired myocardial reperfusion was consistent

Table 1. Association of Different ID Definitions With the Absence of ST-Segment Resolution ≥50% or ≥70% After Primary PCI

	No ID	ID	P value
	No ST-segment resolution ≥ 50%		
TSAT <20%	51 of 401 (12.7%)	222 of 541 (41.0%)	<0.001
Serum iron ≤13 µmol/L	28 of 226 (12.4%)	245 of 716 (34.2%)	<0.001
Guideline definition	118 of 480 (24.6%)	155 of 462 (33.5%)	0.002
Serum ferritin <100 ng/mL	208 of 714 (29.1%)	65 of 228 (28.5%)	0.857
	No ST-segment resolution≥70%		
TSAT <20%	165 of 401 (41.1%)	360 of 541 (66.5%)	<0.001
Serum iron ≤13 µmol/L	95 of 226 (42.0%)	430 of 716 (60.1%)	<0.001
Guideline definition	246 of 480 (51.2%)	279 of 462 (60.4%)	0.005
Serum ferritin <100 ng/mL	399 of 714 (55.9%)	126 of 228 (55.3%)	0.870

ID indicates iron deficiency; PCI, percutaneous coronary intervention; and TSAT, transferrin saturation.

Table 2. Multivariable Predictors of Absence of ST-Segment Resolution ≥50% or ≥70% After Primary PCI

Predictors of absence of ST-segment resolution ≥50%			
Variable	**Odds ratio**	**95% CI**	**P value**
Active smoking	0.72	0.51–1.02	0.068
Diabetes	1.80	1.24–2.61	0.002
Symptom onset-to-balloon time, per 10 min	1.02	1.01–1.02	<0.001
TSAT<20%	3.82	2.62–5.56	<0.001

Predictors of absence of ST-segment resolution≥70%			
Variable	**Odds ratio**	**95% CI**	**P value**
Active smoking	0.74	0.55–0.99	0.041
Symptom onset-to-balloon time, per 10 min	1.02	1.01–1.02	<0.001
TSAT<20%	2.45	1.83–3.28	<0.001

PCI indicates percutaneous coronary intervention; and TSAT, transferrin saturation. The fit of the models was good (Hosmer-Lemeshow test P=0.509 and P=0.850 for analyses: top and bottom panels, respectively).

among subgroups, and its magnitude was significantly higher in patients older than 65 years than in those younger than 65 years, with no other interactions observed (Figure 2).

Association Between sTR Levels and Myocardial Reperfusion

Seventy-nine (13.3%) of the 595 patients with sTR measurements had high (≥1.59 mg/L) levels. Impaired myocardial reperfusion was found in 27.1% and 39.2% of patients with normal or high sTR levels, respectively (*P*=0.027). Median sTR values in patients with and without ST-segment resolution ≥50% were 1.1 (0.9–1.3) and 1.1 (0.9–1.4), respectively (*P*=0.012). sTR values were not significantly associated with optimal reperfusion (56.0% and 60.8% of patients with normal or high sTR levels, respectively, lacked ≥70% ST-segment resolution after PCI, *P*=0.427).

Clinical Implications of TSAT<20% in Patients With STEMI

Baseline characteristics and data on clinical presentation and in-hospital course in patients with and without TSAT <20% are summarized in Table 3. As compared with the remaining patients, those with TSAT <20% were less often smokers and more frequently had a history of hypertension or diabetes. They also presented more often without chest pain and with a higher heart rate, lower systolic blood pressure, and a higher Killip class, as well as with a higher frequency of nonsinus rhythm and QRS abnormalities. The magnitude and extent of ST-segment elevation were similar in both groups. Patients with TSAT <20% had higher glucose levels, lower glomerular filtration rates, higher frequency of anemia, and higher calculated risk on admission. Times from symptom onset to balloon inflation were more prolonged in patients with TSAT <20%, who also had more extensive coronary artery disease than the remaining patients.

Patients with TSAT <20% had a lower frequency of TIMI 3 flow at the end of the PCI procedure, a higher peak of cardiac biomarkers, and poorer systolic LV function than the remainder of patients. In-hospital therapy was similar except for lower use of glycoprotein IIb/IIIa antagonists and higher use of intravenous diuretics and inotropes in these patients. Ischemic complications, malignant ventricular arrhythmias, advanced auriculoventricular block, and major bleeding occurred with comparable frequency in both groups, but patients with TSAT <20% had a higher frequency of pulmonary edema, cardiogenic shock, mechanical complications, or paroxysmal atrial fibrillation than the remaining patients. In-hospital mortality was 4 times as high in patients with TSAT <20% than in the rest of the patients (6.1% versus 1.2%, respectively; *P*<0.001).

Of the other ID definitions tested, only that based on low iron levels was significantly associated with in-hospital mortality, cardiogenic shock, or poorer LV function. In contrast, ID defined by guideline criteria, low ferritin levels, or high sTR levels was not related to any major clinical outcomes (Table S4).

Impact of ID Definition on Its Association With Infarct Size and LV Remodeling in Patients With a First Anterior STEMI

Clinical and laboratory characteristics of these patients were reported in the original publication.[11] In summary, 85.6% of patients had Killip class I on admission, 9.6% had mild anemia, and their calculated baseline risk was overall low. The prevalence of ID as per guideline definition

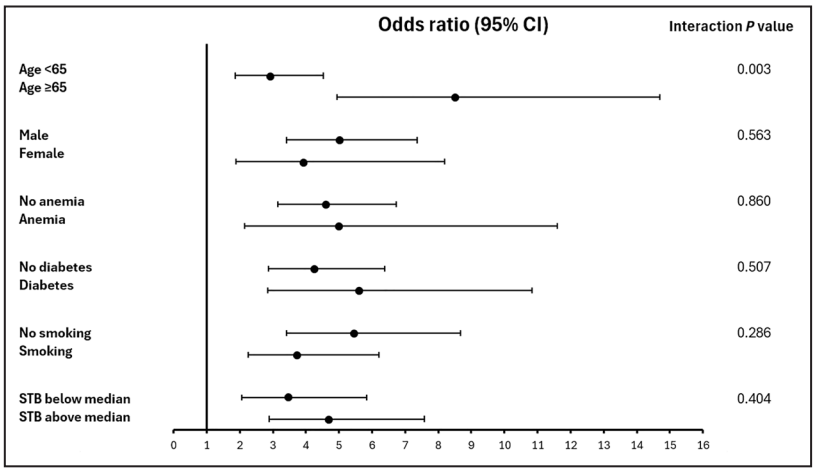

Figure 2. Association between iron deficiency, defined by transferrin saturation<20%, and impaired myocardial reperfusion among some relevant subgroups.
P for interaction is shown. STB indicates symptom-to-balloon time.

Table 3. Baseline Characteristics and Data on Clinical Presentation and In-Hospital Course in Patients With or Without ID as Defined by TSAT<20%

	TSAT ≥20% (n=401)	TSAT <20% (n=541)	*P* value
Age, y	62 (53–73)	63 (54–74)	0.083
Female sex, n (%)	75 (18.7)	124 (22.9)	0.117
Medical history			
Ischemic heart disease, n (%)	50 (12.5)	67 (12.4)	0.969
Heart failure, n (%)	4 (1.0)	9 (1.7)	0.386
Atrial fibrillation, n (%)	14 (3.5)	29 (5.4)	0.174
Stroke, n (%)	4 (1.0)	9 (1.7)	0.386
Vasculopathy, n (%)	18 (4.5)	30 (5.5)	0.466
Severe CKD, n (%)	6 (1.5)	11 (2.0)	0.540
Pulmonary disease, n (%)	49 (12.2)	64 (11.8)	0.856
PCI, n (%)	38 (9.5)	47 (8.7)	0.676
Cardiac surgery, n (%)	4 (1.0)	7 (1.3)	0.911
Active smoking, n (%)	207 (51.6)	215 (39.7)	<0.001
Hypertension, n (%)	197 (49.1)	320 (59.1)	0.002
Diabetes, n (%)	74 (18.5)	147 (27.2)	0.002
Dyslipidemia, n (%)	213 (53.1)	315 (58.2)	0.118
Time symptom onset-FMC, min	72 (35, 160)	73 (33, 174)	0.730
No chest pain, n (%)	30 (7.5)	79 (14.6)	<0.001
Heart rate, beats per min	75 (63, 87)	78 (64, 95)	0.004
Systolic blood pressure, mm Hg	142 (121, 160)	137 (115, 158)	0.013
Killip class, n (%)			<0.001
I	342 (85.3)	348 (64.3)	
II	36 (9.0)	109 (20.1)	
III	4 (1.0)	14 (2.6)	
IV	19 (4.7)	70 (12.9)	
Nonsinus rhythm, n (%)	27 (6.7)	71 (13.1)	0.001
Initial Q waves, n (%)	75 (18.8)	129 (23.9)	0.057
Right bundle branch block, n (%)	12 (3.0)	54 (10.0)	<0.001
No. of leads with ST elevation	5 (4, 6)	5 (4, 6)	0.093
Maximal ST elevation, mV	3.0 (2.0, 4.0)	3 (2.0, 4.0)	0.394
Initial glucose, mg/dL	131 (111, 164)	147 (120, 202)	<0.001
Initial creatinine, mg/dL	0.85 (0.73, 0.99)	0.91 (0.77, 1.09)	<0.001
Estimated GFR, mL/min per 1.73 m^2	95 (78, 111)	86 (66, 104)	<0.001
Anemia on admission, n (%)	51 (12.8)	110 (20.6)	0.002
GRACE score>140, n (%)	73 (18.2)	208 (38.4)	<0.001
Time symptom onset-balloon, min	177 (127, 277)	190 (137, 339)	0.013
Left main/3-vessel disease, n (%)	60 (15.0)	135 (25.0)	<0.001
Initial TIMI flow grade, n (%)			0.060
0	260 (64.8)	375 (69.3)	
1	25 (6.2)	32 (5.9)	
2	35 (8.7)	57 (10.5)	
3	116 (28.9)	134 (24.8)	
Final TIMI flow grade, n (%)			0.003
0	2 (0.5)	6 (1.1)	
1	2 (0.5)	5 (0.9)	
2	6 (1.5)	33 (6.1)	
3	391 (97.5)	497 (91.9)	

(*Continued*)

Table 3. Continued

	TSAT ≥20% (n=401)	TSAT <20% (n=541)	*P* value
No. of leads with ST elevation post-PCI	2 (0, 3)	3 (2, 5)	<0.001
Maximal ST elevation post-PCI, mV	1.0 (0.0, 1.5)	1.5 (0.5, 2.5)	<0.001
Peak creatine kinase MB, ng/mL (n=365)	214 (89, 294)	262 (125, 379)	0.005
Peak troponin I, ng/mL (n=302)	93 (39, 211)	176 (55, 380)	<0.001
Peak high-sensitivity troponin I, ng/mL (n=455)	66 (23, 125)	95 (35, 125)	0.015
LVEF, %	50 (42, 56)	46 (36, 55)	<0.001
LVEF ≤40%, n (%)	85 (21.3)	195 (36.0)	<0.001
Treatments			
Glycoprotein IIb/IIIa inhibitors, n (%)	109 (28.6)	111 (21.3)	0.012
β-Blockers, n (%)	310 (77.3)	409 (75.7)	0.576
Intravenous diuretics, n (%)	58 (14.5)	189 (35.2)	<0.001
Inotropic drugs, n (%)	43 (10.7)	108 (20.0)	<0.001
Complications			
Reinfarction, n (%)	6 (1.5)	8 (1.5)	0.982
Cerebrovascular accident, n (%)	4 (1.0)	11 (2.0)	0.209
Worse Killip class III or IV, n (%)	26 (6.5)	107 (19.8)	<0.001
Worse Killip class IV, n (%)	22 (5.5)	88 (16.3)	<0.001
Mechanical complications, n (%)	4 (1.0)	16 (3.0)	0.039
Cardiac arrest, n (%)	50 (12.5)	79 (14.6)	0.346
Paroxysmal atrial fibrillation, n (%)	27 (7.0)	77 (15.1)	<0.001
Advanced atrioventricular block, n (%)	18 (4.5)	38 (7.0)	0.104
Major bleeding, n (%)	13 (3.2)	19 (3.5)	0.821
In-hospital death, n (%)	5 (1.2)	33 (6.1)	<0.001
Length of hospital stay, d	5 (3, 6)	5 (4, 8)	<0.001

CKD indicates chronic kidney disease; FMC, first medical contact; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; ID, iron deficiency; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; and TSAT, transferrin saturation. Most cardiac arrests (120 of 129) were caused by ventricular arrhythmias.

was 43.2%, with 31.2% having TSAT <20%, 67.2% having serum iron ≤13 μmol/L, and 23.2% having ferritin <100 ng/mL. Only 5 patients (4.0%) had sTR levels ≥1.59 mg/L, for which reason patients with values in the upper quintile (≥1.29 mg/L) were compared with the remaining patients regarding sTR. ID was associated with a higher cardiac biomarker peak. CMR data for each ID definition are shown in Table 4. In summary, a TSAT level <20%, but not ferritin-based ID, was significantly associated with higher infarct size (as a percentage of LV mass or of the area at risk) in the acute phase and with higher increases in LV volumes, lower improvement of LV ejection fraction, and an increased frequency of adverse LV remodeling at 6 months. Low iron- or high sTR-based ID criteria showed a weaker association with infarct size and microvascular obstruction as compared with TSAT <20% and were not significantly related to postinfarction remodeling.

DISCUSSION

The present study showed that ID is strongly and independently associated with impaired myocardial reperfusion in patients with STEMI treated with primary PCI. In addition, our results indicated that this association is dependent on the ID definition, being very robust for TSAT <20%, less pronounced for low serum iron, and absent for ferritin-based criteria. In consonance with these results, TSAT <20%, but not low ferritin, identified patients with larger infarcts, poorer LV function, and higher rates of severe heart failure, mechanical complications, and mortality during hospitalization and of adverse LV remodeling after discharge. sTR values were related to some of these outcomes but were less discriminative of myocardial reperfusion status, in-hospital complications, or postinfarction LV remodeling than TSAT.

Few studies have addressed the implications of ID in patients with ACS.[5–12] These studies showed a prevalence of ID ranging between 29% and 60% but differed with respect to the populations included, ID definitions, timing of blood sampling, and outcomes of interest. ID was associated with a worse functional recovery at 30 days[5] or with an increased long-term frequency of nonfatal myocardial infarction or cardiovascular death[6] or total mortality[7–9] in unselected patients with ACS. By

Table 4. Association of Different Definitions of ID With Infarct Size in the Acute Phase and With LV Remodeling at 6 months Assessed by CMR Imaging in Patients With a Reperfused First Anterior STEMI

	Guideline definition			TSAT <20%			Serum iron ≤13 μmol/L			Serum ferritin <100 ng/mL			Serum sTR ≥1.29 mg/L		
	No ID	ID	*P* value	No ID	ID	*P* value	No ID	ID	*P* value	No ID	ID	*P* value	No ID	ID	*P* value
Area at risk, g*	43.7±18.8	39.6±14.0	0.266	40.6±17.6	44.5±15.1	0.310	37.6±15.8	43.6±17.1	0.135	43.6±17.2	37.1±15.0	0.115	41.9±17.6	42.1±13.4	0.967
Area at risk, % of Left ventricle*	35.3±13.1	32.6±10.6	0.296	34.7±12.8	32.9±10.3	0.501	33.4±14.0	34.4±11.3	0.713	35.1±12.4	31.5±10.8	0.227	34.5±12.5	32.5±9.8	0.533
Infarct size, g	20.7±13.5	30.1±20.4	0.003	20.5±13.2	34.8±21.8	<0.001	19.8±12.4	27.4±19.1	0.023	25.1±18.5	23.8±13.6	0.734	22.3±14.4	34.9±24.4	0.025
Infarct size, % of left ventricle	16.8±9.8	22.8±10.2	0.002	17.6±10.0	23.8±10.2	0.002	17.2±9.6	20.6±10.7	0.097	19.1±10.6	20.3±10.0	0.591	18.2±10.0	24.2±11.0	0.013
Infarct size, % of the area at risk*	52.8±24.4	68.0±22.6	0.004	55.7±23.7	67.3±25.1	0.038	56.4±26.1	60.9±24.2	0.449	57.2±25.7	66.2±20.5	0.134	57.6±24.6	67.8±23.9	0.126
No. of segments with MVO	0 (0–2)	2 (0–3)	0.002	0 (0–2)	2 (1–3)	0.001	0 (0–2)	1 (0–3)	0.098	1 (0–2)	1 (0–3)	0.356	1 (0–2)	3 (0–4)	0.005
≥3 segments with MVO, %	12 (17.9)	20 (40.0)	0.008	18 (22.0)	14 (40.0)	0.045	9 (22.5)	23 (29.9)	0.396	22 (24.7)	10 (35.7)	0.255	19 (20.2)	13 (56.5)	<0.001
Relative increase in LVEDV, %†	3.7±19.9	15.9±27.2	0.012	4.8±20.8	17.1±27.9	0.011	5.6±25.1	10.3±23.2	0.328	9.5±24.4	5.9±21.8	0.531	7.9±24.1	12.5±23.1	0.446
Relative increase in LVESV, %†	−7.2±23.8	9.3±31.5	0.002	−5.7±25.4	10.8±31.0	0.004	−4.0±27.6	1.5±28.7	0.337	−0.5±29.2	0.3±25.4	0.907	−1.8±29.4	6.3±22.1	0.259
Increase in LVEF, %†	6.4±6.9	3.9±7.7	0.080	6.4±7.1	3.3±7.3	0.037	6.2±6.6	5.0±7.6	0.435	5.7±7.1	4.1±8.1	0.337	5.9±7.4	3.0±6.5	0.116
Adverse LV remodeling, %†	9 (14.1)	17 (37.8)	0.004	13 (17.6)	13 (37.1)	0.025	8 (21.6)	18 (25.0)	0.695	20 (23.3)	6 (26.1)	0.777	19 (21.1)	7 (36.8)	0.244

Values are mean±SD or median (25–75 percentiles). CMR indicates cardiac magnetic resonance; ID, iron deficiency; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MVO, microvascular obstruction; STEMI, ST-segment–elevation myocardial infarction; sTR, soluble transferrin receptor; and TSAT, transferrin saturation.

*Values from 90 patients with adequate measurements.

†Values from 109 patients with CMR imaging repeated at 6 months.

contrast, in a study of patients with STEMI undergoing primary PCI, those with ID had higher troponin levels but a less complicated in-hospital course and, among those with CMR imaging performed, similar infarct size, higher myocardial salvage index, and less microvascular obstruction than those without ID.[10] In patients with cardiogenic shock complicating acute myocardial infarction (with or without ST-segment elevation, more than one-half were resuscitated), ID did not predict the occurrence of death or renal replacement therapy at 30 days.[12] In contrast, we previously observed that, in patients with a first anterior STEMI treated with primary PCI, ID was associated with larger infarcts, more extensive microvascular obstruction, and a higher frequency of adverse LV remodeling at 6 months.[11] We provided a mechanistic explanation for these results by demonstrating in a murine model that diet-induced ID reduces myocardial tolerance to ischemia/reperfusion, at least in part by inhibiting the endothelial nitric oxide synthase/soluble guanylyl cyclase/protein kinase G pathway and involving increased oxidative/nitrosative stress and the proteasome-dependent degradation of endothelial nitric oxide synthase.[11] The reasons for these discrepancies regarding the short-term implications of ID are unclear, but they could be explained in part—beyond the many factors influencing prognosis in cardiogenic shock—by differences in the relative proportions of patients with ID who have low ferritin or low TSAT, given the distinct implications of these criteria on myocardial reperfusion and outcomes shown herein.

The prevalence of ID in our study varied depending on the criteria used but was overall comparable to that observed previously in patients with ACS.[5–11] The results had strong internal consistency because ID was associated with both impaired and suboptimal reperfusion, not only in the overall sample but also in patients who underwent reperfusion <6 hours after symptom onset, a time window in which any influence on the tolerance to ischemia should be more evident.[30] In addition, this association was present among all subgroups examined, and TSAT <20% was also related to a worse TIMI flow grade after PCI, a higher cardiac biomarker peak, poorer LV function, and an increased frequency of heart failure, mechanical complications, and mortality, while it was not associated with ischemic or arrhythmic complications, less related to infarct size than the former.

In agreement with previous studies,[31–33] independent predictors of impaired or suboptimal myocardial reperfusion were ischemic time, diabetes, and absence of smoking. However, ID defined by TSAT <20% also retained a strong association with impaired ST-segment resolution, which was independent of baseline variables and anemia. It seems unlikely that differences in antithrombotic therapy had affected these results because virtually all patients received dual antiplatelet therapy, and $P2Y_{12}$ blockade was started per protocol as soon as the diagnosis of STEMI was made. Glycoprotein IIb/IIIa inhibitors, which also have shown protective effects against ischemia/reperfusion injury[34] were administered less often to patients with ID than to the remaining patients. However, the rates of use of these drugs were similar in patients with and without impaired myocardial reperfusion, and the results were the same after adjusting for glycoprotein IIb/IIIa inhibitor use. Therefore, it seems highly plausible that ID has a direct, deleterious effect against myocardial salvage after reperfusion.[11,13]

Our results also showed that low TSAT was the ID criterion most closely associated with impaired reperfusion and adverse short-term outcomes. Low serum iron levels performed somewhat worse than low TSAT, and low ferritin showed no association in this respect. These results are in line with the distinct prognostic implications of different ID definitions previously observed in patients with CHF[19–22] and in unselected patients with ACS[7,9] and support the notion that no prognostication, let alone management decisions, should be made in these patients based solely on low ferritin levels. At variance with a recent study showing that sTR levels predicted total long-term mortality after an ACS,[9] our study showed that high serum sTR levels had only a borderline association with impaired reperfusion and short-term adverse outcomes and were clearly inferior to low TSAT in this respect. Moreover, sTR levels in our study were overall comparable to those reported by some studies[29] but significantly lower than those reported by others,[9,35] which suggests that sTR measurements should be better standardized before their use in clinical practice.

Some methodological considerations and limitations need to be discussed. Many patients admitted with STEMI during the study period could not be included, but, in the majority of these cases, the reasons were hypothetically not related to the outcomes of interest, making it unlikely that this issue affected the results. In fact, the proportions of impaired or optimal reperfusion after PCI or of a high-risk GRACE (Global Registry of Acute Coronary Events) score on admission were comparable in patients included in the study and in those excluded (data not shown). The ECG post-PCI was not performed exactly at the same time in all patients, which could have influenced the rates of ST-segment resolution observed. However, this influence seems unlikely because there is no reason to suspect that the timing of the ECG was different in patients with and without ID. It would have been interesting to assess the association between ID and myocardial blush grade after PCI, but data on the latter were unavailable in most patients. Myocardial ID was associated with anemia, a predictor of poorer outcomes in patients with ACS,[36] as well as with other

comorbidities and with longer ischemic times, but remained significantly associated with impaired myocardial reperfusion after adjusting for all of these variables. Finally, the observational nature of our study prevents us from drawing causal inferences, which would require a randomized clinical trial. It could even be alleged that the increased frequency of ID in patients with impaired reperfusion might be the consequence and not the cause of increased myocardial damage. In this respect, reductions in plasma iron and transferrin concentrations have been described following an acute myocardial infarction.[37] However, the results of our sensitivity analysis in the subset of patients tested for iron metabolism within 24 hours after symptom onset completely replicated (even with some numerically larger differences) those in the overall cohort, which argues against this possibility.

CONCLUSIONS

ID is strongly associated with impaired myocardial reperfusion, poorer LV function, and worse short-term outcomes in patients with STEMI treated with primary PCI. A TSAT level <20% is the ID criterion that shows a more robust association with myocardial reperfusion status and adverse outcomes. The association of other ID criteria with those end points is weaker or, in the case of a low ferritin, absent. Because of the frequency and adverse clinical significance of impaired myocardial reperfusion in patients with STEMI despite state-of-the-art management, the potential preventive or therapeutic strategies targeting ID in this clinical setting merit investigation in appropriately designed clinical trials.

ARTICLE INFORMATION

Received January 7, 2025; accepted April 14, 2025.

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Sources of Funding

This study was funded by Instituto de Salud Carlos III, Spain, through the projects AES PI16/00232 and AES PI23/00068 and the research network CIBERCV (CB16/11/00479), both co-funded by European Regional Development Fund, and by the Sociedad Española de Cardiología y Fundación Española del Corazón (SEC/FEC-INV-BAS 23/11).

Disclosures

None.

Supplemental Material

Tables S1–S4

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