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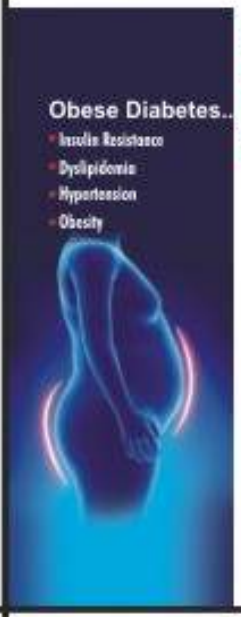

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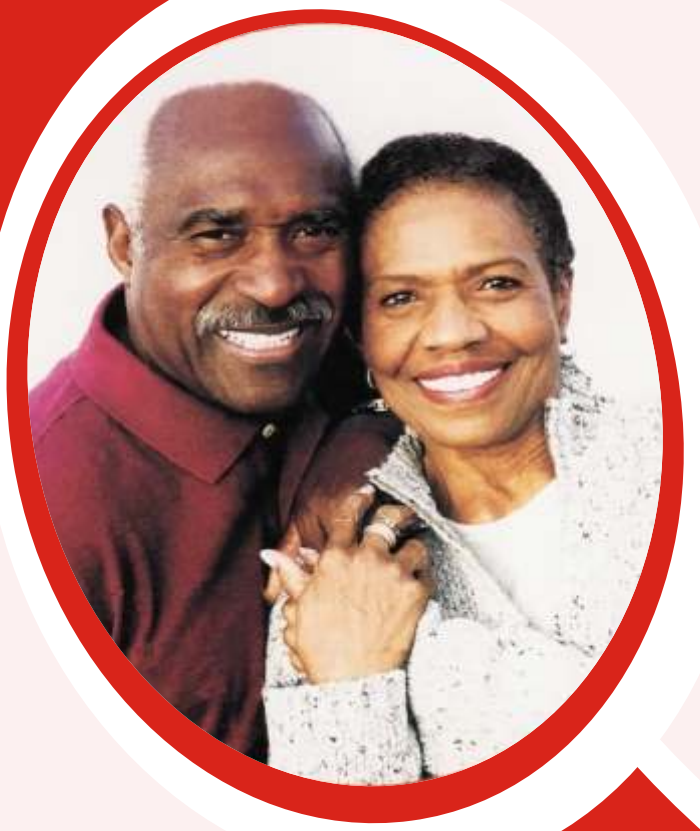

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Predictors of Revascularization in Patients with Unstable Angina

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Abstract

Background: The factors that determine the necessity of coronary artery revascularization in patients with unstable angina (UA) have been supported by limited data. Therefore, this study aimed to identify the predictors of revascularization in patients with UA.
Methods: The study included the recorded data of 3668 patients with UA who underwent cardiac catheterization (age 66 ± 9.2, men 70%); 2615 of them (71%) underwent revascularization (percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), or hybrid revascularization. The remaining 1053 patients (29%) had no significant coronary stenosis and were regarded as controls. Multivariable logistic regression analysis was performed to separate the predictors of revascularization.
Results: It was found that severe angina (OR 2.7, 95%CI 1.9–3.7), male gender (OR 1.4, 95%CI 1.1–1.7), and hyperlipidemia were the predictors of revascularization. It was also noted that intraventricular conduction disorders including left and right bundle branch blocks and a history of previous revascularization and myocardial infarction were associated with lower odds of revascularization.
Conclusion: Overall, however, the predictive value of the studied factors proved to be poor and may still point to the multifactorial nature of significant coronary artery stenosis and the need for revascularization in patients with UA.
Keywords: acute coronary syndrome; percutaneous coronary intervention; unstable angina; coronary artery bypass graft

1. Introduction

It is estimated that 10% of patients with acute coronary syndromes (ACS) suffer from UA, known as a clinical condition characterized by myocardial ischemia at rest or during minimal exertion without acute myocardial necrosis/injury. It is also characterized by specific clinical findings, including prolonged (>20 min) angina at rest; angina that is escalating in frequency or duration, or lowering in threshold; the sudden onset of severe angina; or angina that occurs after a recent episode of MI [1]. UA and myocardial infarction belong to the ACS spectrum, given the close pathophysiological link between them (plaque erosion plays a significant role in both) [2].

The first record of UA appeared in 1937 when Sampson, Eliaser, and Feil described several patients with prolonged, severe anginal pain that preceded the occurrence of myocardial infarction [3,4]. The term unstable angina, coined by Fowler and Conti in 1971, marked a significant event in the history of ACS [5,6]. The term was described as a continuum between stable angina and myocardial infarction.

Noteworthily, although the clinical characteristics of UA have

persisted unchanged over time, the biomarkers of myocardial necrosis have undergone fundamental evolution. This clarifies the enduring challenge in the clinical diagnosis and management of UA that patients have been facing over the years. For example, in most UA patients, their troponin levels will be below the 99th percentile. However, there are still recorded cases of patients diagnosed with UA who have elevated troponin levels and a pattern that does not change[7].

The key element for differentiating between UA and Non-ST-segment elevation myocardial infarction (NSTEMI) is the assessment of the levels of cardiac injury biomarkers. In the 1980s and 1990s, the MB fraction of creatine kinase (CK-MB) and first-generation cardiac troponin (cTn) assays were routinely applied. However, both lacked optimal sensitivity and specificity for detecting myocardial necrosis. The very high incidence of UA in the 1990s therefore appears to have been an overestimate[8].

The introduction of an assay for cardiac-specific troponin I and T provided a more sensitive and specific marker than CK-MB for detecting myocardial necrosis more frequently and more accurately[9,10]. This assay became a breakthrough in the classification of patients with ACS. Additionally, the introduction of improved high-sensitivity (hs) cTn assays led to an increase in the detection of NSTEMI and a reciprocal decrease in the diagnosis of UA. This has also influenced our comprehension of previously established risk stratification strategies[7,11,12]. The more accurate high-sensitive troponin assays revealed a decrease in the prevalence of UA from 35–61% to 7–9%[13,14,15]. It was then shown that an increase in hsTnT had prognostic value. A hsTnT value above the upper reference level (URL) is associated with a twofold increase in cardiovascular death or myocardial infarction (MI) within 1 year[16]. Conversely, low levels of troponins on admission allow for the early and safe discharge of over two-thirds of patients with suspected ACS[17].

Despite advancements in the tools assisting in detecting UA, a few issues still need to be addressed to improve UA diagnosis and therapeutic strategy. For example, in many clinical studies, UA and NSTEMI are still commonly classified together as non-ST-segment elevation ACS (NSTE-ACS), given that there are few analyses of patients with UA only[18]. There is also a lot of uncertainty in the management of patients with UA, as evidence for the benefits of an invasive strategy within 72 h is low[19,20]. Moreover, the correct qualification of UA patients for adequate interventional treatments is still problematic, as the amount of PCI in UA is lower than even in stable coronary artery disease (CAD)[21]. Additionally, the diagnosis of UA remains challenging, given the subjective assessment of index symptoms; this may cause a high risk of bias, leading to the frequently overused diagnosis of UA becoming an indication for urgent CA. The question of which UA patients should be qualified for early invasive strategies remains unresolved.

Lastly, as mentioned before, the data indicating the parameters that determine the presence of significant stenosis in UA patients (and, consequently, clarifying their PCI performance) is still limited. Hence, the low percentage of PCI in patients with UA motivated this study. It was the study's objective to look for the clinical factors contributing to significant coronary artery stenosis.

2. Materials and Methods

2.1. Study Population

This single-center retrospective study included 3668 consecutive adult patients (≥18 years old) with diagnosed UA hospitalized in the Department of Cardiology in Multidisciplinary Hospital Nowa Sól, Poland between January 2012 and December 2016.

UA was defined as myocardial ischemia at rest or during minimal exertion in the absence of acute cardiomyocyte injury/necrosis, based on the contemporary TnI and high sensitivity Troponin T (hs-TnT) level (below 99th percentile URL) in the cTn-assay used[1,22]. A 0 h/3 h algorithm assay was applied along with clinical and ECG findings to rule out NSTEMI. When classifying angina symptoms, an internal questionnaire was devised in which the patient was asked about clinical symptoms. Anginal pains were classified as: Class I—mild, Class II—moderate, Class III—severe, and Class IV as very severe.

When assessing stenosis, quantitative coronary angiography (QCA) and the procedural expertise of a skilled cardiologist were employed. Notably, a reduction in the diameter of epicardial arteries exceeding 70% (by contemporary standards) was deemed significant, warranting revascularization[1]. In instances where ambiguity persisted, fractional flow reserve (FFR) evaluations were conducted, adhering to the guidelines outlined by the European Society of Cardiology (ESC). It is noteworthy that the utilization of FFR was sporadic, primarily due to the limited availability of the procedure in Poland during the implementation of the project.

The patients were qualified for diagnostic CA based on the algorithm for NSTE-ACS management. CA was performed in all 3668

patients. In the case of 2615 patients, coronary revascularization (PCI, CABG) was carried out due to the presence of significant coronary artery stenoses. In the remaining 1053 individuals, the presence of significant stenoses was not observed, and they were not qualified for revascularization. They were considered the control group. The data were collected from electronic health records.

The management of the study population followed the current recommendations of the European Society of Cardiology. The study was retrospective, conducted in adherence to the principles of the Helsinki Declaration, and did not necessitate a separate approval from the bioethics committee. Exclusion criteria involved: patients with incomplete documentation and laboratory exams; patients with significant coronary artery stenoses (who had not undergone CABG previously) eligible for conservative treatment; patients who were not qualified for either CABG or PCI due to technical issues.

2.2. Laboratory Assessments

The blood samples were obtained at baseline. Venous blood was drawn from the basilic vein. In the analysis, the peripheral blood count was marked with CELL-DYN Ruby (Abbott Diagnostics, Santa Clara, CA, USA). Fibrinogen, D-dimer, aPTT and INR were determined using STACompact Max (Diagnostica Stago, Parsippany, NJ, USA). Creatinine, total cholesterol, high-density lipoproteins, and triglycerides were analyzed using a photometric test (Roche Diagnostics GmbH, Mannheim, Germany).

The assessment of cardiac troponin involved the use of two assays: (a) a traditional immunoassay technique carried out from January 2012 to September 2014 (TnI-Ultra from Siemens, Advia Centaur, Deerfield, IL, USA), featuring a limit of detection of 6 pg/mL (0.006 ng/mL), a 99th percentile reference limit of 40 pg/mL (0.04 ng/mL), and a total imprecision of 10% at a concentration of 30 pg/mL (0.03 ng/mL) [23]; (b) the blood samples taken between October 2014 and December 2016 were analyzed by high sensitivity assays for cTnT (Roche Diagnostics, Basel, Switzerland), which have a limit of detection at 5 ng/L and a 99th percentile reference limit of 14 ng/L, with a total imprecision of 10% at a concentration of 13 ng/L.

2.3. Statistical Analysis

Continuous variables with a normal distribution were presented as mean and standard deviation. Non-normal variables were reported as the median and interquartile range. Student's t-test was used to test the significance of the assessed parameters between the two groups in the case of variables with a normal distribution. For the variables that were not normally distributed, the Mann–Whitney test was employed to compare the groups. The frequencies of categorical variables were compared using the Chi-square or Fisher's exact test when appropriate. Aiming to determine the cut-off point of the predictors for significant coronary artery stenosis in patients with UA, a receiver-operating characteristic (ROC) curve was created. The cut-off points of the analyzed predictors, (which differentiated the patients with PCI + CABG from the patients with a hybrid treatment), were estimated based on the Youden index, and their quality was assessed using two indicators: sensitivity and specificity. A logistic regression model was used to assess the need for PCI + CABG or hybrid treatment.

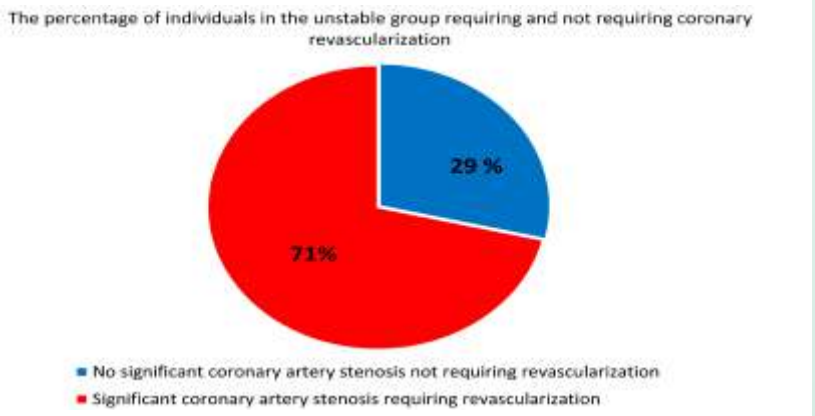
Subsequently, one-dimensional logistic regression models were applied, followed by the multi-dimensional logistic regression model (MLR). The MLR model was constructed using the backward stepwise logistic regression method. The results obtained were presented as an odds ratio (OR) with a 95% confidence interval (CI). Statistical analysis was performed using Statistica 13.3 software (StatSoft, Tulsa, OK, USA). All the tests were analyzed at alpha significance level = 0.05.

3. Results

3.1. Patient Characteristics

All 3668 patients with diagnosed UA underwent CA; 2615 (71%) patients underwent revascularization due to significant coronary stenosis (Figure 1). The mean age was 66 ± 9.2.

Figure 1. The percentage of UA individuals requiring and not requiring coronary revascularization.



3.2. Predictors of Revascularization in UA—Multivariate Analysis

The multivariate logistic regression model was built using the backward stepwise logistic regression method. Stenocardial pain of class III, male sex, total cholesterol concentration above 155 mg%, LDL concentration above 87 mg%, and platelet count above 210.000/mL were the independent predictors of revascularization in the study group. Additional parameters that characterized the patients in this analysis included: an MCV less than 90.9 fl, prothrombin time (PT) less than or equal to 14.2 s, RDW less than 11.6%, and TSH less than 1.05 IU/mL (Table 2). Moreover, patients who underwent revascularization less frequently had LBBB and RBBB at baseline ECG.

3.3. Predictors of Revascularization in Patients with UA—ROC Curves

The diagnostic value of the factors associated with revascularization due to significant coronary stenosis were evaluated through ROC curve analysis. The results demonstrated that the total cholesterol levels > 155 mg/dL (OR = 1.46, 95% CI: 1.23–1.74, $p < 0.001$), HDL-cholesterol level < 54 mg/dL (OR = 1.25, 95% CI: 1.05–1.49, $p = 0.010$), LDL-cholesterol level > 87 mg/dL (OR = 1.61, 95% CI: 1.35–1.91, $p < 0.001$), MCV < 90.9% (OR = 1.26, 95% CI: 1.08–1.46, p = 0.002), MPV < 8.8% (OR = 1.40, 95% CI: 1.21–1.63, $p < 0.001$), PLT levels > 210 × 103 mL (OR = 1.48, 95% CI: 1.27–1.71, $p < 0.001$), prothrombin time < 14.2 s (OR = 1.53, 95% CI: 1.26–1.85, $p < 0.001$) RDW level < 11.2% (OR = 1.48, 95% CI: 1.27–1.79, $p < 0.001$), and TSH level < 1.05 µU/mL (OR = 1.42, 95% CI: 1.20–1.68, $p < 0.001$) were identified as independent predictors of revascularization attributed to significant coronary artery stenosis

Table 1. Baseline characteristics of the study groups with UA.

Parameter	Unstable Angina with Revascularization *n* = 2615	Control Group *n* = 1053	*p*-Value
Age (years)	65.7 ± 9.3	66.6 ± 9.1	*p* = ns
BMI (kg/m^2)	28.0 ± 4.7	28.5 ± 4.9	*p* = ns
Male gender (%)	70.16	63.13	*p* = ns
Hypertension (%)	93.8	93.64	*p* = ns
DM type 2 (%)	25.43	23.93	*p* = ns
DM type 1 (%)	0.42	0.19	*p* = ns
Stenocardial pain class I (%)	0.54	0.95	*p* = ns
Stenocardial pain class II (%)	80.84	92.21	*p* = ns
Stenocardial pain class III (%)	18.35	6.74	*p* < 0.001
Stenocardial pain class IV (%)	0.27	0.09	*p* = ns
Chronic Kidney Disease (CKD) (%)	3.56	3.51	*p* = ns
Peripheral Artery Disease (PAD) (%)	6.0	7.12	*p* = ns
Previous MI (%)	20.42	27.45	*p* < 0.001
Previous PCI (%)	34.38	49.29	*p* < 0.001
Previous CABG (%)	8.3	7.47	*p* < 0.001
Stroke (%)	3.17	4.75	*p* = 0.022
Current Smoking (%)	18.45	13.64	*p* < 0.001
Family history of CAD	25.74	30.96	*p* < 0.001
ECG findings Sinus rhythm	71.14	72.46	*p* = ns
LBBB	1.53	3.23	*p* = 0.002
RBBB	0.65	1.9	*p* = 0.001
AF	2.6	3.8	*p* = ns
Heart Rate (bpm)	73.0 ± 13.7	73.1 ± 14.4	*p* = ns
SBP (mmHg)	123.8 ± 16.1	123.9 ± 16.0	*p* = ns
DBP (mmHg)	81.1 ± 11.0	80.7 ± 10.6	*p* = ns

in patients with UA (Figure 2, Figure 3, Figure 4, Figure 5 and Figure 6).

4. Discussion

Most ACS events are caused by the rapture or erosion of an atheromatous plaque that is not angiographically critical. The angiographic extent and severity of coronary artery stenosis are strongly associated with survival [24]. SYNTAX and Gensini scores, established to define the severity of coronary artery disease, are useful for assessing cardiovascular events [25].

The overall rate of UA amounts to 8.9% in the APACE registry, 11.1% in the RAPID-CPU registry, and 17% in the PLATO trial [26,27,28]. However, in a prospective survey of over 10,000 patients, the proportion of UA was 41.9% [29]. Interestingly, the more sensitive the cTn assay used, the lower the prevalence of UA. In the RAPID-CPU registry, CA and revascularization were performed at a rate of 71.8%. In other registries, the revascularization rate in UA varies and ranges from 21% to 78.3% [14,30].

The rates of CA and revascularization (PCI, CABG) were very high in our study. All 3668 (100%) patients received invasive CA. The revascularization rate was high at 71.3%, probably given that it was in a group of high-risk patients (a high percentage of patients with previous PCI procedures, high LDL cholesterol levels, and smokers).

It is noteworthy that the patients who did not undergo revascularization were more likely to have pre-existing CAD and prior coronary revascularization procedures (PCI and CABG; 49.29% vs. 34.38%, $p < 0.001$) [31]. Moreover, a positive history of heart failure or ischemic stroke was more common in the control group.

The above facts may indicate a different approach being required for the non-revascularization group

Table 1. Baseline characteristics of the study groups with UA.

Parameter	Unstable Angina with Revascularization *n* = 2615	Control Group *n* = 1053	*p*-Value
ALT (U/L)	29.9 ± 42.5	28.1 ± 23.0	*p* = ns
AST (U/L)	29.1 ± 56.8	26.7 ± 25.1	*p* = ns
Urea (mg/dL)	40.5 ± 16.3	41.8 ± 18.7	*p* = ns
Na+ (mmol/L)	140.9 ± 2.9	141.1 ± 2.6	*p* = 0.033
K+ (mmol/L)	4.4 ± 0.4	4.4 ± 0.4	*p* = ns
TSH (µU/mL)	1.5 ± 1.5	1.7 ± 1.6	*p* = ns
Cholesterol (mg/dL)	182.1 ± 53.7	172.9 ± 49.3	*p* < 0.001
TG (mg/dL)	146.3 ± 107.5	144.0 ± 104.2	*p* = ns
LDL (mg/dL)	112.7 ± 47.1	103.4 ± 43.6	*p* < 0.001
HDL (mg/dL)	51.1 ± 14.5	52.6 ± 16.0	*p* = 0.019
Creatinine (mg/dL)	1.05 ± 0.5	1.04 ± 0.5	*p* = ns
GFR (mL/min)	76.8 ± 21.1	75.8 ± 20.3	*p* = ns
CRP (µg/mL)	1.8 ± 3.8	1.3 ± 3.1	*p* = ns
Fibrinogen (mg/dL)	410.9 ± 98.9	408.6 ± 104.5	*p* = ns
APTT (s)	31.6 ± 11.8	31.8 ± 9.9	*p* = ns
HbA1c (%)	7.0 ± 1.5	6.7 ± 1.3	*p* = ns
Haemoglobin (g/dL)	14.4 ± 1.6	14.3 ± 1.6	*p* = ns
HCT (%)	42.7 ± 4.5	42.5 ± 4.3	*p* = ns
RDW (%)	12.3 ± 1.2	12.4 ± 1.2	*p* < 0.001
MCV (%)	91.1 ± 4.9	91.6 ± 5.4	*p* = 0.013
PLT (10^3/mL)	233.3 ± 67.9	233.1 ± 73.1	*p* < 0.001

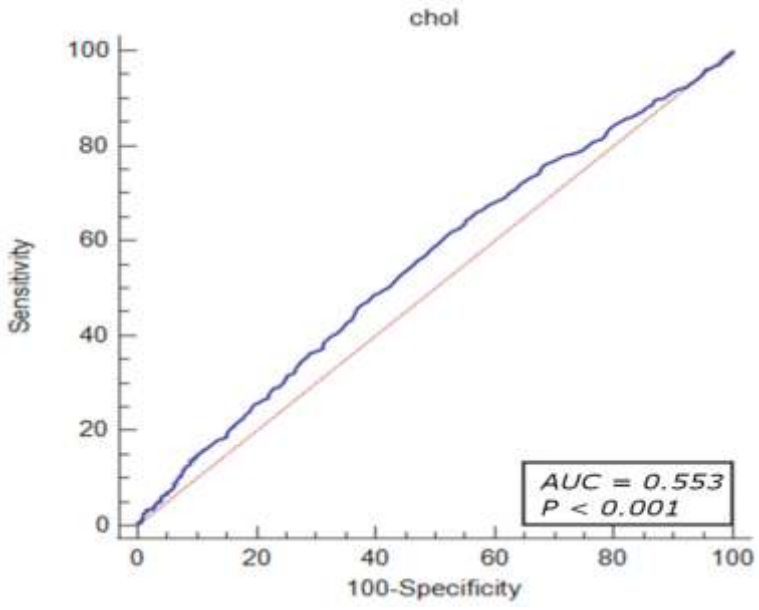
The data are expressed as mean ± SD or as percentage. Abbreviations: BMI = body mass index; CRP, C-reactive protein; MCV—mean corpuscular volume; HCT—hematocrit; GFR, glomerular filtration rate; PLT—platelets; hs-TnT, high-sensitive troponin T; CABG = coronary artery bypass grafting; DBP = diastolic blood pressure; RBBB—right bundle-branch block; LBBB—left bundle-branch block; MI = myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; AF—atrial fibrillation; CKD—chronic kidney disease; CAD—coronary artery disease; APTT—activated partial thromboplastin time; ECG—electrocardiography; DM—diabetes mellitus; TC—total cholesterol; TG—triglycerides. Stenocardial pain class I—mild, class II—moderate, class III—severe, class IV—very severe.

Table 2. Predictors of revascularization in patients with UA—results from multivariate logistic regression modeling using the backward stepwise logistic regression method.

Variable	OR	95% CI	p-Value
LBBB	0.51	0.29–0.89	0.018
RBBB	0.33	0.15–0.71	0.004
Male gender	1.49	1.21–1.84	<0.001
PLT > 210 (10^3/mL)	1.34	1.10–1.64	0.003
LDL > 87 mg/dL	1.49	1.22–1.82	<0.001
PT ≤14.2 s	1.35	1.04–1.75	0.023
MCV < 90.9%	1.27	1.05–1.55	0.015
Stenocardial pain class III	2.78	2.01–3.86	<0.001
RDW < 11.6%	1.31	1.03–1.66	0.025
Previous CABG	0.66	0.49–0.89	0.008
TSH < 1.05 uIU/mL	1.31	1.07–1.61	0.009
Family history CAD	0.49	0.39–0.61	<0.001

The data are shown as odds ratio (OR) with 95% confidence intervals. Abbreviations: LBBB = left bundle-branch block; RBBB = right bundle-branch block; PCI = percutaneous coronary intervention; PLT—platelets; CCS—Canadian Cardiovascular Society; LDL—low density lipoprotein; PT—prothrombin time; RDW—red cell distribution width; TSH—thyroid stimulating hormone; MCV—mean corpuscular volume; CABG—coronary artery bypass grafting; CAD—coronary artery disease.

Figure 2. ROC curves of total cholesterol levels for the diagnostic ability of revascularization in UA. AUC for total cholesterol (blue line), reference line (red line).



of patients, including their quicker qualification for invasive procedures based on their medical history and the risk of an impending heart attack. The paradox in the fact that patients with greater comorbidities were less likely to undergo revascularization was also observed by other authors [32]. This suggests that physicians place greater weight on comorbidities (previous MI and revascularizations) and the associated risks.

Among the factors that predicted revascularization due to significant coronary artery stenosis in the multifactorial analysis model were: stenocardial pain of class III, male gender, total cholesterol above 155 mg%, LDL above 87 mg%, MCV below 90.9 fl, PLT above 210 × 10^3/mm^3, PT less than or equal to 14.2 s, RDW below 11.6%, and TSH below 1.05 IU/mL.

Stenocardial pain of class III, recognized as severe angina, was significantly more common in the revascularization group. The above result highlights how significant clinical examination is in the diagnosis of UA. The more severe the angina, the greater likelihood of ischemia requiring revascularization in the context of significant coronary stenoses.

Similarly, the male gender was an independent predictor of revascularization caused by significant coronary stenosis. Other authors also found an association between the male gender and obstructive coronary artery disease [33,34].

It was also found that RDW and MCV were significantly lower in patients who underwent revascularization. Geng et al. demonstrated that the baseline RDW was closely associated with in-stent restenosis at follow-up in patients with UA pectoris who underwent successful percutaneous coronary interventions with drug-

Figure 3. ROC curves of HDL and LDL-cholesterol levels for the diagnostic ability of revascularization in UA. AUC for HDL and LDL cholesterol (blue lines), reference lines (red lines).

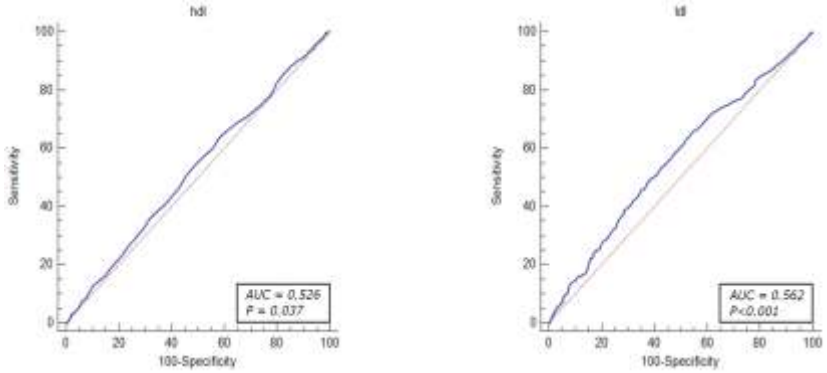


Figure 4. ROC curves of MCV and MPV for the diagnostic abilities of revascularization in UA. AUC for MCV and MPV (blue lines), reference lines (red lines).

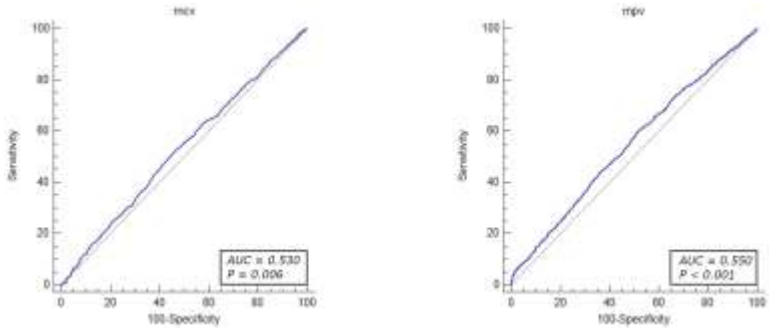
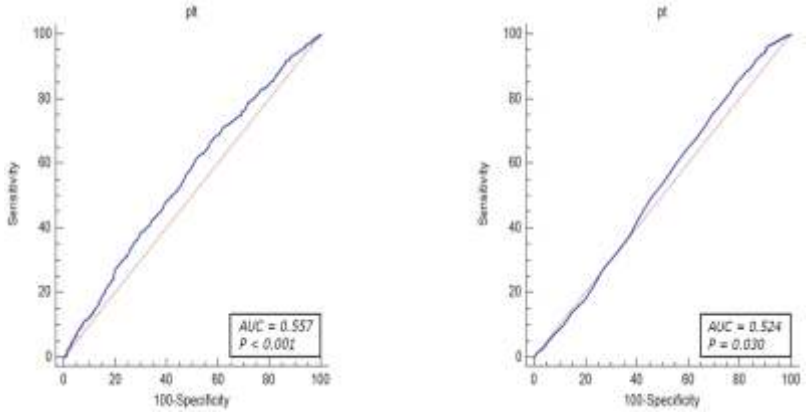


Figure 5. ROC curves of platelets and prothrombin time for the diagnostic abilities of revascularization in UA. AUC for PLT and PT (blue lines), reference lines (red lines)



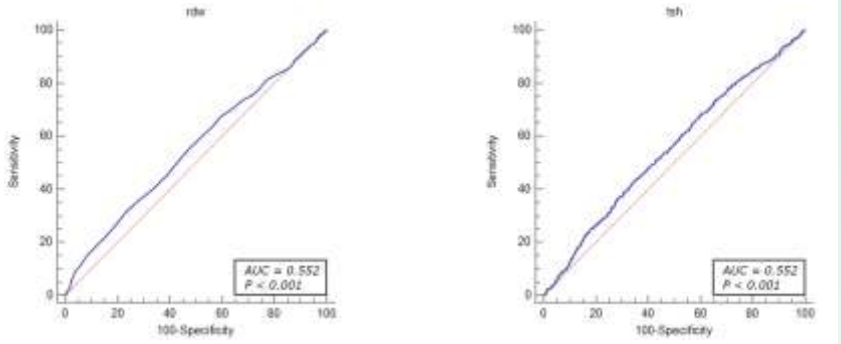
eluting stents [35]. In the study of Gul et al., RDW was associated with long-term cardiovascular mortality in NSTEMI and UA [36]. In another study, elevated RDW was also an independent predictor of hospital readmission in patients with UA (hazard ratio: 1.35 (95% confidence interval (CI): 1.02–1.79), p = 0.033) [37].

Current research has also shown that increasing MPV is associated with MI and UA, while a rising platelet volume is related to an increased risk of mortality due to CVDs [38,39,40]. In the study of Sun et al., low MCV predicted a high risk of in-stent restenosis [41]. Decreased MCV is associated with microcytic anaemia, iron deficiency, and inflammation, which contributes to atherosclerosis [42].

The ROC curve analysis indicated that the factors associated with revascularization due to significant coronary stenosis included the parameters linked to hyperlipidemia (total cholesterol levels > 155 mg/dL, HDL-cholesterol level < 54 mg/dL, LDL-cholesterol level > 87 mg), as well as hematological indices such as MCV < 90.9%, MPV < 8.8%, PLT levels > 210 × 103/mL, prothrombin time < 14.2 s, RDW level < 11.2%, and TSH level < 1.05 µU/mL. However, the sensitivity and specificity of these parameters were limited due to the multifactorial characteristics of the atherosclerotic coronary lesions.

With regards to the prevalence of LBBB and RBBB, both exhibited a significantly higher occurrence in the control group. The bundle branch blocks in the control group were more frequently detected, given the greater tendency of primary care physicians to recognize ACS and refer such patients to the hospital even if the symptoms are not very severe. The same applies to a positive history of myocardial infarction, coronary angioplasty, heart failure, or ischemic stroke.

Figure 6. ROC curves of RDW and TSH for the diagnostic abilities of revascularization in UA. AUC for RDW and TSH (blue lines), reference lines (red lines).



Other research has highlighted the role of other tools that may help select patients for CA and revascularization procedures in patients with UA. For example, new biomarkers, selected using machine learning and metabolomics techniques, may be used to improve the clinical diagnosis of UA [43,44]. Furthermore, an artificial neural network employing simple, easily available clinical variables may be used to non-invasively identify a group of patients with chest pain without obstructive CAD [45]. Our study, nevertheless, has demonstrated that the high percentage of patients with significant coronary artery stenosis requiring revascularization due to UA are well qualified for invasive procedures.

Limitations of the Study

There are several limitations to this work: The revascularization/no revascularization analyses were retrospective and single-centered, which makes them subject to a potential bias. The troponin measurements displayed variability within the study group. The extent of new cardiac troponin (cTn) increases depended on the analytical sensitivity of both the current (standard) assay in use (2012–2014) and the high-sensitivity assay (2014–2016) scheduled for implementation. Essentially, the transition from CKMB and early cTn assays to innovative high-sensitivity (hs-cTn) assays may have led to a notable increase in the positivity rate (values > 99th percentile), coupled with a decrease in the incidence of unstable angina (UA). However, when shifting from sensitive contemporary cTn to hs-cTn assays, this change may have been mitigated or absent [46].

The diagnosis of UA relies on the subjective decision of the attending physician. There is also a possibility that the interpretations of a patient's symptoms may differ markedly between clinicians. Perhaps it would be advisable to pay more in-depth and detailed attention to imaging tests of cardiac ischemia, which would precede a referral to CA. Additionally, coronary artery stenoses were assessed by the operating physician, with no independent assessors reviewing the lesions. This may indicate the possibility of interpersonal differences in the lesions' interpretation.

Unfortunately, the Fractional Flow Reserve (FFR) assessment in all the cases was hindered by the restricted availability of the procedure in Poland in 2012–2016, which coincided with the execution of the project. All the patients followed a prescribed medical therapy according to the guidelines for managing NSTE-ACS. However, detailed data on the administered pharmacotherapy were not available. This limitation is inherent in retrospective studies, and such information is excluded from the analysis.

5. Conclusions

The data presented indicate that UA is still a challenging diagnosis and a significant clinical problem in daily practice. In the registry shown, the proportion of patients with UA among all the ACS patients as well as the percentage of revascularization were very high. It was found that severe angina symptoms, male gender, and hyperlipidemia were independent predictors of revascularization in UA. Paradoxically, patients with a greater burden of comorbidities (previous MI, previous revascularization, intraventricular conduction disorders) were less likely to undergo revascularization.

Author Contributions

Conceptualization, P.B. and J.B.; Methodology, P.B., J.B. and W.F.; Validation, J.H. and P.B.; Formal Analysis J.B., P.B. and W.F.; Investigation, J.B., W.F., P.B., J.R., M.S., D.H. and J.O.; Resources, W.F. and J.H.; Data Curation, J.B., W.F. and P.B.; Writing—Original Draft Preparation, J.B. and W.F.; Writing —Review and Editing, J.B. and W.F.; Visualization, J.B. and P.B.; Supervision, J.H. and P.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This retrospective study was conducted in adherence to the principles outlined in the Helsinki Declaration and did not necessitate separate consent from the bioethics committee.

Informed Consent Statement

Not applicable.

Data Availability Statement

The data presented in this study can be made available upon request from the corresponding author.

Conflicts of Interest

The authors have disclosed no conflicts of interest.

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Understanding the impact of endometriosis on women's life: an integrative review of systematic reviews

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Abstract

Background

Endometriosis is a challenging chronic condition with a significant impact on women's well-being. This systematic review of systematic reviews aims to assess the evidence investigating the intricate interplay between endometriosis and quality of life (QoL).

Methods

A systematic review was performed for English-language studies up to January 2022 to identify systematic reviews with and without meta-analysis analyzing quantitative or qualitative data The following databases were searched: Scopus, PubMed, Embase, Web of Science and Cochrane Central Register of Controlled Trials. Participants/population were women with endometriosis, and the outcomes included were all reported outcomes evaluating the impact of endometriosis on women's QoL (PROSPERO 2021 CRD42021289347).

Results

15 systematic reviews were identified. 8 included meta-analysis: 4 explored the prevalence of mental health problems, and 1 analyzed, respectively, the overall impact of endometriosis, headache migraine, and sexual function. 7 articles reported on the mental consequences, and three sexual functioning. One was a qualitative review. The impact of the relationships with the healthcare system was analyzed in 3 reviews. Pain is a hallmark of endometriosis. Infertility and sexual problems are also frequent. Depression, anxiety, and stress represent significant contributors to lessening women's QoL. Women have frustrating relationships with the healthcare system: the complex and long diagnostic process, lack of treatment effectiveness, and persistence of symptoms contribute to emotional challenges. Negative cognitive patterns developed by women with emotional distress, such as catastrophizing and fear-avoidance behaviors, amplify the experience of pain.

Conclusion

The limitations of this review are the high degree of heterogeneity of papers that include many factors, including comorbidities, and use of medical care that may impact QoL, and that most of them were cross-sectional. Endometriosis is a chronic disease that significantly impacts all domains of women's lifes. Pain, infertility, and stress linked with depression, and anxiety significantly influence QoL. Women are dissatisfied with the care they receive.

Background

Endometriosis is a challenging chronic condition affecting millions of women of reproductive age worldwide[1]. It is manifested by the presence of functionally active endometrial stroma and glands outside the uterine cavity[2]. Women with this condition experience chronic pelvic pain, dyspareunia, dysmenorrhea, dysuria, and dyschezia[3]. Infertility is also frequently associated with endometriosis[4]. Symptoms tend to worsen with advanced stages, especially in case of deep infiltrating endometriosis. Several theories have been proposed to explain its pathogenesis, but the complex processes behind the development of endometriosis remain unclear [5,6,7]. Increasingly, endometriosis is considered not only as a pelvic localized process but a systemic condition, as it features chronic

neuro-inflammation and hormone changes leading to multidimensional effects of the disease with a higher prevalence of other conditions [8, 9] including mental health problems [10]. Diagnosis of endometriosis is challenging, because of the absence of specific biomarkers, while imaging may not be definitive. There is no specific symptom either that could be solely attributed to endometriosis [11]. Delayed diagnosis and ineffective treatments stemming from a lack of understanding of endometriosis etiology and its variability in progression pose significant challenges in disease management [12]. The diversity in clinical course and diagnostic complexities also contributes to the variability in estimates of its prevalence and incidence [13], which are dependent on the type of data and the design used for those analyses [14]. Overall, endometriosis has detrimental effects on women's functional status and physical, mental, social, and sexual well-being [15,16,17,18,19]. All listed disruptive physical and psychosocial symptoms can be disabling.

Given that endometriosis mostly affects women of reproductive age, which is also active work age, imposes a considerable social and economic burden, both for women as well as for society's economy at large [20,21]. Although presenting with debilitating symptoms that sometimes remain invisible to the clinician's eye, endometriosis continues to be experienced and lived by the patient.

QoL is a broad concept that has been defined by the World Health Organization as individuals' perceptions of their position in life in the context of the culture and value systems in which they live and about their goals, expectations, standards, and concerns, that incorporate physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment [22]. The QoL of women with endometriosis has been investigated from different perspectives and methods. However, these analyses focus on specific aspects or domains, limiting to providing a comprehensive perspective of such a diverse and heterogeneous health condition. This review aims to systematize the available evidence investigating the intricate interplay between endometriosis and QoL, considered from a broad perspective, including physical and mental well being, and to provide an integrated understanding of the challenges faced by women living with endometriosis.

Methods and materials

A systematic review of systematic reviews was performed following the recommendations of the Centre for Reviews and Dissemination and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23] and AMSTAR [24]. This review was registered at the International Prospective Register of Systematic Reviews PROSPERO (Prospero ID: PROSPERO 2021 CRD42021289347).

A systematic review of the literature search was performed for English-language studies up to January 2022 using the terms "life", "quality of life", "health related quality of life", "social well-being", "mental wellbeing", "sexual life", "relationships", "depression", "anxiety" in combination with "endometriosis". Only systematic reviews with and without meta-analysis analyzing quantitative or qualitative data with full-text availability were included. Additional articles were identified by manual searching of the references of the retrieved reviews.

The following databases were searched for the potentially eligible studies: Scopus (1), PubMed (2), Embase (3), Web of Science (4), and Cochrane Central Register of Controlled Trials (CENTRAL) (5). Grey literature (6) also was searched. The search strategy included terms refer to the two key domains of interest: (1), endometriosis and systematic review (2).

The search terms within each domain included:

1) "endometriosis" OR "pelvic pain" OR "endometriosis health profile" AND.

2) "systematic review".

Studies were eligible if they evaluated the impact of endometriosis on women's QoL using systematic review and(or) meta-analysis methodology. Studies were excluded if they meet one of the following conditions: (1) focus specifically on the properties of the different available instruments to measure QoL, (2) non-research-based articles, such as conference abstracts, commentaries, opinion pieces, book chapters, and editorials; (3) narrative, descriptive, scoping and realist literature reviews; (4) are not written using the Latin alphabet, Russian or Kazakh; (3) abstract was not available; (5) or full text was not available. The condition or domain being used was the impact of endometriosis on women's QoL. Participants/ population were women diagnosed with endometriosis, and the out comes were all reported outcomes evaluating the impact of endometriosis on women's QoL.

Data extraction (selection and coding)

Titles and abstracts were screened following inclusion criteria by a first reviewer (AK). A random sub-sample of 20% of titles and abstracts were screened by a second reviewer (TM, DM) to ensure the accuracy of

selection. All included papers were read in full and assessed again for relevance to the research question and inclusion criteria (AK, TM, DM). During the full-text review, articles were independently assessed for eligibility by the primary reviewer (AK) and review team members (TM, DM). In case of discrepancies, the topic of disagreement was resolved through discussion with a third reviewer (ASS). A data extraction form was developed and piloted with a random selection of 10% of the included papers. Extracted data was collated in a table produced in MS Excel. The following elements were extracted from each review: Authors, Search period, Quality assessment, Number of articles reviewed, Meta-analysis, Fndings, Implications for research, and Implications for clinical practice. AMSTAR [24] critical appraisal tool for systematic reviews was used to assess the quality of included studies. A narrative synthesis approach [25] was applied to explain and integrate our findings. This process included the following steps:

1) Preliminary synthesis, which aims to describe patterns across the included studies in terms of the differences in QoL. Textual descriptions of studies and tabulation were used as specific tools.
2) Exploring relationships in the included data, which aims to take into consideration the experiences of women diagnosed with endometriosis.
3) Generalising conclusions on the outcomes of interest.

Results

The PRISMA flow diagram (Fig. 1) shows the exclusion of studies after a rigorous check on screening and full-text assessment at each of the stages. After eliminating duplicates, a total of 919 articles were screened, and 100 papers were checked for suitability according to the predefined inclusion criteria, of which 13 systematic reviews were selected; additionally, 2 reviews were included from the references of papers found in the initial stages.

15 papers were subjected to data extraction (for details, see Table 1) and for generating the main themes analyzed in this paper [3, 10,26,27,28,29,30,31,32,33,34,35,36,37,38]. 8 papers included quantitative synthesis performing meta-analysis: 4 explored the prevalence of mental health problems, and 1 analyzed, respectively, the overall impact of endometriosis [27], headache migraine [30], and sexual function [34]. Seven articles reported on the mental consequences [3,10,30,32,36,37]. Three articles explored sexual functioning and relationships [23,34,35]. One qualitative review was on patients' experiences living with endometriosis [38]. The impact on QoL of the relationships with the healthcare system and professionals was specifically investigated in 3 reviews [27,36,38], however, all 15 indicated recommendations to improve clinical care for women with endometriosis, as well as 14 of them included recommendations for further research.

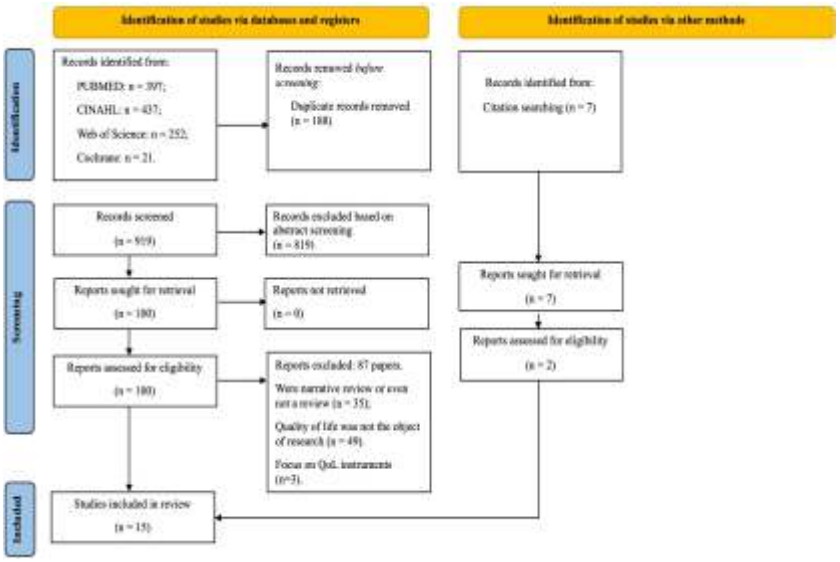
Results from the reviews confirm the significant impact on QoL of endometriosis, and how their diverse and interrelated symptoms and impairments influence numerous aspects of women's lives at specific points of time but also over the years, from adolescence through menopause, affecting physical, mental, and emotional health, family, social life and leisure time, work productivity [39], hampers educational attainment [40], alters career choices and success [41] and impairs sexual and couple's life [42].

Table 2 shows the risk assessment of the selected studies based on the AMSTAR criteria. Most of the studies had a quality. The main problem is that several of these reviews did not have clear inclusion and exclusion criteria in their respective methods section, as indicated by explicit PICO questions.

The most relevant findings of this review address the following major themes are reflected in Fig. 2.

Pain

Fig. 1



PRISMA flow diagram

Chronic pain is the most prominent symptom of endometriosis [43] as well as the major stressor and most relevant contributor to lower scores in QoL [37,44]. Women describe pain as a controller of their life; they are concerned by pain's duration and quality not just site and duration as screened by health professionals [38]. Leite Ferreira et al. mentioned the disabling effect of pain on the daily routines of women as it disturbs sleeping, eating, and moving but also during sexual intercourse, bladder expansion, and bowel movements [33]. Jia et al. explored differences in QoL comparing patients with chronic pelvic pain with and without endometriosis, finding no differences between those having or not having endometriosis [31]. Of note, pain is not directly correlated with the extent of the endometriosis stage or extension [45] but is found to be greater in the presence of concurrent depression, anxiety, and catastrophizing disorders [32].

Social impact of endometriosis

The symptoms and effects of endometriosis have a significant influence on women in all domains of their lives [33,38]. Young et. al's qualitative review described women's experiences of endometriosis in public when they had to plan their life around the symptoms and the feeling of losing their life to the condition [38]. Significant losses of productivity due to absenteeism and presenteeism have been reported [33]. Avoidance of disease reporting to employers and discussion with colleagues - especially men - are measures taken by women so as not to be blamed for making a disease an excuse for missing work and duties [38]. Some women are forced to reduce their workload or leave the job due to severe symptoms

Table 1.

Endometriosis SR QoL evidence table

Authors	Search period	Quality assessment	Number of articles reviewed	Meta-analysis	Findings	Implications for research	Implications for clinical practice
1. van Barneveld et al., 2022 [3]	Until June 2020	Newcastle -Ottawa	47 for SR, 17 for MA	Yes	Anxiety and depression are frequent in endometriosis and interrelated with pain perception. Other intercorrelated factors included age, QoL, quality of sleep, fatigue, sexual function, gastrointestinal symptoms, comorbidity, self-esteem, emotional self-efficacy, coping style, social adjustment, pain imagery, and pain sensitization.	Investigate the process that may link endemotriosis, depression, anxiety and pain	Integrated patient-centred approach to medical, medical, psychological and sexual issues.
2. Brasil et al., 2020 [8]		Newcastle -Ottawa	15	Yes	Stress has a high prevalence in endometriosis and may have an important role in enhancing inflammatory and pain mechanisms, which is also linked with sexual function and infertility, although the ethipatogenic mechanisms are unclear.	Better understanding of the underlying mechanisms linking endometriosis, pain and psychological stress.	Interdisciplinary team providing psychological care beyond pain management aiming to emotion aiming to emotion regulation strategies adapted to women's needs
3. Barbara et al., 2017 [26]	January 2000 - September 2016	not mentioned	9	No	Women with endometriosis have frequent sexual dysfunctions not limited to deep dyspareunia suggesting the effect of psychosocial factors, including emotional distress associated with the disease and quality of intimate relationships.	Investigate the global sexual impact of endometriosis, focusing not only on pain during intercourse but also on psychological and relational dimensions, including the partner's sexual functioning.	Personalized management program, cooperation between different professional figures, routine "screening" on sexual health, training in sexual health for medical students.
4. Chaman-Ara and Bahrami, 2017 [27]	Until November, 19, 2016	Checklist designed based on STROBE	7	Yes	Endometriosis affects all aspects of women's QoL and has the most negative effect on control and powerlessness and infertility. Also, it has the least negative effect on the self-image as well as in the relationship with medical profession.		Early diagnosis and developing effective treatment protocols are very important to prevent the reduction of QoL due to endometriosis.

[38] or may feel guilty for not being able to work [46].

Physical impact of endometriosis

Women with endometriosis suffer from diverse physical health ailments. This could be related to somatization, but also to systemic syndrome mediated by neuro-endocrine-inflammatory mechanisms associated with endometriosis, which currently is being considered not a localized pelvic but a systemic conditon [10]. Thus, the association between migraine and endometriosis was reported in several studies [30]. The findings were attributed to the biochemical changes in chronic inflammation accompanying endometriosis with raised levels of prostaglandins also contributing to migraine pathogenesis [47].

Mental health impact of endometriosis

Women with endometriosis also show consistently higher intensity and severity of depression and anxiety [29,37]. While the Global burden of mental health in women of reproductive age is estimated at 4.5-7% for depressive and 5.5-6% for anxiety disorders [48], the prevalence of depression and anxiety among women with endometriosis ranges from 20 to 85% [3,28,36]. And, remarkably, in women with endometriosis, the presence and severity of pain are a key determinant of higher scores of depressive symptoms [28,29].

Brasil et al. demonstrated high rates of psychological stress levels in nearly 70% of women with endometriosis [10], suggesting that stress-induced central sensitization and neuro-immunological pathways activated by high levels of cortisol could be contributing factors in endometriosis [10]. Psychological distress that represents living with chronic pain is lined with the severity of

Table 1. Endometriosis SR QoL evidence table

Authors	Search period	Quality assessment	Number of articles reviewed	Meta-analysis	Findings	Implications for research	Implications for clinical practice
5. Delanerolle et al., 2021 [28]	November November 1995–30 2020		34 papers the meta- and 15 in analysis.	Yes	Depression are frequently reported and anxiety in endometriosis. Studies investigating mental health problems in endometriosis present significant limitations, preventing to provide a valid estimates of the impact of those problems. Pain and dyspareunia are also recurring themes in endometriosis.	Good designed and powered enough studies to analyze the complex relationships and directionality between endometriosis, pain and mental health problems.	Holistic management requires understanding the applicability of existing instruments to assess QoL and whether these could be harmonized. Finally, the mental burden and its associated pain disorders should be determined to improve clinical practices.
6. Gambadauro et al., 2019 [29]	September 2017	Modified Newcastle-Ottawa Scale	27	Yes	The association between endometriosis and depressive symptoms is largely determined by chronic pain but may also be modulated by psycho-social individual and context vulnerabilities. Self-esteem and self-efficacy are associated with psychological well-being, independently of pelvic pain.	Investigate the clinical and social burden associated with early diagnosis and treatment of depression as well as the interaction in infertile women.	Awareness of the complex relationship between endometriosis and depressive symptoms has to inform tailored patient-centered care. New paradigm of care has to be directed toward improving the mental health of all women with pelvic pain and depression, shifting care from a clinical focus on lesions and their removal, to more pragmatic on treating symptoms.
7. Jenabi et al., 2021 [30]	all existing publications until May 2020	Newcastle Ottawa Statement Manual	9	Yes	There is a significant association between endometriosis and migraine headaches. Endometriosis and migraine share some symptoms and risk factors, having many similarities regarding epidemiology, pathogenesis, and physical or psychiatric comorbidities.	Investigate the molecular physiopathology of these two conditions, exploring the possible effect of biochemical mediators, like prostaglandins or up-regulation or dis-regulation of nitric oxide synthesis.	Consider migraine as a differential diagnosis in headaches in women with endometriosis.
8. Jia et al., 2012 [31]	Until May 2012	standardized checklist with small modifications	39	No	Women with endometriosis reported significant impairments in QoL, since pelvic pain intensity was negatively associated with QoL.	Investigate the directionality and independent effect on QoL of pain, infertility and features as extension, duration of endometriosis.	Endometriosis management from the woman's point of view has to address the associated emotional, sexual, and social problems. Thus, a multidisciplinaria strategy involving a pain clinic and counseling is recommended.

depression or anxiety which are better predictors of QoL than the severity or extension of endometriosis lesions [48, 49, 50].

Sexual life and couple relationships impact of endometriosis

Up to 60–70% of women complain of some form of sexual dysfunction affecting QoL. Conditioned experience of painful intercourse led to a disturbed sexual life characterized by partial or complete avoidance of it [26,34]. Dyspareunia brings other detrimental effects that further aggravate the sexual life of a woman such as diminished sexual desire, arousal, lubrication, and orgasm. The meta-analysis of Perez-Lopez et al. reported that women with endometriosis score lower in each domain of the Female Sexual Function Index (desire, arousal, lubrication, orgasm, satisfaction, pain) and showed higher levels of pain scores for dyspareunia and chronic pain compared to those without endometriosis [35]. Emotional distress and the quality of sexual relationships also affect couples' lives, as found by Norinho et al., who explored the topic by examining couples' perceptions of relationships and sexual life. A significant finding is the correlations between sexual problems and dyspareunia and worse sexual performance with mental anguish and the subsequent detrimental effect on relationships, which alters the reproductive goals of couples, and also generates negative emotions in women's partners [34].

Infertility

Infertility is a problem commonly associated with endometriosis however its impact on women's QoL is not consistent. Chaman-Ara, Wang, and Leite Ferreira found this association in their

Table 1. Endometriosis SR QoL evidence table

Authors	Search period	Quality assessment	Number of articles reviewed	Meta-analysis	Findings	Implications for research	Implications for clinical practice
9. Kalfas et al., 2022 [32]	Until April 2021	Quality assessment criteria developed by the authors	27	No	Catastrophising and anxiety were the factors most consistently associated with greater pain, whilst depression, anxiety, and stress were related to worse QoL. Findings regarding depression and pain were mixed, and research on social factors was limited.	Investigate psychosocial approaches that may improve emotional functioning, reduce pain impact, and enhance women's QoL: how social factors influence the perception of women of their health and disease: and the role that protective factors for pain and QoL (e.g., cognitive flexibility, acceptance) may have.	Care for women with endometriosis has to focus on their individual needs, exploring the whole socio-psychological dimenions. Pain has to be properly estimated and addressed in clinical care which has to focus on what is important for women, potentially reducing distress and impact.
10. Leite Ferreira et al., 2016 [33]	January 2010 - October 10th 2015	not mentioned	18	No	Endometriosis affects the everyday lives of women, hindering their daily activities, in personal relationships, and interfering with their reproductive capacity. Endometriosis has a physical, mental, and adverse impact on social well-being and thus negative effect on QoL. The impact of endometriosis is related to the complex interactions between pain, fertility, sexuality, and ability to work and maintain personal relationships.	Investigate the development and implementation of biopsychological model of care that consider the multidimensionality of endometriosis including that includes emotional support, stress reduction, social support, coping strategies, psychosexual treatment and focus on sex and relationships, control of pain and career counseling.	To improve QoL, it is necessary to understand patients according to their clinical condition. Women have to be informed of the treatment options and decide on how best to adapt to their needs. Treatment should not only aim to eradicate the underlying condition but improve QoL and also the emotional, sexual and social problems that come with the disease. Patients have to learn how to deal with chronic pain, to explore ways to have sexual intercourse without pain and to strengthen relations with its partners and friends so that they are in solidarity in dealing with the disease.
11. Norinho et al., 2020 [34]	January 2000 - December 2020	not mentioned	10	No	Dyspareunia is a frequent complaint, but lack of communication about sexuality, sexual problems or dysfunction, and avoidance of sexual intercourse have an impact on sexual function and relationships. Catastrophising pain and depression and anxiety symptoms may have, indirectly, also an impact. Endometriosis has a profound impact on partners, affecting many life domains including sex, intimacy, and the relationship in general.	Future research is needed to investigate ways to address the male partner and the relationship as a whole. Data suggests that male partners should not be overlooked in the treatment of endometriosis and that psychosocial support including sexual and couple therapy might be beneficial.	Partners should not be overlooked in the treatment of endometriosis and that psychosocial support including sexual and couple therapy might be beneficial

meta-analysis [27,33,37], suggesting that the inability to have a child causes depression and feelings of inadequacy among women, uncertainty about future fertility, and affects sexual and intimate relationships. This, in turn, can negatively influence patients' self-esteem and even cause problems in marital relationships, exerting persistent psychological pressure on patients. Over time, this can lead to further deterioration in the QoL of endometriosis patients. However, the results of other reviews [3,31] did not confirm this effect.

Relationship with healthcare

There are frequent complaints from women with endometriosis of dissatisfaction and frustration with the care they receive. The complexities and uncertainties of the disease (related to pathophysiology, staging, severity, and treatment responses) and its clinical manage- ment [27], generate a feeling of lack of control, loss of vitality and energy, decreased self-esteem, difficulties regulating emotions, and low sleep quality, contributing to a vicious cycle of catastrophizing that further deteriorate their QoL [51]. The long time required to diagnose endometriosis leads to frustration and isolation and increases psychological distress, shame, anxiety, and depressive symptoms. Delayed diagnosis may contribute to the exacerbation of symptoms, prolonged pain, increased stress, and sexual dissatisfaction [12,13,14,32], and may impact initiating treatment, and hence the QoL. The disease may also progress, and worsen every cycle; meanwhile, the woman will suffer from the consequences of the progression of the disease in their routines. Patients heve to learn how cope with the daily impact of

Table 1. Endometriosis SR QoL evidence table

Authors	Search period	Quality assessment	Number of articles reviewed	Meta-analysis	Findings	Implications for research	Implications for clinical practice
12. Perez Lopez et al., 2020 [35]	Until March 9 2020	Newcastle–Otawa	4	Yes	Women with endometriosis have an increased risk of sexual dysfunction and dyspareunia. There is no association between anatomical or clinical symptoms, dyspareunia, chronic pain, and sexual distress. Metacognitive beliefs may have more influence on sexual distress than pain. Alterations of sexual function in women with endometriosis are related to anxiety, depression, sleep problems, excessive body weight, and less physical activity.	Investigate dyspareunia along with the use of tools that evaluate depressive/anxiety symptoms, and emotional and sexual function.	Consider the impact on sexual function in women with endometriosis, and severity of dyspareunia and chronic pelvic pain
13. Pope et al., 2020 [36]	Until December 2014	not mentioned	18	No	Women with endometriosis are at risk for psychosocial disturbances and psychiatric distress. Pain is not associated with the stage of the condition and did not dissipate with treatment, but has a multifactorial etiology, including central sensitization. Chronic pain is associated with negative psychological, physical, and social consequences, depression and anxiety. Long delays in diagnosis and hard-to-manage symptoms increase stress, sexual dissatisfaction, and decreased self-esteem, and increase the risk for psychiatric complications.	Investigate the directionality of the associations between psychosocial disruptions, pain, sexual dysfunction and the effect that fertility has as well as the role that systemic inflammatory conditons may play.	Women with endometriosis should be be screened for potential social, relationship, and psychiatric disturbances.

endometriosis, manage pain, and explore ways to maintain their sexuality, couples and social life [32].

Women with endometriosis express that often they experience stigma, invalidation, and dismissal from health professionals, especially primary care professionals. In the opinion of women, doctors' attitudes and courses of action further delayed diagnosis. Some women had to persuade their primary care providers to refer them to a gynecologist, and they felt vindicated when they were finally diagnosed after having their symptoms dismissed or disbelieved by relatives, friends, colleagues but also health professionals. Diagnosis validated women's experiences and provided a medical term with which they could explain their symptoms to others.

Discussion

The purpose of this review of systematic reviews was to provide a comprehensive overview of the literature assessing the burden that endometriosis represents on women's lives and how it impacts their QoL and wellbeing. In total, this review incorporates the findings of 15 systematic studies, including 6 meta-analyses, that have explored the impact of endometriosis on QoL of women. Findings reflect the complex interaction between different factors, which span from biomedical through psycho-social and medical care. This review may help to emphasize the need for develop integrative research projects as well as to develop comprehensive support and empathy for those affected by the condition. QoL is critical in chronic health problems like endometriosis, as it represents the most important predictor of total direct and indirect costs [52].

Findings from this review provides support for the need to

Table 1. Endometriosis SR QoL evidence table

Authors	Search period	Quality assessment	Number of articles reviewed	Meta-analysis	Findings	Implications for research	Implications for clinical practice
14. Wang et al., 2021 [37]	Until May 2020	Newcastle-Ottawa	44 (31 related to depression, 22 related to anxiety, and 17 using the SF-36.	Yes	Endometriosis is associated with depression, anxiety and reduced QoL, probably due to pain. The psychological effects of endometriosis extend beyond mental health, as patients display somatization, sensitivity, fatigue and insomnia. Endometriosis has persistant long time effects on economic pressure, career development, sexual relations, marital status.	Investigate the directionality of the association between endometriosis and mental health and their effect on QoL, and study psychosocial interventions for endometriosis.	The purpose of treatment for endometriosis should be pain control, improvement of quality of life, prevention of disease recurrence, fertility preservation, and the reduction of anatomical damage. Consider psychological factors for managing the disease and selecting the most appropriate therapy.
15. Young et al., 2015 [38]	not mentioned	Quality assessment criteria developed by the authors	18	No	Endometriosis affects all areas of a woman's life, most notably sex life, social life and work life. Despite the many symptoms associated with endometriosis (such as nausea, diarrhoea and fatigue), pain (including during intercourse) and infertility are mostly investigated. Women report frustration in their relationship with care they receive. Painful sexual intercourse, work productivity losses because of the lack of flexibility to accommodate the needs of women with endometriosis; emotional difficulties to the ramification of living with a complex condition; pain and delays in diagnosis are factors that affect women's QoL.	Investigate women's experience with infertility taking also into account fertility goals; and how endometriosis inhibits social participation. Ensure diversity ensure diversity among participants in terms of age, socioeconomic status, cultural and linguistic background, and sexual identity.	Given the chronic nature of endometriosis, long-term management plans are necessary, with a focus on supporting women and enhancing their experience with healthcare: diagnostic process, impact of symptoms on women's life: explore the impact on sex life.

Table 2.

Quality of included systematic reviews and meta-analysis based on AMSTAR criteria

	Author	PICO	Review methods	Selection of study designs	Comprehensive search	Duplicate selection	Duplicate extraction	Justify exclusions	Detail description of included studies	Risk of bias
1	Barbara	Partial	Yes	Yes	No	Yes	Yes	Yes	Yes	No
2	Barnevald	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Bourdel	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Brasil	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Chaman-Ara	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Delanerolle	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Denny	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes
8	Gambadauro	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
9	Jenabi	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
10	Jia	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Partial	No
11	Jones	Yes	Yes	Yes	Yes	No	No	Yes	Partial	Yes
12	Leite Ferreira	Partial	Yes	Yes	Yes	No	No	Yes	Yes	No
13	Norinho	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
14	Perez Lopez	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15	Pope	Partial	Yes	Yes	Yes	No	No	No	Yes	No
16	Wang	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17	Young	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No
18	Kalfas	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Fig. 2

Interconnections of factors associated with lowered Quality Life of Women with Endometriosis

consider the interconnected and multifactorial effects (physical, mental, and emotional) that extend across women's lifespan, together with the complex relationship with the healthcare system [53]. Throughout a lifetime, these difficulties make it harder for women to reach certain milestones, including completing school or continuing education, deciding on a career path, establishing stable, fulfilling relationships, or starting a family [41].

Chronic pelvic pain, of variable type, duration, and intensity, is a hallmark symptom of endometriosis. Pain may be associated with menstruation, sexual activity, or other activities [54]. However, there is no connection between the severity of the extension of the endometrial lesion or the progression of the disease and pain [55]. The exact mechanisms causing pain in endometriosis are not fully understood but mutual influences between central and peripheral nervous sensitizations play a key role in pain modulation [19]. Chronic systemic inflammation, prostaglandins, and cytokines [56] as well as circulating immune cells, and hormonal changes may contribute to both peripheral – through heightened responsiveness of sensory nerves to pain signals – and central sensitization – involving changes in the central nervous system that amplify the perception of pain reducing pain thresholds [57]. Psychological factors, such as anxiety and depression, may activate the sympathetic nervous system leading to increased release of stress hormones and exacerbate central

sensitization by influencing the perception and processing of pain signals. Pain may also be exacerbated by possible interactions with the emotional distress generated by frequent problems occurring in endometriosis, like deteriorated sexual relationships [58] or infertility [59], and ultimately worsening QoL [60].

Migraine is also frequent in endometriosis, and may also increase excitability of the central nociceptive system resulting in hypersensitivity to sensory inputs [61]. Fatigue and sleep disturbances further impact daily functioning [62]. Fatigue may be related to systemic inflammatory or endocrinology disturbances of endometriosis. However, chronic pain and sleep disturbances can also lead to fatigue.

Negative cognitive patterns developed by women with emotional distress, such as catastrophizing and fear-avoidance behaviors, can amplify the experience of pain [63]. Women with positive coping strategies adapted to stress better report less depression [64], and enjoy a better QoL despite pain or infertility, while women experiencing negative self-image, feelings of loss, hopelessness, alexithymia, worthlessness, frustration, isolation, low self- esteem, and self-efficacy are common emotional responses generating emotional distress, anxiety, and depression that significantly deteriorate their QoL.

To fully understand endometriosis and to improve the effectiveness of medical care, studies that analyze longitudinal quantitative and qualitative data from a systems perspective are needed: a comprehensive and integrative perspective, considering the entire network of biological and psychological interactions, including genetic, epigenetic, and gene expression, immune responses, hormone regulation, and tissue remodeling, toward supporting women in achieving their full life potential.

A critical transformation would also be necessary in the care that women receive. Chronic diseases, like endometriosis, impact and change patients' lives. Endometriosis become part of women's lives, who have to find new ways to cope with their changed situation and develop coping strategies [65]. Women with endometriosis report important deficiencies and frustration with healthcare reflecting a generalized and global deficit in "patient-centered care" in endometriosis [66]. Identifying valid biomarkers for early diagnosis and developing new pharmacological alternatives could prevent the reduction of women's QoL, but would probably not be enough to overcome the negative experience of women with healthcare [41,67]. Current guidelines include pain treatment as a major component of endometriosis management [1], however, they usually provide an assessment of the efficacy of the diverse therapeutic options to control pain but do not consider the diverse implications that endometriosis has for women. Patients with long-term conditions value that health professionals provide with clear and tailored information, build a trust context, support changes, and take into account their perspectives and living circumstances [69].

The chronic nature, long-term burden, substantial recurrence of symptoms, and the impact that the disease has on various aspects of women's lives and the concurrent impact on QoL and consequent direct and indirect costs, suggest the need to redefine endometriosis care [20]. Patient-centered care based on a proactive multidisciplinary coordinated healthcare delivery system, and activation of patients could be appropriate for endometriosis care [68,70].

Endometriosis care should be based on a fundamental principle: maintaining and improving women's QoL. This requires considering the clinical process from two dimensions: early diagnosis and initiation of effective treatment protocols to prevent emotional distress associated with delayed diagnosis and its impact on QoL; and patient-centered long-term management plans focused on supporting women and improving their healthcare experience [71].

Limitations

Although almost all included reviews and meta-analysis had a very good quality, some have some limitations in the definition of patients with endometriosis. The papers included in the reviews had a high degree of heterogeneity concerning study design, patients' demographics, disease extension, stage, specific location, severity and duration, diagnostic methods, treatments received measures of QoL, and data presentation. These factors may influence the impact of endometriosis on QoL but this review has not considered the possible influence that may have on QoL. Typical studies included in the reviews were cross-sectional limiting the possibility of determining the directionality of the complex interactions in endometriosis. Endometriosis has also been linked with diverse comorbidities: this review has not considered either the possible effects of these conditions on endometriosis QoL. This work has not investigated how any healthcare, medical, pharmaceutical or surgical intervention may influence women's QoL. The search strategy included both quality of life and mental and physical well-being, so some of the included reviews focus more on symptom burden and life

circumstances among women with endometriosis.

Finally, this review does not attempt to investigate the complex interactions of the diverse factors identified, but just to describe them. In this sense, it may provide with a relevant source for research aimed at investigating the multi-directional influences among them, as well as to develop new models of care better suited to women's needs.

Conclusion

The strength of the review is the broad scope it had to assess how endometriosis affects women's lives. Pain and infertility are significant symptoms in women with endometriosis. Stress, linked with the presence of depression, anxiety, and co-occurring catastrophic disorders appear to significantly influence QoL. Women with endometriosis are dissatisfied with the care they receive, which needs to be reoriented to address the complex interactions between physical and mental health as well as sexual life. Focusing on biomarkers and early detection is essential, but the implementation of new models of care that offer effective, women-centered, comprehensive clinical, psychological, and sexual management and long-term goals empowering women to develop positive coping strategies are necessary to reduce the harmful consequences of endometriosis [42]. For patients with endometriosis, healthcare providers are of particular importance. While on many occasions they are perceived as barriers, they should be facilitators for improving their QoL, changing the course of the care trajectory, and significantly impacting a patient's care experience [72].

Data availability

No datasets were generated or analysed during the current study.

Abbreviations

QoL: Quality of life

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Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies

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Abstract

Anemia and iron deficiency are important and common comorbidities that often coexist in patients with heart failure. Both conditions, together or independently, are associated with poor clinical status and worse outcomes. Whether anemia and iron deficiency are just markers of heart failure severity or whether they mediate heart failure progression and outcomes and therefore should be treated is not entirely clear. Treatment of anemia in patients with heart failure with erythropoiesis-stimulating agents has been evaluated intensively during the past several years. Unfortunately, these agents did not improve outcomes but were associated with a higher risk of adverse events. Iron deficiency in patients with heart failure can be absolute, when total body iron is decreased, or functional, when total body iron is normal or increased but is inadequate to meet the needs of target tissues because of sequestration in the storage pool. Whereas iron replacement is appropriate in patients with anemia resulting from absolute iron deficiency, it has been unclear whether and how absolute or functional iron deficiency should be treated in nonanemic patients with heart failure. Recently, small studies found that administration of intravenous iron in patients with heart failure and absolute or functional iron deficiency with or without anemia improves symptoms and exercise capacity, but long-term outcomes and safety data are not yet available. In this review, we discuss the causes and pathogenesis of and treatment options for anemia and iron deficiency in patients with heart failure.

Remarkable advances in our understanding of the pathogenesis of heart failure (HF) have led to rational therapies with considerable improvement in patient outcomes.[1] Despite this, however, the prognosis of HF remains poor.[2] Anemia and iron deficiency (ID) are 2 important comorbidities common in patients with HF and are associated with poor clinical status and worse outcomes. If anemia and ID are indeed mediators of poor outcomes in patients with HF, correcting these comorbidities would be attractive and novel therapeutic targets to improve outcomes. Although several small studies showed that use of erythropoiesis-stimulating agents (ESAs) to increase hemoglobin in patients with HF with reduced ejection fraction (HFrEF) is associated with beneficial effects on clinical outcomes,[3,4] the neutral results of the large pivotal RED-HF trial (Reduction of Events With Darbepoetin Alfa in Heart Failure)[5] suggest that anemia by itself is probably not a mediator of poor outcomes but rather a marker of HF severity. Although data from recent trials suggest that treating ID itself may be of benefit, significant knowledge gaps exist in our understanding of when, how, and for how long anemia or ID should be treated in HF and the mechanisms underlying the observed effects of treatment. In this review, we describe the magnitude of the problem of anemia and ID in patients with HF, discuss their impact on long-term outcomes, and examine whether and how they should be managed in light of recent clinical trial data.

Prevalence of Anemia in HF

The prevalence of anemia in patients with HF (defined as hemoglobin <13 g/dL in men and <12 g/dL in women)6 is ≈30% in stable and ≈50% in hospitalized patients, regardless of whether patients have HFrEF or HF with preserved ejection fraction, compared with <10% in the general population (although prevalence increases with age, exceeding 20% in subjects ≥ 85 years old).[3,7–10] Compared with nonanemic patients with HF, anemic patients are older and more likely to be female and to have diabetes, chronic kidney disease (CKD), severe HF with worse functional status, lower exercise capacity, worse health-related quality of life (QoL), greater edema, lower blood pressure, greater requirement of diuretics, and higher neurohormonal and proinflammatory cytokine activation.[3,9,11–13] However, anemic subjects have a better left ventricular (LV) ejection fraction (LVEF): Hemoglobin is inversely

related to LVEF,[8,11,14] and an increase in hemoglobin over time is associated with a decrease, not an increase, in LVEF.[11,15]

Causes of Anemia in HF

In the general elderly population, anemia is caused by nutritional deficiencies (primarily iron), chronic inflammation/CKD, or unexplained anemia of the elderly (a hypoproliferative anemia with blunted erythropoietin response) in approximately one third each, with primary hematologic diseases or other conditions accounting for smaller proportions.[10] Guidance is available on evaluation and management of anemia in the elderly.[10] Identification of absolute ID mandates a search for its cause, particularly gastrointestinal blood loss from benign or malignant conditions.[16]

The pathogenesis of anemia in HF (reviewed previously[3]) is multifactorial (Figure 1). ID is common in HF and is discussed separately. However, deficiencies of hematinic vitamins (B_{12} or folate) are infrequent. Erythropoietin, which stimulates the production of red blood cells (RBCs), is produced primarily within the renal cortex and outer medulla by specialized peritubular fibroblasts and is often abnormal in HF. Low Po_2 is the primary stimulus for erythropoietin production. Renal dysfunction is common in HF, but structural renal disease, which could reduce erythropoietin production, is infrequent. However, an imbalance between oxygen supply and demand related to increased proximal tubular sodium reabsorption caused by low renal blood flow and glomerular filtration rate[17,18] reduces renal Po_2, activates hypoxia-inducible factor-1 α and induces erythropoietin gene transcription. Therefore, erythropoietin levels are increased in proportion to HF severity but are lower than expected for the degree of anemia, suggesting blunted erythropoietin production.[12,19] However, the relationship between renal blood flow and erythropoietin secretion during HF is complex and not fully understood.[20]

Inflammation is an important component of HF. Tumor necrosis factor- α ,interleukin-6 and several other proinflammatory cytokines,[12,21] and C-reactive protein are increased in HF11 and inversely related to hemoglobin level.[13] Interleukin-6 and tumor necrosis factor- α also inhibit renal erythropoietin production by activating transcription factors GATA binding protein 2 (which binds nucleotide consensus sequence GATA in target gene promoters) and nuclear factor κ light-chain enhancer of activated B cells and may explain the blunted erythropoietin response. These cytokines also inhibit bone marrow erythroid progenitor cell proliferation. However, in some patients with HF, erythropoietin levels are excessively elevated, and high erythropoietin levels are associated with worse outcomes.[19]

The renin-angiotensin system plays an important role in erythropoietin pathophysiology through multiple pathways. First, angiotensin II decreases Po_2 by reducing renal blood flow and increasing oxygen demand and thereby stimulates erythropoietin production. Angiotensin II also directly stimulates bone marrow erythroid progenitor cell production. Therefore, angiotensin-converting inhibitors and angiotensin receptor

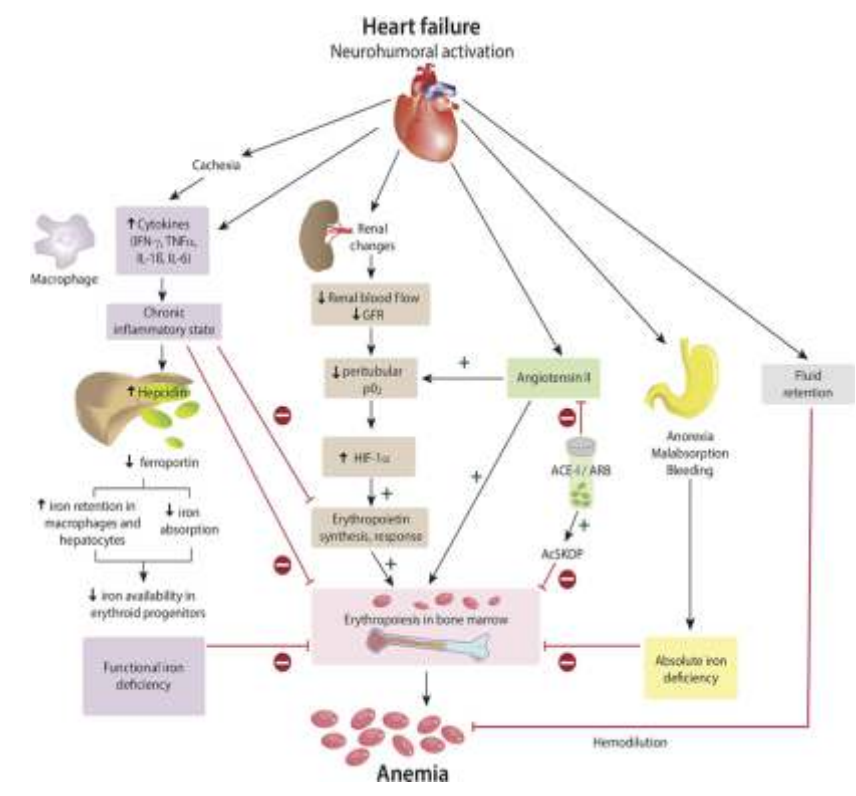

Figure 1. Potential mechanisms involved in the pathogenesis of anemia in heart failure (HF). Multiple, interrelated mechanisms contribute in various degrees to the development of anemia in HF. Of these, functional or absolute iron deficiency, erythropoietin synthesis and response, and the effects of various medications may represent the most important factors. ACE-I indicates angiotensin-converting enzyme inhibitor; AcSDKP, N-acetyl-seryl-aspartyl-lysyl-proline; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; HIF-1α, hypoxia-inducible factor-1α; IFN-γ, interferon-γ; IL, interleukin; and TNF-α, tumor necrosis factor-α.

blockers cause a modest reduction in hemoglobin[11] by decreasing production of erythropoietin[22] and erythroid progenitors and by preventing breakdown of the hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline.[23] Finally, anemia might be related to hemodilution,[20] although clinically euvolemic patients have normal plasma volume,[24] and measurement of hemoglobin reflects "true anemia" as assessed by RBC volume in the vast majority of anemic patients with HF.[14]

Opasich and colleagues[12] identified a specific cause of anemia in only 43% of 148 patients with stable HF. ID was seen in only 5% of patients. In the remaining 57% of patients, proinflammatory cytokine activation, inadequate erythropoietin production, or defective iron utilization was found despite adequate iron stores, indicative of anemia of chronic disease (functional ID). Therefore, an activated proinflammatory state and anemia of chronic disease[25] could be the most frequent underlying cause of anemia in HF. Recent reports show that mutation (eg, clonal hematopoiesis of indeterminate potential) or deficiency of genes that regulate hematopoiesis results in an increase in inflammatory cytokines, including interleukin-1 βand -6, and is associated with an increased incidence of coronary heart disease in humans and with worsening of cardiac remodeling in mice.[26,27] Future studies may further elucidate such mechanistic interactions between the hematopoietic and cardiovascular systems.

Pathophysiological Consequences of Anemia

In patients with very severe anemia (hemoglobin, 4–6 g/dL)[28,29] and normal LV function, usually seen with helminthic infections in developing countries, reduced oxygen-carrying capacity evokes nonhemodynamic and hemodynamic compensatory mechanisms (reviewed previously[3]). There is an increase in RBC 2,3-diphosphoglycerate that displaces the hemoglobin-oxygen dissociation curve to the right, increasing tissue oxygen delivery. A low number of circulating RBCs reduces systemic vascular resistance[28] by decreasing whole-blood viscosity, and low hemoglobin enhances nitric oxide–mediated vasodilation.[29,30] The resulting decrease in arterial blood pressure causes baroreceptor-mediated neurohormonal activation,[28] identical to that seen in low-output HF.[17,18] Increased sympathetic and renin-angiotensin activity decreases renal blood flow and glomerular filtration rate, resulting in renal retention of salt and water with the expansion of extracellular and plasma volumes. Therefore, severe anemia itself may cause the syndrome of high-output HF in subjects with normal LV function, and correction of severe anemia in these patients causes a rapid and complete regression of high-output HF.[28] Although these hemodynamic and neurohormonal responses are observed in severe anemia, it is unclear whether and to what extend these mechanisms are also operative in patients with HFrEF with less severe anemia. Detailed hemodynamic and echo-cardiographic studies have not been reported in patients with HFrEF before and after treating anemia. However, when hemoglobin was increased from 8.5 to 10 to 14 g/dL with erythropoietin in patients with CKD and moderate anemia, cardiac output (7.0 to 6.6 to 5.2 L/min) and LV fractional shortening (36% to 33% to 29%) decreased progressively, proportional to the increase in hemoglobin.[15] Therefore, all this evidence implies that increasing hemoglobin in patients with HFrEF would increase systemic vascular resistance, raise the LV afterload, and cause the LVEF to decrease. This sequence of events could explain the observed inverse relationship of hemoglobin with LVEF[8,9,12] and the findings that an increase in hemoglobin over time is associated with a decrease in LVEF.[9,13] These findings might also explain why correction of anemia in patients with HFrEF has not improved outcomes.

Association of Anemia with Outcomes

Anemia is independently associated with increased mortality and hospitalizations in patients with both HFrEF and HF with preserved ejection fraction.[3,7,8,31] The association of hemoglobin level with mortality is not linear, and most of the increased risk occurs at low hemoglobin.[3,32,33] Some studies have reported a J-shaped relationship between hemoglobin and mortality in the normal population[34] and patients with coronary artery disease,35 acute coronary syndromes,36 and HF.[31,33] The lowest mortality risk was observed in the hemoglobin range of 13 to 16 g/dL, and the risk increased with hemoglobin concentrations below or above this range. Thus, the concern is that excessive increases in hemoglobin may be associated with increased mortality. In a meta-analysis of 33 studies involving >150 000 patients with HF, anemia doubled the relative risk of death.[37] A similar relationship was observed in patients with new-onset anemia and in patients with a decrease in hemoglobin over time.[11] Moreover, a spontaneous increase in hemo- globin and the resolution of anemia over time were associated with a better

prognosis, similar to that of patients without anemia.[38] Anemia and CKD often coexist in patients with HF. Whereas anemia doubles the risk of death in patients with HF, the adjusted risk of death is further increased 1.5-fold in the presence of CKD.[39] These findings, however, do not clarify whether anemia is a mediator or just a marker of HF severity.

Mechanisms Associated with Poor Outcomes in HF with Anemia

Multiple mechanisms appear to contribute to poor outcomes in these patients. Reduced oxygen delivery to metabolizing tissues in anemic subjects triggers a host of hemodynamic, neurohormonal, and renal alterations,[28] leading to increased myocardial workload, which could cause adverse LV remodeling and LV hypertrophy.[40,41] Moreover, patients with HF and anemia have several comorbidities, including CKD, cardiac cachexia-associated poor nutritional status, and low albumin,[8,11,39] all of which could worsen outcomes. Finally, the neurohormonal and proinflammatory cytokine activation seen in patients with HF may have diverse deleterious consequences.[13,21,28]

Treatment Options

Should Anemia in Patients With HF Be Treated?

Most of the aforementioned observational studies suggest that anemia is common in patients with HF and is associated with poor clinical status and worse prognosis. It is therefore reasonable to consider whether treatment of anemia might improve outcomes. Unfortunately, few options are available to increase hemoglobin.

Whereas packed RBC transfusion can be used as a short-term therapy, transfusions are associated with many risks and provide only temporary benefit. Kao and colleagues[42] examined the large public discharge database on 596 456 patients admitted for HF. Anemia was present in 27% of patients with HF. Whereas untreated anemia was associated with ≈10% increased adjusted risk of mortality, the adjusted risk of mortality was ≈70% higher in anemic patients with HF who received transfusions. Although these data might raise serious concerns about the potentially harmful effects of transfusing patients with HF, there are important limitations in the analysis of this database. For example, the severity of anemia and clinical reasons for which a transfusion was required were not available and adjusted for. These and other residual measured and unmeasured confounders could have affected the results of the multivariable analysis. Prospective randomized controlled trials (RCTs) are required to clarify the role of packed RBC transfusions in patients with anemia and HF. Nevertheless, the TRICS III trial (Transfusion Requirements in Cardiac Surgery) in moderate- to high-risk patients undergoing cardiac surgery recently found that the composite primary outcome of death resulting from any cause, myocardial infarction (MI), stroke, and new-onset renal failure with dialysis occurred in 11.4% of those randomized to receive intraoperative or postoperative transfusions for hemoglobin <7.5 g/dL compared with 12.5% in the more liberal strategy of transfusions for hemoglobin <9.5 g/dL, indicating that, in such patients, a restrictive transfusion strategy is noninferior to a liberal strategy.[43] These findings suggest that packed RBC transfusion in patients with HF and anemia is not necessarily beneficial and may even be associated with worse outcomes. Routine blood transfusion in asymptomatic patients, particularly those with nonacute anemia, therefore cannot be recommended.[6] Because the hemoglobin threshold for packed RBC transfusions varies between clinical practice guidelines (summarized by Goodnough and Schrier[10]), careful consideration of individual factors, including age, comorbidities, and need for surgical intervention, is advisable when determining clinical indications for transfusion in patients with HF.

In the routine treatment of anemia, identification and correction of hematinic deficiencies (iron, B_{12}, or folate) or hypothyroidism, if present, should clearly be the first step. However, because many patients are thought to have anemia of chronic disease, stimulating erythropoiesis with ESAs has been investigated.

Treatment with ESAs

Between 2000 and 2010, 13 small uncontrolled or randomized placebo-controlled studies tested the effects of increasing hemoglobin with ESAs (summarized in Table I in the online-only Data Supplement). Most studies found symptomatic improvement with use of ESAs. In 2011, Kotecha and colleagues4 published a meta-analysis based on 11 of these RCTs of 794 patients comparing any ESA with placebo with 2 to 12 months of follow-up. Nine studies were placebo controlled and 5 were double-blind. Five studies used epoetin and 6 used darbepoetin. ESAs improved exercise duration by 96.8 seconds (P=0.04) and 6-minute walk distance (6MWD) by 69.3 m (P=0.009) compared with controls (Figure I in the online-only Data Supplement). Significant changes were also observed in peak oxygen consumption (Vo_2; 2.29 $mL \cdot kg^{-1} \cdot min^{-1}$; *P*=0.007), New York

Heart Association (NYHA) class (- 0.73; *P*<0.001), LVEF (5.8%; *P*<0.001), BNP (brain natriuretic peptide; - 227 pg/mL; *P*<0.001), and QoL indicators with a mean increase in hemoglobin of 2 g/dL. HF-related hospitalizations were reduced by 44% (*P*=0.005) with ESA therapy, but the reduction in all-cause mortality (42%) was of borderline significance (*P*=0.047; Figure II in the online-only Data Supplement). Adverse effects of ESAs were rare, with no significant increase in the development of hypertension (odds ratio, 1.37; 95% confidence interval [CI] 0.65–2.87; *P*=0.41), stroke (odds ratio, 1.70; 95% CI, 0.52–5.62; *P*=0.38), MI (odds ratio, 0.67; 95% CI, 0.28–1.61; *P*=0.37), and thromboembolic events (odds ratio, 0.60; 95% CI, 0.17–2.11; *P*=0.43). In contrast, use of darbepoetin in patients with moderate to severe HFrEF was not associated with any increase in exercise capacity in STAMINA-HeFT (Study of Anemia in Heart Failure Trial), the largest (n=319) of these small studies.[44]

The encouraging results of these small studies were not supported by the large pivotal RED-HF trial, published in 2013.[5] RED-HF was a double-blind placebo-controlled trial that randomized 2278 patients with HFrEF, NYHA class II to IV HF, LVEF ≤40%, and mild to moderate anemia (hemoglobin, 9.0–12.0 g/dL) receiving guideline-recommended HF therapy. Patients with ID defined as a transferrin saturation (TSAT) of <15%, unless corrected, were ineligible. Patients with a history of bleeding or other correctable causes of anemia, serum creatinine >3 mg/dL, or blood pressure >160/100 mm Hg were excluded. Patients were randomized 1:1 to receive either darbepoetin alfa to achieve a hemoglobin target of 13 g/dL or placebo. Patients in the darbepoetin group received a starting dose of 0.75 µg/kg every 2 weeks until a hemoglobin of 13.0 g/dL was reached on 2 consecutive visits. Thereafter, patients received monthly darbepoetin to maintain a hemoglobin of 13.0 g/dL but not exceeding 14.5 g/dL. Iron indexes were assessed 3 monthly during the trial. If TSAT fell below 20%, oral and, if necessary, intravenous iron was administered. Patients had a median age of 72.0 years; 41% were women; 65% had NYHA class III or IV HF; the median LVEF was 31%; and the median estimated glomerular filtration rate was 45.7 mL/1.73m^2 body surface area. Baseline median hemoglobin was 11.2 g/dL in both groups. One month after randomization and throughout the study thereafter, median attained hemoglobin remained ≈1.5 g/dL higher in the darbepoetin group (13.0 g/dL; interquartile range, 12.4–13.4 g/dL) compared with the placebo group (11.5 g/dL; interquartile range, 10.7–12.2 g/dL; *P*<0.001). After a median follow-up of 28 months, darbepoetin had no effect on the primary composite outcome of death resulting from any cause or hospitalization for worsening HF (hazard ratio [HR] 1.01; 95% CI, 0.90–1.13; P=0.87) or on its individual components. The lack of any effect of darbepoetin was consistent across all prespecified subgroups examined; no subgroup experienced any benefit from darbepoetin. There was also no significant difference in any secondary outcome, including fatal or nonfatal MI, fatal or nonfatal strokes, hypertension, and HF. More patients had fatal or nonfatal strokes in the darbepoetin than in the placebo group, although the difference was not significant. This finding becomes important because thromboembolic adverse events were significantly higher in the darbepoetin (13.5%) compared with the placebo (10.0%; *P*=0.01) group. Cancer-related adverse events were similar in the 2 groups. Although the rate of clinical events was not reduced by darbepoetin, treatment of anemia improved the Overall Summary and Symptom Frequency scores on the Kansas City Cardiomyopathy Questionnaire. However, the average between-group difference and the difference in the proportion of patients with a clinically meaningful improvement in these scores were of questionable importance. It is important to emphasize that all patients were iron repleted at baseline. The darbepoetin group received more iron during the study because of greater iron requirement for erythropoiesis. Neither group became ID during the study.

In summary, this large pivotal trial failed to confirm the results of previous smaller studies that treating mild to moderate anemia in patients with HFrEF with ESAs improved clinical outcomes. Although an increase in hemoglobin was associated with a modest improvement in QoL, this was of questionable importance, particularly because the use of darbepoetin was associated with a significant increase in thromboembolic events. Similar findings in CKD and cancer populations for cardiovascular safety have raised concerns about the use of ESAs to increase hemoglobin to relatively higher levels.[45] Therefore, a brief examination of the CKD data may be helpful.

Are There Real Risks of Increasing Hemoglobin With ESA Therapy?

In the 1990s, several trials were conducted to assess whether complete normalization of hemoglobin with ESAs would produce additional benefits in patients with CKD. NHCT (Normal Hematocrit Cardiac Trial) randomized 1223 patients with CKD on hemodialysis to epoetin-alfa to

achieve a hematocrit of 45% versus 30%.[46] The study was terminated early because of a trend to increased risk of the composite of death or nonfatal MI and a higher incidence of vascular access thrombosis in the normal hematocrit group (39% versus 29%; P=0.001). Two trials published more recently (CREATE [Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta][47] and CHOIR [Correction of Hemoglobin and Outcomes in Renal Insufficiency][48]) further raised serious concerns about the cardiovascular safety of higher hemoglobin with the use of ESAs in patients with CKD. In CREATE, 603 patients (hemoglobin, 11.6±0.6 g/dL) were randomized to epoetin - beta to normalize hemoglobin (13.0–15.0 g/dL) or to epoetin only if hemoglobin declined to <10.5 g/dL. There was a trend to an increase in the relative risk of mortality (34%; P=0.14) with higher hemoglobin. The CHOIR trial randomized 1432 patients (hemoglobin, 10.1±0.9 g/dL) to epoetin to achieve a hemoglobin of 13.5 or 11.3 g/dL. The trial was stopped early for presumed futility but showed a 34% (*P*=0.03) increase in the composite of death, MI, hospitalization for HF, and stroke in the high hemoglobin group. Subsequently, a meta-analysis of 9 randomized trials, including the 3 trials mentioned earlier, compared the low and high hemoglobin target strategies and found a relative increase in all-cause mortality of 17% (*P*=0.03), arteriovenous access thrombosis of 34% (*P*=0.0001), and poorly controlled blood pressure of 27% (P=0.004) in the high hemoglobin groups.[45]

With that background, TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy),[49] the largest RCT, was designed to compare darbepoetin with placebo (achieved hemoglobin, 12.5 versus 10.6 g/dL) in 4038 patients with diabetes mellitus and CKD. Unlike previous trials that compared using ESA to achieve a high or a low hemoglobin, TREAT tested the more appropriate strategy of comparing an ESA with placebo. Darbepoetin had a neutral effect on the 2 primary composite outcomes (death or a cardiovascular event; death or a renal event) but was associated with a doubling of the risk of stroke. In a post hoc analysis of the TREAT trial of 1347 patients (33.4%) with HF at baseline, darbepoetin also had a neutral effect on all-cause mortality (HR, 1.10; 95% CI, 0.93–1.29) or nonfatal HF events (HR, 1.02; 95% CI, 0.87–1.20), similar to the entire cohort.[50] Therefore, increasing hemoglobin to relatively higher levels in patients with CKD is associated with either neutral or deleterious effects on cardiovascular morbidity and mortality with increases in thrombotic and stroke risk. Consequently, the current (2017) US Food and Drug Administration–approved label for ESAs carries Black Box statements for patients with CKD:

> (a) In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL, (b) No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks, and (c) Use the lowest ESA dose sufficient to reduce the need for RBC transfusions.[50a]

Consistent with the aforementioned guidance, Kidney Disease Outcomes Quality Initiative guidelines recommend interrupting or holding ESAs at a hemoglobin of 11.0 g/dL in patients with CKD.[51] The US Food and Drug Administration and the Kidney Disease: Improving Global Outcomes guidelines[6] recommend initiating ESA therapy at a hemoglobin cutoff of <10 g/dL in patients with CKD on dialysis and individualizing ESA initiation at this level in patients with CKD not on dialysis, although the rationale for initiating ESAs at hemoglobin <10 g/dL rather than an even lower hemoglobin is not entirely clear if the only indication is to avoid transfusions. However, in a subgroup analysis of 816 TREAT-like patients with CKD and diabetes mellitus in RED-HF with baseline hemoglobin 11.0±0.8 g/dL, the use of darbepoetin to raise hemoglobin had an overall neutral effect on mortality (HR, 0.89; 95% CI, 0.73–1.09) but was associated with a 2-fold increase in stroke risk (HR, 2.07; 95% CI, 0.98–4.38), supporting the US Food and Drug Administration and Kidney Disease: Improving Global Outcomes guidelines on interrupting/holding ESAs at an upper level of hemoglobin $\geq$11 g/dL.

The overall consequences of correcting anemia in HF with ESAs are a tradeoff between the favorable effects of improving oxygen delivery and the putative cardioprotective effects of ESAs[52] and the unfavorable effects of higher hemoglobin on increasing viscosity, vascular resistance, and blood pressure and of ESAs on hypercoagulability.[11,28,29] Moreover, the starting, achieved, change-in, and rates of rise in hemoglobin and the dose of ESA may influence the net effect of treatment.[53]

Taken together, data from small, short-term trials and meta-analyses of ESA in HF and the pivotal RED-HF trial suggest that correcting anemia with ESAs does not improve outcomes but does increase the risk of thromboembolic events. The findings do not support the use of these agents to increase hemoglobin in patients with HFrEF and mild to moderate anemia to higher levels. Therefore, although

HF guidelines recommend a diagnostic workup to seek and treat correctable causes of anemia, they provide a Class III (no benefit), Level of Evidence BR recommendation: "In patients with HF and anemia, ESAs should not be used to improve morbidity and mortality."[1]

Iron Deficiency and HF

Normal Iron Metabolism and Homeostasis

Iron is the most important essential trace element in the body. Apart from its role in maintaining the oxygen-carrying capacity of the blood through erythropoiesis, iron is independently crucial for oxygen transport, delivery, and utilization. It is a key component of hemoglobin, myoglobin, and diverse enzymes involved in cellular respiration, oxidative phosphorylation, citric acid cycle, nitric oxide generation, oxygen radical production, and several critical body functions.[54] Metabolic active cells, including myocytes and skeletal muscle cells, are dependent on iron for their function and structural integrity.[55,56] Iron distribution and metabolism in healthy individuals are illustrated in Figure 2.

Iron Deficiency in HF

ID is a very common comorbidity in HF regardless of sex, race, anemia, and LVEF.[57,58] Overall, nearly 50% of patients with HF with or without anemia have low levels of available iron.[59,60] ID can be absolute, when total body iron is decreased, or functional, when total body iron is normal or increased but inadequate to meet the needs of target tissues because of sequestration in the storage pool (iron maldistribution; Figure 3).

Diagnosis of ID

Figure 2.

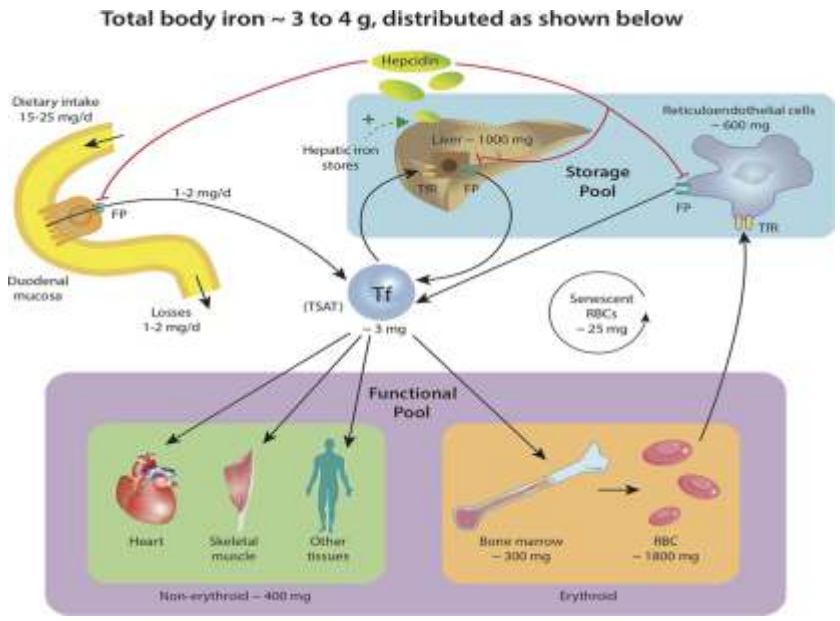

Figure 2. Normal iron metabolism and homeostasis. The total body iron in healthy men is 35 to 45 mg/kg; it is often lower in menstruating women. Approximately 1.5 to 2 g of this is in the erythroid pool and ≈400 mg is in myoglobin, various enzymes, and other tissues (nonerythroid pool). About 1.6 g is in the storage pool: 1.0 g in the liver and 0.6 g as ferritin or hemosiderin in the RES. Iron balance is maintained by intestinal absorption of 1 to 2 mg/d (5%–10% of dietary intake of 15–25 mg), equivalent to losses from the gut, skin, urine, and menstrual bleeding. Destruction of senescent red cells by the RES recycles ≈25 mg iron daily, sufficient for the production of new red cells. FP expressed on the basolateral membrane of duodenal enterocytes, hepatocytes, and RES cells regulates intestinal iron absorption and the release of iron from the liver or RES. Hepcidin produced by the liver binds to ferroportin and induces its internalization and degradation, serving as the "master regulator" of ferroportin expression and iron absorption and distribution. Normally, hepcidin levels are regulated by plasma iron, iron stores, and erythropoietic activity and demand. Increasing hepatic iron upregulates hepcidin, inhibiting further intestinal iron absorption and release from tissue stores. Conversely, increasing erythropoietic activity, which requires iron, suppresses hepcidin via production of erythroferrone, increasing intestinal iron absorption and export from iron stores. In the blood, Tf binds and transports ≈3 mg iron (reflected in TSAT) that is physiologically usable by cells after uptake via the TfR-1. FP indicates ferroportin; RBC, red blood cells; RES, reticuloendothelial system; Tf, transferrin; TfR-1, transferrin receptor; and TSAT, transferrin saturation.

In the absence of inflammation or chronic disease, serum ferritin correlates strongly with body iron stores: 1 µg/L serum ferritin corresponds to ˜10 mg tissue iron. Serum ferritin of 100 µg/L thus reflects ˜1 g tissue iron stores. In healthy individuals, ferritin below ˜30 µg/L and TSAT below ˜16% define ID.[64] In inflammatory states (including HF), however, ferritin is nonspecifically elevated as an acute-phase reactant, making identification of absolute or functional ID complex and uncertain.[16,65] Consequently, in patients with HF, ferritin <100 µg/L or <300 µg/L if TSAT is <20% has been used to include patients with both absolute and functional ID in iron replacement trials.

Table 1 summarizes tests

Figure 3.

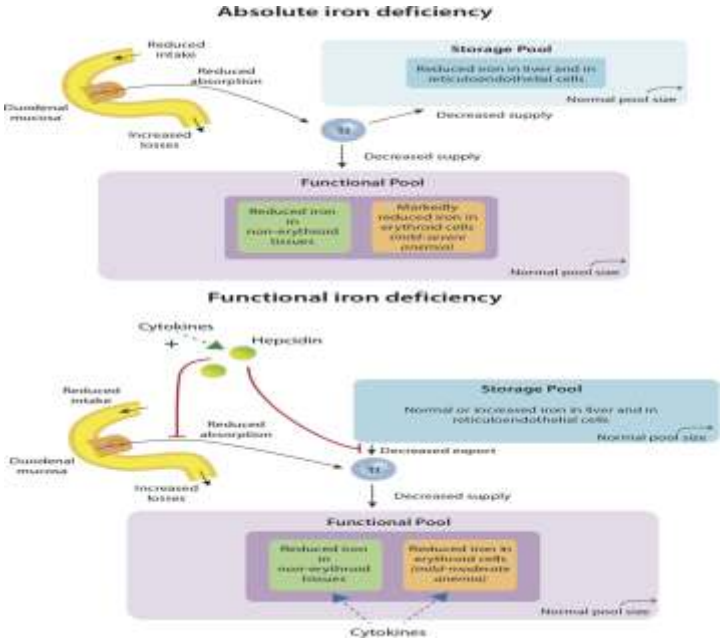

Figure 3. Absolute and functional iron deficiency. Iron deficiency can be absolute, when total body iron is decreased, or functional, when total body iron is normal or increased but sufficient iron is not available to target tissues because of iron sequestration in the storage pool (iron maldistribution). Both storage and functional pools are smaller in absolute iron deficiency, whereas only the functional pool is reduced in functional iron deficiency. Either condition can occur independently or coexist in an individual patient. Absolute iron deficiency in HF can result from reduced intake because of anorexia, cardiac cachexia, impaired iron absorption resulting from intestinal edema, and hepcidin-induced downregulation of iron transporters such as ferroportin. Other causes include gastrointestinal blood losses related to use of aspirin, antiplatelet agents, or anticoagulants or important coexisting conditions such as malignancies of the gastrointestinal or genitourinary tract.61–63 Functional iron deficiency in HF results from mechanisms similar to those responsible for the anemia of chronic disease or inflammation.59,61,63 HF is associated with increased levels of inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-18, and tumor necrosis factor-α. These cytokines, particularly IL-6, upregulate hepatic hepcidin production via Janus kinase/signal transducer and activator of transcription 3, which binds, internalizes, and degrades ferroportin. This results in impairment of iron absorption into the blood from enterocytes and entrapment of iron in the storage pool (liver and reticuloendothelial cells). Together, these effects result in relative iron depletion in erythroid cells and nonerythroid tissues (functional pool). Inflammatory cytokines also blunt renal erythropoietin production and erythroblast responsiveness to erythropoietin. Erythroblast proliferation is also directly inhibited by elevated levels of hepcidin, further impairing hemoglobin synthesis. HF indicates heart failure; and Tf, transferrin.

available to diagnose ID.[65,71,72] The soluble transferrin receptor (sTfR) level is increased in ID and is not affected by inflammation. Among the blood parameters, sTfR or TSAT may have the strongest correlation with bone marrow iron depletion.[69,70] Although not commonly available in clinical practice, sTfR, sTfR: log (ferritin) ratio, or hepcidin levels may provide better discrimination of absolute and functional ID.[73] Improving the diagnostic accuracy of tests to identify ID remains an area of active investigation.

Bone Marrow Iron Content for the Diagnosis of ID

Bone marrow iron depletion is very specific for ID, is not influenced by inflammation, and remains the gold standard for the definitive diagnosis of ID.[16] However, its clinical applicability is limited because its assessment is invasive, expensive, somewhat subjective (relying on staining and observer interpretation), and difficult to perform serially. Few studies have correlated bone marrow iron with blood parameters of ID in HF. One small study in 37 hospitalized patients with decompensated HF and anemia found depleted bone marrow iron in 73% of patients despite normal serum iron, ferritin, and erythropoietin.[74] Unpredictable and inconsistent variability in measured levels of ferritin and TSAT75 may partly explain discrepancies between blood parameters and bone marrow iron. Recently, Grote Beverborg and colleagues[69] examined bone marrow iron in a relatively small cohort of 42 patients with HFrEF undergoing coronary artery bypass surgery and found bone marrow ID in 17 patients (40%). The commonly used definition of ID (ferritin <100 µg/L or 100–300 µg/L with TSAT <20%) had a sensitivity of 82% and a specificity of 72% for true ID. As single parameters, TSAT ≤19.8% and serum iron ≤13 µmol/L (≤72.6 µg/dL) were highly correlated with absolute or functional bone marrow ID (sensitivity, 94% for both; specificity, 84% and 88%, respectively; P<0.05). TSAT was calculated with the use of transferrin rather than total iron-binding capacity in the denominator (thus, TSAT=iron/ transferrin). It is notable that patients with low ferritin (<100 ng/mL) but normal TSAT (>20%) did not have bone marrow ID. In 387 patients with HF, TSAT or serum iron (but not ferritin) below these cutoffs was independently associated with higher all-cause mortality (P=0.015 and P=0.022, respectively), underscoring their prognostic significance. An individual patient data meta-

Table 1. Laboratory Tests Available for the Diagnosis of ID and Their Sensitivity and Specificity

Parameter	Normal Range*	Absolute Iron Depletion Without Anemia	Absolute ID With Anemia	Functional ID Without or With Anemia	Sensitivity, %†	Specificity, %†
Bone marrow iron stores	Normal	Absent from both erythroid progenitors and reticuloendothelial cells	Absent from both erythroid progenitors and reticuloendothelial cells	Low in erythroid progenitors, normal in reticuloendothelial cells	Gold standard	Gold standard
Hemoglobin, g/dL	M: 13.5–17.5; F: 12.0–15.5	N	↓ / ↓↓	N / ↓	Poor	Poor
Mean red cell volume, fL	M: 81–95; F: 82–98	N / ↓	↓ / ↓↓	N / ↓	Poor	88.3
Ferritin, µg/L	M: 24–336; F: 11–307	≈20	<15–30	N / ↑	35–48	75–100
Serum iron, µg/dL‡	M: 50–150; F: 35–145	↓	↓	↓	Poor	Poor
Total iron binding capacity, µg/dL, or transferrin, mg/dL	250–400; 200–360	N	↑	N / ↓	Poor	Poor
TSAT, %‡	≈15–50	≈30	<15	N / ↓	59–88	63–78
sTfR, mg/L§?	1.8–4.6	↑	↑↑	↓	70–81	59–71
sTfR:log (ferritin) ratio?	≤1.0366	↑	↑↑	↑	81	83
Hepcidin, ng/mL?[67]	M: 29–254; F: 17–286	N	↓	↑	50–92.5	85–90
ZPP, µmol ZPP/mol heme?[68]	<70	↑	↑	↑	38	87
Hypochromic RBC, %	<2.5	N / ↑	↑	N / ↑	64–78	77–78
CHr, pg	≈28–35	N / ↓	↓	N / ↓	53–78	53–100

Chr indicates reticulocyte hemoglobin content; F, female; ID, iron deficiency; M, male; MCV, mean red cell volume; N, normal; NA, not available; RBC, red blood cells; RES, reticuloendothelial cell; sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; TSAT, transferrin saturation; and ZPP, red cell zinc protoporphyrin.

*
The normal ranges for various parameters may vary in individual laboratories.

†
Data from von Haehling and colleagues65 or as otherwise referenced.

‡
Grote Beverborg and colleagues69 reported that the sensitivity and specificity (as single parameters) of TSAT were 94% and 84%, respectively, and for serum iron were 94% and 88%, respectively, for absolute or functional ID, confirmed by bone marrow examination in patients with heart failure undergoing coronary artery bypass grafting.

§
Jankowska and colleagues70 reported that the sensitivity and specificity of sTfR were 67% and 97%, respectively, for ID confirmed by bone marrow examination in patients with coronary artery disease.

?
These tests may not be routinely available in clinical laboratories.

analysis of 4 clinical trials (n=839) of the effects of intravenous ferric carboxymaltose (FCM) in patients with HFrEF found that TSAT ≤19.8% (but not serum iron [interaction P=0.077] or ferritin) identified patients who experienced reduction in cardiovascular hospitalizations and mortality (risk reduction 0.45 [95% CI, 0.29–0.71] versus 1.55 [95% CI, 0.69–3.47] for patients with TSAT >19.8%; interaction P=0.009).[69] Thus, although the conventional definition of ID (ferritin <100 µg/L or 100–300 µg/L with TSAT <20%) performs reasonably well in diagnosing ID in patients with HF, a single parameter (TSAT ≤19.8% alone) performed at least as well in detecting true ID and identified subjects who responded to intravenous FCM on retrospective analysis. Ferritin levels may be more relevant for monitoring iron overload rather than diagnosis of ID in patients with HF.

Pathophysiological Consequences of ID

Although ID is associated with several clinical consequences related to erythropoiesis, chronic ID by itself, independently of anemia, impairs oxidative metabolism, cellular energetics, and immune mechanisms that can cause structural and functional change in the myocardium, decreasing oxygen storage in myoglobin and reducing tissue oxidative capacity, leading to mitochondrial and LV dysfunction.[76,77] Myocardial iron stores may be depleted in HF but correlate poorly with circulating markers of iron stores.[78] Melenovsky and colleagues[55] found that myocardial iron content in 91 patients with HF was lower than in 38 normal control organ donors (156±41 versus 200±38 µg/g dry weight, respectively; P<0.001). Reduced myocardial iron correlated with lower activity of

citric acid cycle enzymes (aconitase and citrate synthase); diminished reactive oxygen species (ROS) protecting enzymes, including catalase, glutathione peroxidase, and superoxide dismutase; and reduced mitochondrial oxygen consumption. Myocardial ID in patients with HF might therefore further promote glucose rather than fatty acid utilization and, coupled with impaired protection against ROS, contribute to myocardial dysfunction and adverse remodeling. That severe myocardial ID can cause mitochondrial dysfunction is supported by the observation that isolated cardiac ID (induced by myocardial transferrin receptor 1 inactivation) induces mitochondrial respiratory dysfunction and fatal cardiomyopathy in mice.[79] Iron supplementation partly prevented these adverse effects, suggesting a possible mechanism for the clinical benefit of intravenous iron in patients with HF (discussed below).

Impact of ID on Exercise Capacity, QoL, and Outcomes

Several studies showed that ID in patients with HF is associated with reduced exercise capacity, impaired QoL, and poor prognosis independently of anemia and LVEF.[58,60,80,81] In a prospective study on 443 patients with stable HF and a mean LVEF of 26%, ID (serum ferritin <100 µg/L or 100–300 µg/L with TSAT <20%) was present in 35%. Peak Vo_2 was significantly lower in those with ID compared with those without ID (peak Vo_2, 13.3±4.0 versus 15.3±4.5 mL·min^{-1}·kg^{-1}). In multivariable models, ID was associated with reduced peak Vo_2 independently of demographics and clinical variables, including anemia.[80]

Several observational studies have shown that the presence of ID in patients with HF with and without anemia is significantly associated with mortality independently of other prognostic factors.[57,60,82] In 546 Polish patients with HF, absolute or functional ID (ferritin <100 µg/L or 100–300 µg/L with TSAT <20%) was present in 37% of patients; 57% were anemic and 32% were not anemic.[82] On multivariable analysis, ID but not anemia was associated with a higher risk of death or heart transplantation (HR, 1.58; 95% CI, 1.14–2.17; *P*<0.01). In a pooled international cohort comprising 1506 patients with HF, anemia, higher NYHA class, higher NT-proBNP (N-terminal pro-BNP) levels, lower RBC mean corpuscular volume, and female sex predicted ID. ID but not anemia remained a strong independent predictor of mortality in multivariable models that included NYHA class and NT-proBNP (HR, 1.42; 95% CI, 1.14–1.77; P=0.002),[60] underscoring the importance of ID over anemia in predicting outcomes in HF. Similar findings were reported in an Asian cohort.[57] Adverse effects of ID on exercise capacity in patients with HF may therefore be a consequence of the nonhematopoietic (rather than erythroid) effects of iron on energy metabolism and myocardial structure and function.[76–79] This possibility needs to be examined prospectively.

Intravenous Iron Replacement Therapy in HF

Although the role of ID in HF pathogenesis is only just being clarified, investigators have been testing the safety and efficacy of intravenous iron in patients with HFrEF and ID for >10 years. As of 2017, 8 studies (2 small uncontrolled studies and 6 RCTs [3 small and 3 medium-sized trials]) reported the effects of intravenous iron in patients with HFrEF (Table II in the online-only Data Supplement). The primary objective of these studies was to investigate the safety and efficacy of intravenous iron on exercise capacity, NYHA class, and QoL. Clinical events were recorded as safety and secondary outcomes. Five studies (n=103 patients) used intravenous iron sucrose; 3 studies (n=504) used FCM. Therefore, the highest level of evidence for the safety and efficacy of intravenous iron therapy in patients with HFrEF and ID is with FCM. Four meta-analyses of published data reported the effects of intravenous iron on the secondary outcomes of HF hospitalizations and mortality.[83–86] In addition, a robust meta-analysis of intravenous FCM on mortality and hospitalizations using individual patient data extracted from 4 RCTs, including data from 2 small previously unreported studies (FER-CARS-01 and EFFICACY-HF [Effect of Ferric Carboxymaltose on Exercise Capacity and Cardiac Function in Patients With Iron Deficiency and Chronic Heart Failure]), has recently been published.[87]

Bolger and colleagues[88] first reported an uncontrolled open-label study of 16 anemic (hemoglobin ≤ 12 g/dL) patients with HF given intravenous iron sucrose for 12 to 17 days and followed up for 92±6 days. Iron treatment increased serum iron, ferritin, TSAT, and hemoglobin (11.2±0.7–12.6±1.2 g/dL; P=0.0007) and improved NYHA class, Minnesota Living With Heart Failure Questionnaire score, and 6MWD. In another open-label study, intravenous iron sucrose treatment in 32 patients with anemia and ID was associated with favorable effects on LV remodeling and NYHA functional class.[89]

The first randomized study was a double-blind, placebo-controlled trial in 40 anemic patients with HF.[90]

Table 2. Intravenous Iron Preparations Available for Clinical Use in the United States and Europe

Iron Preparation	Maximal Single Dose in Adults*	Administration in Adults*	Indications*	Most Common Adverse Effects	Evaluated in Heart Failure†
Ferric carboxymaltose	750 mg. Can be repeated at least 7 d later for a maximal total dose of 1500 mg per course. Courses can be repeated if ID recurs	Slow intravenous push at 100 mg/min or diluted in normal saline and infused over at least 15 min.	Treatment of ID anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron or those who have non–dialysis-dependent chronic kidney disease.	Nausea, hypertension, flushing, hypophosphatemia, and dizziness. Warnings: hypersensitivity reactions, hypertension.	Yes
Iron sucrose	100–400 mg, depending on clinical setting. Limited experience with 500 mg. Doses can be repeated at various intervals, depending on setting. Courses can be repeated if ID recurs.	Slow intravenous injection of 100–200 mg over 2–5 min. Infusion schedules vary depending on dose and setting.	Treatment of ID anemia in patients with chronic kidney disease.	Diarrhea, nausea, vomiting, headache, dizziness, hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection site reactions, chest pain, and peripheral edema. Warnings: hypersensitivity reactions, hypotension, iron overload.	Yes
Sodium ferric gluconate	125 mg (adults). 1.5 mg/kg (pediatric patients).	Adults: slow intravenous injection at 12.5 mg/min or diluted in normal saline and infused over 1 h per dialysis. Pediatric patients: dose diluted in normal saline and infused over 1 h per dialysis.	Treatment of ID anemia in adult patients and in pediatric patients ≥6 y of age with chronic kidney disease receiving hemodialysis who are receiving supplemental erythropoietin therapy.	Nausea, vomiting and/or diarrhea, injection site reaction, hypotension, cramps, hypertension, dizziness, dyspnea, chest pain, leg cramps and pain. In patients 6–15 y of age: hypotension, headache, hypertension, tachycardia, and vomiting. Warnings: hypersensitivity, hypotension, iron overload, benzyl alcohol toxicity.	No
Ferumoxytol	510 mg. Second 510-mg dose 3–8 d later.	Diluted in normal saline or 5% dextrose and infused over at least 15 min.	Treatment of ID anemia in adults with chronic kidney disease.	Diarrhea, nausea, dizziness, hypotension, and constipation. Black Box warning: fatal and serious hypersensitivity reactions, including anaphylaxis.	No

Table 2. Intravenous Iron Preparations Available for Clinical Use in the United States and Europe

Iron Preparation	Maximal Single Dose in Adults*	Administration in Adults*	Indications*	Most Common Adverse Effects	Evaluated in Heart Failure†
Iron dextran	100 mg daily. Total dose calculated on the basis of body iron deficit.	Slow intravenous injection not to exceed 50 mg/min.	Treatment of ID anemia when oral administration is unsatisfactory or impossible.	Most common side effects not separately listed in the label. Black Box warning: fatal and serious hypersensitivity reactions, including anaphylaxis.	No
Iron isomaltoside‡	20 mg iron/kg. Cumulative dose based on Ganzoni formula.	Intravenous injection not to exceed 250 mg iron/min; dose ≤ 500 mg 3 times a week; diluted in normal saline. Intravenous infusion: diluted in normal saline and infused over 15 min (dose ≤ 1000 mg) or 30 min (dose > 1000 mg).	Treatment of ID when oral iron preparations are ineffective or cannot be used or when there is a clinical need to deliver iron rapidly. Not recommended for age <18 y.	Nausea, injection site reactions. Special warnings and precautions: hypersensitivity reactions including serious and potentially fatal anaphylactic/ anaphylactoid reactions. Administer with caution/avoid in patients with liver dysfunction or acute/chronic infection. Hypotension if infused too rapidly. Injection site irritation or discoloration with leakage.	No

ID indicates iron deficiency.

There are several potential advantages of intravenous vs oral iron: It can be administered in a few doses; it rapidly restores iron stores even in the presence of inflammatory conditions; it causes fewer gastrointestinal side effects; and it does not depend on patient adherence/compliance. However, intravenous iron preparations are considerably more expensive, require facilities equipped for cardiopulmonary resuscitation because they can cause potentially fatal hypersensitivity reactions, and can cause iron overload if not appropriately monitored.

*
According to the regulatory agency–approved drug label. Total body iron deficit, and therefore the total iron dose required, can be estimated with the Ganzoni formula: body weight×(15- Hb)×2.4+iron stores. Clinically, however, dose and frequency of administration are usually determined by product labels, local protocols, and indication for treatment. Adequacy of replacement is assessed by improvement in hemoglobin, ferritin, and transferrin saturation.

†
In patients with heart failure, the highest level evidence is available for the use of ferric carboxymaltose.[87,92,93] Furthermore, ferric carboxymaltose can be administered at a relatively large dose (750 mg) over a short period (7.5 min) because it is a stable, high-molecular-weight polynuclear iron (III) hydroxide carbohydrate complex that makes iron available in a controlled manner after uptake and regulated export by reticuloendothelial cells and releases less labile iron that could cause iron toxicity.[94]

‡
Approved in Europe but not in the United States.

Twenty control subjects received intravenous saline and 20 received 200 mg intravenous iron sucrose weekly for 5 weeks. After 6 months, hemoglobin increased by a mean of 1.4 g/dL (P<0.01), and there was improvement in creatinine clearance and Minnesota Living With Heart Failure Question- naire score, a decrease in C-reactive protein and NT-proBNP, and an increase in LVEF and 6MWD in the intravenous iron but not placebo group. FERRIC-HF (Ferric Iron Sucrose in Heart Failure)91 was the first trial to use an inclusion criterion of ID defined as ferritin <100 µg/L or 100 to 300 µg/L with TSAT <20%. This definition of ID has since been used in all subsequent trials. Eighteen anemic (hemoglobin, <12.5 g/dL) and 17 nonanemic (hemoglobin, 12.5 – 14.5 g/dL) patients with ID and peak Vo_2 ≤18 $mL \cdot kg^{-1} \cdot min^{-1}$

were randomized to open-label, observer-blinded treatment with placebo or intravenous iron sucrose 200 mg/ wk for 4 weeks during the initial ID correction phase (using the Ganzoni formula; Table 2) and additional iron sucrose 200 mg/mo as required during the maintenance phase or to no treatment for the next 3 months. The iron requirement was higher in patients with anemia than in those without anemia (1051 versus 781 mg). Iron therapy increased serum ferritin and improved NYHA class, but unlike the previous 2 studies, hemoglobin did not increase. Peak Vo2 increased significantly in anemic but not in nonanemic patients.

FAIR-HF (Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure) is the largest randomized study reported so far.[92] Patients (n=459) with HF and ID (ferritin <100 µg/L or 100–300 µg/L with TSAT <20%), with anemia (hemoglobin 9.5–12.0 g/dL) or without anemia (hemoglobin 12.0–13.5 g/dL), were randomly assigned 2:1 to intravenous FCM (n=304) or saline (n=155). FCM increased ferritin levels in all patients with a modest increase in hemoglobin only in anemic patients (0.9 g/dL; P<0.001 versus controls) but not in those without anemia (0.2 g/dL; P=0.21). FCM improved patients' global assessment and NYHA class (both *P*<0.001), the coprimary end point. The beneficial effect of iron was similar in patients with and without baseline anemia. QoL and 6MWD also improved. However, there were no significant effects on all-cause mortality (3.4% versus 5.5%, FCM versus control) or first hospitalization (17.7% versus 24.8%). FCM was generally well tolerated. Adverse events were similar in both groups.

The design of CONFIRM-HF (A Study to Compare the Use of Ferric Carboxymaltose With Placebo in Patients With Chronic Heart Failure and Iron Deficiency)[95] was very similar to that of FAIR-HF except for higher doses of FCM given for a longer duration (52 weeks). Patients (n=304) with LVEF =45%, elevated natriuretic peptides, and ID (ferritin <100 µg/L or 100–300 µg/L if TSAT <20%) were randomized 1:1 to intravenous FCM (n=152) or placebo (saline; n=152). FCM significantly improved the primary end point of 6MWD at week 24 compared with placebo, a benefit sustained at 1 year. This was associated with significant improvements in secondary end points, including NYHA class, patient global assessment, QoL, and fatigue score. FCM treatment was also associated with a significant reduction in the risk of hospitalizations for worsening HF (HR, 0.39; 95% CI, 0.19–0.82; P=0.009) with no difference in all-cause mortality. These findings indicate that the benefits of FCM on functional capacity, symptoms, and QoL in symptomatic, iron-deficient patients with HF are sustainable over a 1-year period. Unlike previous studies, CONFIRM-HF95 also showed that the use of intravenous iron may be associated with a reduction in the risk of hospitalization for worsening HF.

The most recent study, EFFECT-HF (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure),[96] randomized 172 patients with HFrEF and ID (ferritin <100 µg/L or 100–300 µg/L if TSAT <20%), NYHA class II to III HF, LVEF <45%, BNP >100 pg/mL or NT-proBNP >400 pg/mL, hemoglobin <15 g/dL, and peak Vo2 of 10 to 20 mL·kg?1·min?1 to FCM (n=86) or standard care (n=86, who could receive oral iron as needed). At 24 weeks, the primary end point of change in peak Vo_2 from baseline

Figure 4. Subgroup analyses for outcomes by baseline tertiles of hemoglobin, seru

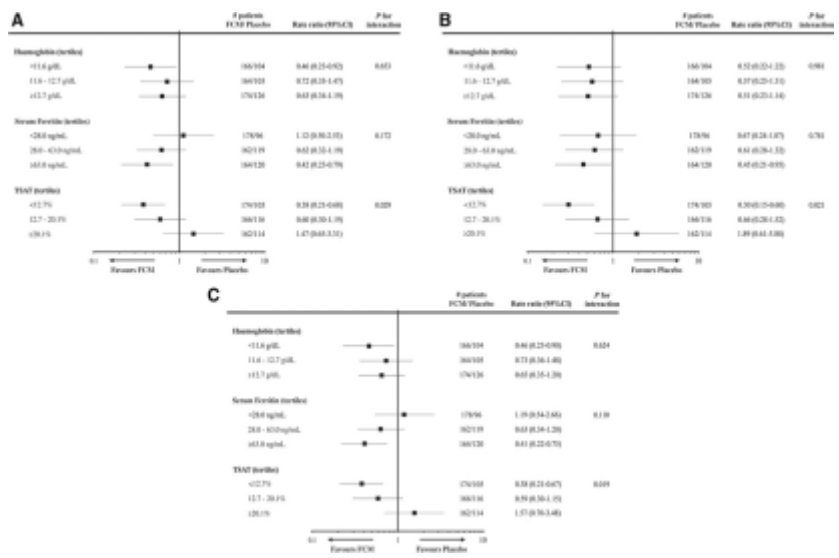

Figure 4. Subgroup analyses for outcomes by baseline tertiles of hemoglobin, serum ferritin, and transferrin saturation (TSAT). Subgroup analyses for (A) recurrent cardiovascular hospitalizations and cardiovascular mortality, (B) recurrent heart failure hospitalizations and cardiovascular mortality, and (C) recurrent cardiovascular hospitalizations and all-cause mortality from the individual patient data meta-analysis of 4 studies examining the effects of FCM in iron-deficient patients with heart failure. CI indicates confidence interval; and FCM, ferric carboxymaltose. Reproduced from Anker et al[87] with permission of the publisher. Copyright © 2018, John Wiley & Sons.

was no different between the FCM and control groups (Δpeak Vo_2, ?0.16±0.373 mL·min?1·kg?1 in those receiving FCM and ?0.63± 0.375 mL·min?1·kg?1 in controls; P=0.23) in an analysis in which missing data were not imputed. Patients' global assessment and functional (NYHA) class improved on FCM versus standard of care. Outcomes were not assessed.

The meta-analysis by Anker and colleagues[87] explored the effects of intravenous iron on objective cardiovascular outcomes and was reported before the results of EFFECT-HF were available. The authors examined individual patient data extracted from 4 RCTs comparing FCM with placebo in 839 patients with HFrEF and ID, 504 randomized to pooled FCM and 335 to pooled placebo groups. Approximately 90% of the patients were contributed by FAIR-HF and CONFIRM-HF. Patients in the 4 RTCs had very similar baseline characteristics; the same criteria were used to diagnose ID; and the same intravenous iron therapy (FCM) was tested. Therefore, this meta-analysis provides a more accurate and robust assessment of the relative effects of FCM on hard clinical outcomes compared with other recently performed meta-analyses that used different criteria for diagnosing ID, used different intravenous preparations, and included patients prescribed ESAs.[83–86] The main finding of the Anker et al[87] meta-analysis is that FCM treatment is associated with lower rates of recurrent cardiovascular hospitalizations and cardiovascular mortality (rate ratio, 0.59; 95% CI, 0.40–0.88; P=0.009), recurrent HF hospitalizations and cardiovascular mortality (rate ratio, 0.53; 95% CI, 0.33–0.86; P=0.011), and recurrent cardiovascular hospitalizations and all-cause mortality (rate ratio, 0.60; 95% CI, 0.41–0.88; P=0.009). Intravenous iron was not associated with increased risk of adverse events. However, a troublesome and hypothesis-generating finding comes from a prespecified subgroup analysis demonstrating a significant interaction between baseline tertiles of TSAT and treatment effect on all 3 composite outcomes. A TSAT-dependent effect of iron therapy was seen on all 3 composite outcomes, with greatest benefit in the lowest TSAT tertile (<12.7%) but no benefit in subgroups with TSAT of 12.7% to 20.1% and =20.1% (Figure 4).

Indeed, a trend to adverse effects of intravenous iron was seen in the highest TSAT tertile. Separately, Grote Beverborg and colleagues[69] reported in their meta-analysis of this same group of patients that FCM treatment was associated with an improvement in cardiovascular hospitalizations and cardiovascular mortality in those with TSAT ≤19.8% but not in those with TSAT >19.8%. If confirmed in prospective studies, these findings would suggest that there may be no clear benefit of intravenous iron in patients with only a modest degree of ID. These findings would be of great interest because, as discussed below, there are concerns about the deleterious effects of overcorrecting ID, particularly over prolonged periods.

Intravenous Iron Preparations

Parenteral iron preparations (Table 2) have seen enormous development over the past 20 years. At present, 5 intravenous iron preparations are available in the United States and Europe, of which 2 preparation (iron sucrose and FCM) have been tested prospectively in patients with HF. In addition, iron isomaltoside is available in Europe but not yet in the United States. Both iron isomaltoside and FCM enable higher doses of iron to be administered to replenish iron stores more rapidly.

Oral Iron Replacement Therapy in HF

Although oral iron supplementation is convenient, readily available, and inexpensive, oral iron is not absorbed well, particularly in patients with HF because of effects of HF on the gastrointestinal tract and elevated hepcidin, which inhibits iron absorption by reducing transmembrane ferroportin on enterocytes, thereby reducing iron transfer from enterocytes to blood.[97] Moreover, oral iron is associated with adverse effects, particularly gastrointestinal intolerance, that limit compliance. Few studies have investigated the effects of oral iron in patients with ID and HF.[98] The results of IRONOUT HF (Iron Repletion Effects on Oxygen Uptake in Heart Failure), the largest randomized study to examine the effects of high-dose oral iron in patients with HF, was published recently.[99] In this phase 2 double-blind RCT, 225 patients with NYHA class II to IV HF (median LVEF, 25%), hemoglobin of 9 to 15 g/dL (men) or 9 to 13.5 g/dL (women), and ID (ferritin 15–100 µg/L or 100–299 µg/L with TSAT <20%) received either oral iron polysaccharide 150 mg twice daily or placebo. At 16 weeks, there was no significant difference between the groups in the primary end point of change in peak Vo_2 from baseline or in any secondary end point (6MWD, NT-proBNP levels, or Kansas City Cardiomyopathy Questionnaire score), although oral iron increased TSAT, ferritin, and hepcidin and reduced sTfR-1 levels. These findings contrast with the results from trials of intravenous iron therapy in similar patient populations.[87] Reasons for a lack of response to oral iron are not entirely clear. Robust repletion of iron stores may be required to achieve clinical benefit because

oral iron induced only modest iron repletion (median increases from baseline in TSAT of 3% and ferritin of 11 µg/L in IRONOUT HF), in contrast to median increases of 11.3% and 259.5 µg/L, respectively, with intravenous iron in FAIR-HF.[92] This modest repletion of iron stores occurred despite 15-fold more oral iron administered in IRONOUT HF compared with intravenous iron in FAIR-HF (33.6 versus ≈2 g). Patients with higher baseline hepcidin levels demonstrated less improvement in TSAT and ferritin and an attenuated decline in sTfR levels, suggesting that higher hepcidin levels may limit responsiveness to oral iron, perhaps via inhibiting duodenal iron absorption.

In summary, these early studies provide encouraging data raising the possibility that intravenous but not oral iron therapy has a potential role in patients with HFrEF and absolute or functional ID with or without anemia. Most studies found that intravenous iron improved exercise capacity, NYHA class, and QoL. Although no study by itself showed significant improvements in cardiovascular mortality, meta-analyses of 4 trials demonstrated significant improvements in objective cardiovascular outcomes. Overall, intravenous iron was safe in the short term, but data on long-term safety and efficacy are lacking. Nevertheless, the 2016 European Society of Cardiology guidelines interpreted the available data as being adequate to provide a Class IIa, Level of Evidence A recommendation: "Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin 100–299 µg/L and TSAT <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life."[99a] The 2017 American Heart Association/American College of Cardiology guidelines provide a lower Class IIb, Level of Evidence BR recommendation: "In patients with NYHA class II and III heart failure and iron deficiency (ferritin <100 µg/L or 100–300 µg/L if TSAT <20%), intravenous iron replacement might be reasonable to improve functional status and QoL."[1]

Despite these recommendations, long-term clinical studies are still required to confirm the beneficial effects of intravenous iron on outcomes; to provide additional safety data, particularly on the potential adverse effects of iron overload during long-term administration in patients with HF; and to determine which parameters best reflect iron stores to guide iron supplementation. Several large long-term studies examining cardiovascular outcomes are ongoing (Table III in the online-only Data Supplement). Some ongoing studies directly examining changes in myocardial iron content, gene expression, and skeletal muscle metabolism are also likely to provide critical insights into the pathophysiological role of ID in nonerythroid tissues and the clinical effects of its repletion in patients with HF. Data from these studies are likely to provide valuable information to guide clinical decision making.

Potential Adverse Effects of Iron Overload on the Heart

The human body does not possess any mechanism to excrete iron; instead, it regulates duodenal iron uptake.[100] Above TSAT values of 70% to 85%, non–transferrin-bound iron is formed, part of which is called labile plasma iron or labile cellular iron. Labile plasma iron/labile cellular iron catalyzes free radical (ROS) formation, which damages mitochondria, lipids, proteins, and nucleic acids.[101] Under normal physiological conditions, duodenal iron uptake of dietary iron is reduced to prevent iron overload, which could lead to formation of free/unbound iron. However, this protective mechanism is bypassed when iron is administered intravenously. Iron overload can cause cardiomyopathy and HF,[102] increases the risk of bacteremia, and promotes ROS formation, which can cause widespread tissue damage and endothelial dysfunction. These effects may increase the risk of adverse cardiovascular outcomes.[103] Several mechanisms of iron-induced cardiac damage have been described,[104] mainly related to ROS formation, which leads to cardiac myocyte apoptosis, fibrosis, and HF. Myocardial cells have low levels of antioxidant enzymes, and ROS-protective enzyme levels are further reduced by myocardial ID in HF,[55] potentially making the failing heart even more susceptible to iron-mediated damage. Labile plasma iron/labile cellular iron directly enters cardiomyocytes (primarily via L-type calcium channels), increases ROS production, and may inhibit calcium influx, which further adversely influences myocardial excitation-contraction coupling. Intravenous iron given repeatedly over long periods can lead to clinically relevant tissue iron overloading. For instance, the drug label for FCM describes iron overload–induced hemosiderosis, leading to multiple joint disorders, walking disability, and asthenia in 1 patient and hypophosphatemic osteomalacia in another. It is therefore critical to prevent iron overload when correcting ID in patients with HF.

Hepcidin as A Potential Therapeutic Target in HF with Iron Deficiency

Hepcidin is the master regulator of iron absorption and distribution,

and its level is increased in chronic diseases, including HF. Increased hepcidin reduces duodenal iron absorption and simultaneously reduces iron release from stores in reticulo-endothelial cells and hepatocytes, thereby causing functional ID (Figures 2 and 3). Blocking hepcidin might therefore be an effective therapeutic strategy, particularly in functional ID. In early human studies, several investigational antihepcidin agents increased iron bioavailability. Promising strategies include directly blocking hepcidin expression by an anti–hepcidin l–oligoribonucleotide (lexaptepid) or its activity by a fully human anti-hepcidin antibody or blocking hepcidin signaling by a small-molecule inhibitor (LDN-193189) or nonanticoagulant heparins.[16,105] Spironolactone, commonly used in patients with HF, inhibits hepcidin expression in mice, raising the possibility that this drug may be repurposed to this end.[106] Whether strategies that downregulate hepcidin will be of clinical benefit merits prospective evaluation.

Conclusions

Anemia and absolute or relative ID are common comorbidities in patients with HF and are associated with poor clinical status and worse outcomes. Although the cause of anemia in HF is not entirely clear, evidence suggests that neuro-hormonal and proinflammatory cytokine activation and renal dysfunction favor the development of anemia of chronic disease. Whereas ESAs were considered to be a rational therapy to increase hemoglobin and to treat anemia in HF, these agents do not improve outcomes and may be associated with thromboembolic complications. ESAs are therefore not recommended.

Early data from short-term studies in patients with HFrEF and absolute or functional ID with or without anemia suggest that intravenous but not oral iron therapy may have a potential role in improving exercise capacity, NYHA class, and QoL. However, larger, adequately powered trials with cardiovascular mortality and morbidity end points are needed to establish the long-term efficacy and safety of intravenous iron in patients with HF. The numerous long-term ongoing studies are likely to provide valuable information to address these concerns and to help guide future clinical decision making.

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Cholera

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Continuing Education Activity

Cholera is an acute secretory diarrheal illness caused by the bacteria Vibrio cholerae. It is estimated to cause upwards of four million cases per year, worldwide. High-volume fluid loss with electrolyte derangements that can progress to hypovolemic shock and ultimately death characterizes this gastrointestinal disease. This activity describes the evaluation and management of cholera and highlights the role of the interprofessional team in improving care for affected patients.

Objectives:

- Describe the pathophysiology of cholera.
- Outline the typical presentation of a patient with cholera.
- Describe the management considerations for patients with cholera.
- Outline the importance of collaboration and coordination among the interprofessional team to enhance the management of cholera and associated acute secretory diarrheal illnesses in order to improve patient outcomes and prevent spread.

Introduction

Cholera is an acute secretory diarrheal illness caused by the bacteria Vibrio cholerae. It is estimated to cause upwards of four million cases per year, worldwide. High-volume fluid loss with electrolyte derangements that can progress to hypovolemic shock and ultimately death characterizes this gastrointestinal disease.[1,2,3] The infection is transmitted via the fecal-oral route and can vary in severity. The key is replacing the fluid and electrolytes lost as soon as possible.

Etiology

Vibrio cholerae is a facultative, gram-negative, comma-shaped, oxidase-positive rod that is prevalent in developing countries. Two serotypes have been identified to cause outbreaks. O1 is responsible for all recent outbreaks, whereas O139 causes sporadic outbreaks, specifically in Asia. There is no etiologic difference between the two. V. cholerae is found in food (classically shellfish) and poorly sanitized water. The bacteria is known to spread via the fecal-oral route and is thus endemic to areas associated with inadequate food and water hygiene.[4,5]

The organism is acquired via the fecal-oral route and a large dose is required to develop infectivity. Factors that increase susceptibility include:

- Use of proton-pump inhibitors (PPIs) and antihistamines
- Having type 0 blood
- Poor sanitation
- Overcrowding
- Prior vagotomy
- *Helicobacter pylori* infection

Epidemiology

There are about four million cases of cholera worldwide annually, with over 140,000 deaths attributed to the disease. Nearly 1.8 million people worldwide obtain their drinking water from sources contaminated with human feces that may act as a reservoir for the cholera bacteria. Outbreaks are known to occur, specifically in the developing world where sanitation and water filtration standards may not exist. Currently, cholera is known to be endemic in approximately 50 nations, mostly throughout Asia and Africa. The incidence is tied to a seasonal distribution, depending on the timing of the region's rainy season. Epidemics can be more widespread, however, involving other parts of the world, including South and Central America. The introduction of the species to a new region with a collapse of hygiene and health services has been known to lead to the propagation of epidemics.[6,7]

Pathophysiology

Ingestion of V. cholerae can lead to colonization of the small intestine. Its flagella allow the organism to swim through mucus and arrive at the intestinal wall. There, toxigenic V. cholerae produces toxin-coregulated pilus that attaches to gangliosides receptors in the mucosal wall. Cholera toxin is produced, which ADP-ribosylates the Gs subunit of the G protein complex in the gut epithelium. This leads to constitutive action of adenylate cyclase, thereby increasing cAMP intracellularly. As a result, increased secretion of chloride, bicarbonate, sodium, and potassium is observed. The secretion of these electrolytes pulls water out of the intestinal cells osmotically, thereby

causing diarrhea.

Host susceptibility is affected by previous exposure to the organism which can result in immunity, although this is dependent on the biotype and serotype of the previous organism encountered. Since it is a labile acid organism, a large inoculation dose is required to cause infection in a healthy adult. This can explain why lowered gastric acidity (as seen in cases of achlorhydria) can lower the threshold needed for the bacteria to cause infection. Interestingly, blood type O has also been associated with an increased likelihood of infection. The mechanism of this increased susceptibility to disease is not yet clear.[8,9]

The use of proton pump inhibitors and antihistamines can increase the risk of infection and make the patient susceptible to more severe symptoms. The fluid losses typically occur from the duodenum, whereas the colon is insensitive to the toxin. Because the enterotoxin has a local effect and is not invasive, in most cases no neutrophils are observed in fecal specimens.

History and Physical

Clinical manifestations of cholera can range from asymptomatic to profuse diarrhea. Common symptoms include diarrhea, abdominal discomfort, and vomiting. Severe cholera can be distinguished clinically from other diarrheal illnesses due to the profound and rapid loss of fluid and electrolytes. The stools are often described to have a "rice water" consistency, which can be laced with bile and mucus. Adult output can reach as high as one liter per hour whereas, in children, it can reach up to 20 cc/kg/hr.

The resulting hypovolemia results in the characteristic manifestations of fluid loss, including dry oral mucosa, cool skin, and decreased skin turgor. Poor perfusion of body tissue can result in lactic acidosis, thereby causing hyperventilation and Kussmaul breathing. In addition, electrolyte abnormalities such as hypokalemia and hypocalcemia can be responsible for generalized muscle weakness and cramping

Evaluation

The diagnosis of cholera can be based on clinical suspicion. The characteristic high volume diarrhea and travel to an endemic area can be sufficient for a diagnosis. As such, laboratory testing is often not required before initiating treatment. The diagnosis can be confirmed, however, by the isolation and culture of *V. cholerae* from stool isolates. Culture can be enhanced via the use of selective media with a high pH that suppresses the growth of intestinal microflora while allowing *V. cholerae* to multiply. Likewise, rapid tests can be employed to identify the O1 or O130 antigen in stool samples. Dipsticks and darkfield microscopy of the stool are available methods that can be used to identify or visualize the organism rapidly.[1]

Treatment / Management

The mainstay of treatment of cholera is prompt fluid resuscitation based on the degree of volume depletion. If an estimated 5% to 10% of body weight has been lost, oral rehydration solution should be used. Clinical trials have shown that rice-based oral rehydration solution can shorten the duration of diarrhea and the amount of stool loss. In an emergency, a solution can be made, consisting of one liter of water, mixed with six teaspoons of sugar and a half teaspoon of salt. For patients in hypovolemic shock or greater than 10% loss of body weight, intravenous fluids should be administered. Approximately 100 mL/kg of lactated ringers should be administered during the first three hours. Prompt treatment of severe cholera with fluids can reduce the mortality from over 10% to less than 0.5%.[7,10,11]

Once an appropriate volume status has been achieved, antibiotic therapy can be initiated. Tetracyclines are the most commonly used class. A single 300 mg dose of doxycycline or 500 mg of tetracycline every 6 hours for 2 days has been shown to reduce disease duration. However, resistance is common in certain areas, and thus alternative therapies include macrolides such as erythromycin and azithromycin, or fluoroquinolones such as ciprofloxacin.

Differential Diagnosis

- *Escherichia coli* infection
- Salmonellosis
- Shigellosis
- Typhoid fever
- Rotavirus infection

Prognosis

Without hydration, mortality rates in excess of 50% have been reported. The mortality rates are higher in children, pregnant women, and the elderly. Overall, the mortality rates have decreased because of better access to healthcare, improved sanitation, and education.

Complications

- Dehydration
- Acute tubular necrosis
- Renal failure
- Severe hypotension
- Death

Deterrence and Patient Education

In endemic areas, the patient and the family need to be educated about personal hygiene, boiling

water, and improving sanitation. The prevention of cholera rests on improving public health measures like proper sewage disposal and ensuring clean water for drinking. Much of the contaminated water is used to wash the fruits and vegetables, and also to fertilize crops, which creates a never-ending cycle of cholera. Food handlers must be educated on personal hygiene and proper handwashing.

Regarding the prevention of illness in travelers, the centerpiece of counteracting transmission is adequate sanitation and water filtration. They should be educated to avoid undercooked seafood and raw fruits and vegetables. Tap water should be avoided but can be filtered or boiled to reduce the risk of transmission of *V. cholerae*. In the United States, a live attenuated oral cholera vaccine is licensed for use in adults ages 18 to 64 who travel to an area of active cholera transmission. A single dose is taken, ideally 10 days before travel to an endemic area. It should be administered separately from systemic antibiotic use, which can alter the effectiveness of the vaccine. Efficacy was shown to be 80% after 3 months of vaccination. Worldwide, three killed whole-cell oral vaccines are also available for use.

Enhancing Healthcare Team Outcomes

Cholera usually occurs in epidemics and thus is best managed by an interprofessional team. Many guidelines have been established to manage cholera outbreaks. The most important feature of cholera outbreaks is to be aggressive and proactive in rehydration. This infectious disorder can quickly lead to death if not diagnosed early. Rapid identification of the infected patient is vital as prompt treatment will prevent further cases.

Patient education is key. Water should be boiled before consumption. Since contamination via food is common, all foods and fruits should be washed with clean water. Personal hygiene should be improved and hand washing is essential. In many countries, there are now established surveillance and prompt reporting systems set up to contain the cholera epidemic. There is usually a team of nurses and other healthcare workers who provide an alert to outbreaks so that a coordinated response is initiated. The key feature to prevent outbreaks is to modify human behavior and control environmental conditions. Education is key. [Level 5][12,13]

For travelers to the tropics where cholera outbreaks have occurred, the pharmacist should educate them on basic hygiene, washing food with clean water, and only drinking bottled water. Even though vaccines are available, the risk of a traveler acquiring cholera is low. The pharmacist should be aware of the recommendations for use of the cholera vaccine and who should not receive it. [Level 5][6,14]

Outcomes

Today the morbidity and mortality of cholera are much lower than in past eras. The key reason is that healthcare workers are aware of the importance of hydration and replenishing electrolytes. In the past, without hydration, the mortality was close to 50%, but today the mortality rates are less than 5%. The key element of treatment is to start rehydration at the onset of symptoms. [Level 5][15]

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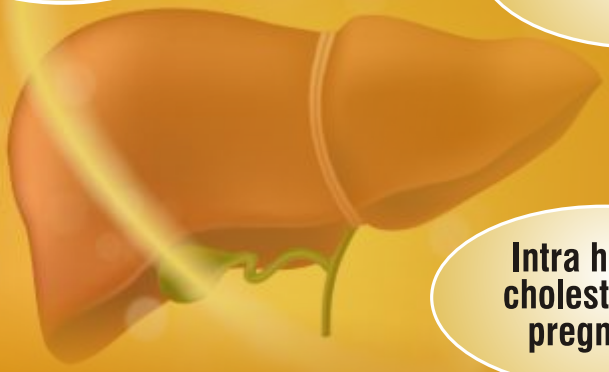

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