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Review Article

Iron Deficiency in Heart Failure and The Benefit of Supplementing: A Systematic Review

Amri Meriam*, Zouad Asmae and Habbal Rachida

Department of Cardiology, CHU Ibn Rochd, Casablanca, Morocco

***Corresponding author:** Amri Meriam, Department of Cardiology, CHU Ibn Rochd, Casablanca, Morocco

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Abstract

Background: Iron insufficiency in heart failure affects outcomes, often overlooked despite its significant impact. The 2023 European Society of Cardiology Congress highlighted the potential benefits of iron supplementation, prompting this systematic review to critically evaluate existing evidence.

Methods: Utilizing PubMed, EMBASE, Web of Science, and Cochrane databases, we identified 61 studies. Twelve met initial criteria, with five meeting inclusion requirements-randomized controlled trials involving 5132 patients.

Results: Intravenous carboxymaltose proves beneficial for iron supplementation in heart failure patients with reduced or moderately reduced ejection fraction. Notably, derisomaltose emerges as a novel avenue.

Discussion: This review emphasizes the efficacy of intravenous carboxymaltose and introduces derisomaltose, expanding iron supplementation options. Future studies must address the challenge of including heart failure patients with preserved ejection fraction. Contributing to the discourse, this concise review adds a critical perspective to the evolving landscape of iron supplementation in heart failure.

Keywords: Iron deficiency; heart failure; martial supplementation

Introduction

The prevalence of iron deficiency (ID) in heart failure (HF) is 50%, with or without anemia, according to the HAS-Haute Autorité de Santé. The European Society of Cardiology (ESC) 2021 guidelines define iron deficiency as follows: Serum ferritin <100ng/mL, or serum ferritin 100-299ng/mL with TSAT (Transferrin saturation) <20%(Table 1). "It is recommended that all patients with heart failure be periodically screened for anemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT." (IC) ESC 2021 ID in HF patients is unrelated to the patient's anemia status. In fact, in 2013, Klip et al. [1]. Showed that the prevalence of ID in HF was 45,6% in non-anemic patients and 61,2% in anemic patients. They also demonstrated that ID was a predictive factor of mortality independent of anemia. Moreover, in 2018, Martens P [2]. Showed that the prevalence of ID increased with the New-York Heart Association (NYHA) class of dyspnea and that all HF groups were concerned not only HF patients with reduced ejection fraction (HFrEF) but also HF with preserved EF (HFpEF). This raises the issue's significance and the number of patients affected. An iron deficiency may result from a number of factors.

The most frequent reason is an insufficient dietary intake of foods high in iron. Even though the diet provides enough iron, there are some factors that prevent the body from absorbing it. Iron stores can be depleted by persistent blood loss, which may lead to ID. In a few cases, underlying health conditions can increase

the body's need for iron. ID can have a major adverse impact on individuals suffering from HF, aggravating their symptoms and deteriorating their prognosis. It may make it even harder to exercise and be physically active. The creation of strong red blood cells, which provide oxygen to the muscles, depends on iron. Without enough iron, the body struggles to carry oxygen, which results in exhaustion, breathlessness, and a reduced ability to exercise. ID has been associated with a decreased response to conventional HF treatments, such as diuretics and medications that improve heart function. Studies have also shown that ID in HF is associated with increased hospitalization rates and a higher mortality risk. Iron-deficient heart failure patients are more likely to experience disease progression, cardiovascular events, and complications, leading to a poorer prognosis.

Table 1: Advantages and limits of the different biological assessments.

Test	Strenghts	Limitations
Ferritin	Measures stored iron	Affected by inflammatory states limiting sensitivity
	Not affected by short-term variations in iron intake	Affected by liver disease
Serum iron	Direct measurement	Does not reflect iron stores
		Highly variable with intake and metabolic requirements
Serum transferrin	Reflects varying metabolic requirements	Falsely low in liver disease
	Not affected by inflammatory states	Not a direct measurement of iron levels
Transferrin saturation	Not affected by inflammatory states	Does not directly measure iron stores
	Measures transported iron available for cell uptake	

After defining iron deficiency, identifying the population affected, its causes, and its effects, our review now focuses on solutions to these issues, namely iron supplementation. The aim of our systematic review is to compare the strengths and weaknesses of the studies that have been published on the potential benefits of iron carboxymaltose (ICM) supplementation in patients with HF up until 2023. Given the fact that there are some discrepancies between studies and obscure areas that require clarification, as we will see, we also desire to promote investigations and the establishment of more in-depth studies on the subject. As a result, we want to increase practitioners' awareness of this frequent and sometimes ignored comorbidity.

Methods

Search strategy and information sources A thorough search of electronic databases, including PubMed, EMBASE, Web of Science, and the Cochrane Library, was conducted to identify relevant studies between 2009 and August 2023. Studies investigating the association between iron deficiency, heart failure, and the effects of iron supplementation were included. We used mesh terms including "iron deficiency" "heart failure" and "martial supplementation".

Study Selection

Types of Studies

Only randomized trials comparing intravenous (IV) carboxymaltose supplementation to standard of care or a placebo in patients with HF and ID were taken into consideration. Other injectable iron molecules besides carboxymaltose were not included in the studies. First of all, we wanted to avoid the bias linked to the use of different molecules as well as the more prominent allergic effects of other molecules. Iron carboxymaltose is the most described in terms of effectiveness in the literature, and it is also the only one available in the country where this systematic review was carried out. Because doing so would raise trial heterogeneity and make it harder to understand the results, trials looking at the use of oral iron in patients with HF and ID were rejected. International guidelines for treating ID in HF do not additionally advise using oral iron. There were no trials that were not in English.

Types of Participants

Studies including adults over 18 with chronic or acute heart failure were included, regardless of whether or not their ejection fraction was reduced or preserved. We therefore sought to include iron deficiency (as previously defined) in our effort to widen the potential benefit of iron supplementation. Patients with or without anemia were included in the studies; anemia was not a selection criterion.

Data Extraction

We gathered information from the pertinent studies using common data extraction forms. The data was independently extracted by two reviewers (MA and AZ) using the pre-determined search words. In the event that an agreement couldn't be reached, a third independent reviewer's viewpoint was requested (RH). Name of author, publication year, study population, sample size, average follow-up time, and study endpoints were all independently extracted. One author read the complete texts of the remaining articles to determine whether they satisfied the eligibility requirements. Full-text articles were disregarded since they failed to respond to the review's main question. The following were present: type of studies (44 studies) did not meet the eligibility requirements, and type of participants (12 studies) did not satisfy the "type of participants" inclusion criteria.

Analysis

We carried out a descriptive analysis by first comparing the types of populations according to chronic or acute heart failure and

the primary and secondary composites of each of the studies. Two impartial reviewers (MA and AZ) undertook an assessment of the risk of bias. Disagreements were settled through conversation and/or the involvement of a third reviewer.

Results

Of the 61 identified studies, 12 were considered eligible, and five met the inclusion criteria of this review. These five studies were randomized controlled trials with a total of 5132 participants. All the studies compared the effect of intravenous carboxymaltose supplementation versus placebo. The population type: acute or chronic heart failure, and the requirements of the primary and secondary composites were the differences between the trials. (Table 2). Firstly, in chronic HFrEF, we had FAIR-HF [3]. In 2009, which included 459 patients with HFrEF with or without anemia. The self-reported Patient Global Assessment and NYHA functional class, both at week 24, served as the main end points. The distance covered in 6 minutes of walking and the quality of life in terms of health were secondary end objectives. It demonstrated that treatment with intravenous ferric carboxymaltose (FCM) improves symptoms, functional ability, and quality of life in patients with chronic HF and ID, with or without anemia; the side-effect profile was also tolerable.

Table 2: Comparison of the studies included in our review.

Study	Year	Authors	Population size	Study population	Primary composite	Secondary composite
Fair HF	2009	Stefan D. Anker	459	Chronic HF, HFrEF	NYHA score at 24 weeks	6 min walk test and quality of life.
CONFIRM HF	2015	Piotr Panikowsi	304	Chronic HF, HFrEF	6 min walk test at 24 weeks	NYHA class and quality of life.
EFFECT HF	2017	Dirk J Van Veldhuisen	172	Chronic HF, HFrEF	VO2 max at 24 weeks	Cardiac biomarkers and quality of life
AFFIRM HF	2020	Piotr Ponikowski	1 132	Acute HF, HFrEF	Hospitalization for decompensation and cardiovascular death up to 52 weeks	Total cardiovascular hospitalizations and total cardiovascular mortality
HEART-FID	2017-2023	Robert J. Mentz	3065	Chronic HF, HFrEF	All-cause mortality (at 1 year), hospitalization for heart failure at 1 year) and the distance covered in the 6-minute walk test at 6 months	Cardiovascular mortality or hospitalization for heart failure

Then, in 2015, there was CONFIRM HF [4]. Which comprised 304 patients with HFrEF. The 6-minute walk test (6MWT) distance change from baseline to week 24 served as the primary endpoint. Secondary outcomes included the change in 6MWT from baseline to weeks 6, 12, 36, and 52, the Patient Global Assessment score at weeks 6, 12, 24, 36, and 52, and the change in NYHA class, fatigue score, and quality of life (QoL) from baseline to weeks 6, 12, 24, 36, and 52. It showed that treatment with IV carboxymaltose for a year in symptomatic individuals with chronic HF and ID led to sustained improvements in exercise capacity, symptoms, and QoL and may be linked to a lower likelihood of hospitalizations owing to worsening HF. In 2017, EFFECT-HF [5]. Included 172 patients with chronic HfrEF. The primary endpoint was the change in peak VO2 from baseline to 24 weeks. Secondary endpoints included the effect on hematologic and cardiac biomarkers, quality of life, and safety. The treatment of the iron deficiency prevented the deterioration of the VO2 peak, assessing the maximum effort capacities, recorded under placebo.

Concerning acute heart failure, we had AFFIRM-HF [6]. In 2020, which was a multicentre, double-blind, randomized trial done at 121 sites in Europe, South America, and Singapore. Eligible patients were aged 18 years or older and hospitalized for acute heart failure with concomitant iron deficiency. The primary outcome was a composite of total hospitalizations for HF and cardiovascular death up to 52 weeks. Secondary outcomes were the composite of total cardiovascular hospitalizations and cardiovascular deaths; cardiovascular deaths; total heart failure hospitalizations; time to first heart failure hospitalization or cardiovascular death; and days lost due to heart failure hospitalizations or cardiovascular deaths, all evaluated up to 52 weeks. Finally, HEART-FID [7]. Presented at the ESC meeting in August 2023, was the most recent English study. The main outcome was a hierarchical composite that included all-cause mortality (at 1 year), heart failure hospitalizations (at 1 year), and the 6-minute walk test distance (at 6 months).

Cardiovascular death, or the occurrence of heart failure hospitalization was the secondary objective. All-cause mortality was modified slightly by the FCM, but it still fails to meet the threshold for significance. This experiment supports FCM's high level of safety, with most side effects being mild and allergic in nature. The large sample size (> 3,000 patients) and high number of cardiovascular events (death and heart failure) are the study's strengths. Additionally, there is a trend toward improvement following iron supplementation (even though it does not yet approach the level of significance). We list multiple treatment interruptions (300 in the FCM group, 264 in the placebo group) as one of the trial's flaws.

Discussion

The included studies, as presented in chronological order, showed the benefit of IV carboxymaltose supplementation. Firstly, in functional capacity, exercise tolerance and quality of life, then secondly the most recent ones studied larger populations and focused on more important events such as hospitalization for decompensation and mortality. This systematic review is thus aligned with European and American guidelines.

In 2021 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure: "Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF<50% and iron deficiency." (IIa) The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guideline on HF provides a Class IIa, Level of Evidence B recommendation that in patients with HFrEF and ID with or without anemia, intravenous iron replacement is reasonable to improve functional status and quality of life (Figure 1).

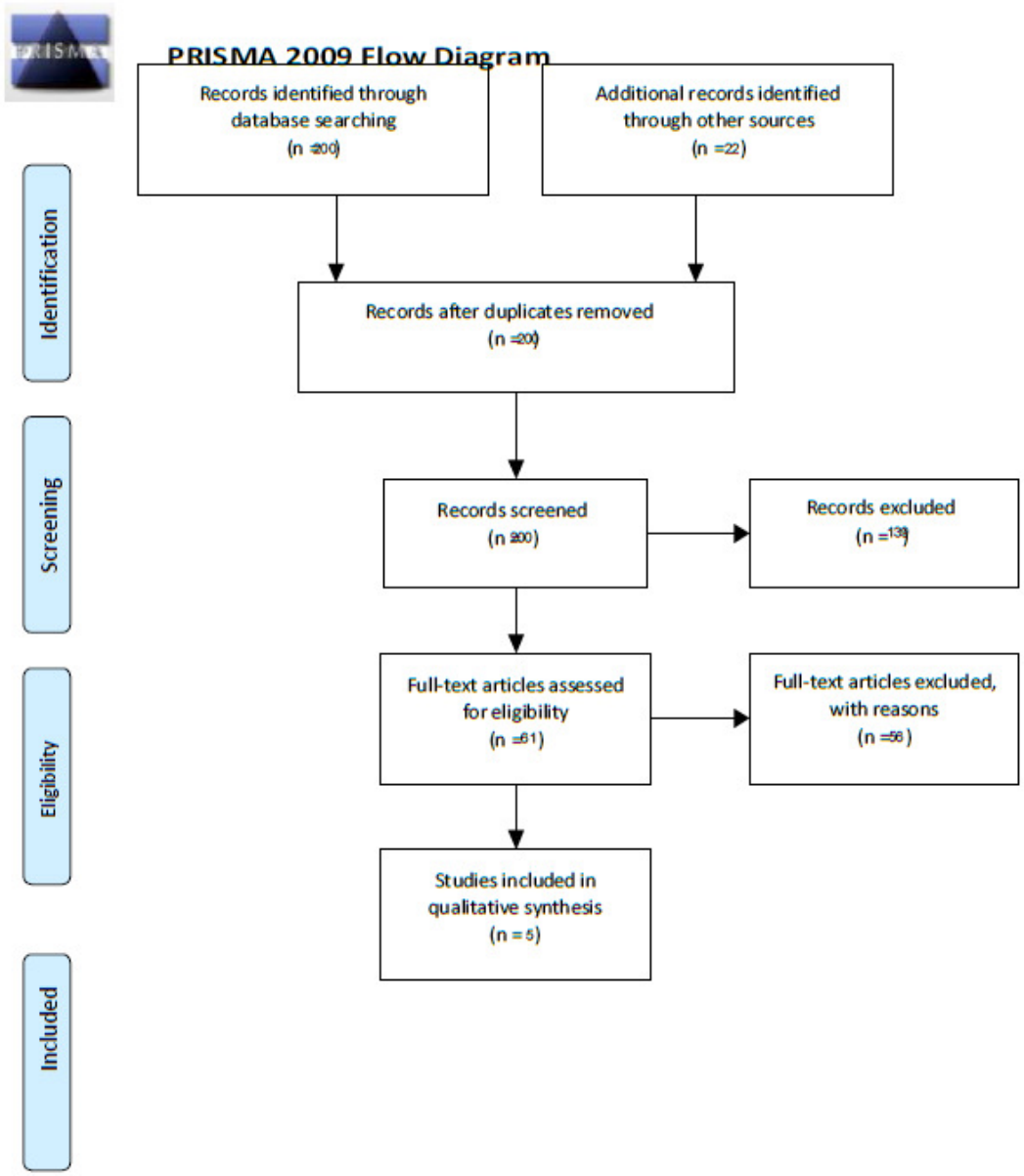

Figure 1

Only the European guidelines specified the carboxymaltose molecule, but both agree that the supplementation should be intravenous. In fact, in 2017, IRONOUT HF [8]. Studied the effect of oral Iron repletion on exercise capacity in HFrEF patients with Iron deficiency. It demonstrated the lack of increase in functional tolerance as measured by the VO2 peak after 16 weeks of treatment as well as the improvement in ferritin and CST levels. However, there have been some studies that have shown the benefit of iron supplementation in heart failure using an intravenous molecule other than carboxymaltose. The best known of them is IRONMAN [9]. Presented at the American Heart Association (AHA) meeting in 2022 was a prospective, randomised, open-label, blinded-endpoint experiment. This trial's objective was to examine the long-term effects of intravenous ferric derisomaltose on cardiovascular events in heart failure patients. Patients with HFrEF were a part of the study, which was conducted in 70 facilities across the UK. Because derisomaltose, rather than carboxymaltose, was employed in this investigation, it was not included in our analysis.

We feel that it is still vital to quote it, nevertheless. After a median follow-up of 3 years, IV iron administration was not linked to a meaningful decrease in the primary endpoint (mortality from cardiovascular causes or hospitalization for HF) in the population as a whole. The primary endpoint was significantly lower after IV iron treatment, according to COVID-19 sensitivity analysis with follow-up censoring from September 2020 (p=0.047). These findings must be interpreted with care and in a nuanced manner. In fact, the authors advise that we continue to consider this study to be statistically significant based solely on the COVID-19 sensitivity analysis, even though the result is not significant when applied to the entire population. The result is also "barely statistically significant" with a p-value of 0.047 in this sensitivity analysis, which calls for extreme caution in the interpretation of these findings. Nevertheless, this study was at the origin of changes in the last guidelines of the ESC published in August 2023 in Amsterdam. Indeed, we find derisomaltose alongside carboxymaltose and the population concerned is also extended to the heart failure population with moderately reduced ejection fraction (HFmrEF).

"Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization". (IIa) Thus, the challenge is now focused on extending indications not only for other types of molecules but also to a larger population. Indeed, if AFFIRM HF was already targeting patients with acute heart failure, we also had META-ANALYSIS [10]. Between 2000 and 2022, that examined the effects of IV iron in patients with HF and ID, regardless of the definition of ID, the participants' left ventricular ejection fraction, or the IV iron formulation. This study included ten trials with 3373 participants in total. The primary outcome was hospitalization for HF (HHF) and cardiovascular mortality. It showed that IV iron reduces the risk of HHF in patients with HF and ID, but it is yet unclear if this is linked to a decrease in cardiovascular or all-cause mortality. This is the challenge that future studies have set themselves. In fact, since 2022, the French CARENFER [11]. Prospective study has been studying the prevalence of ID in a larger population of HF patients (acute and chronic heart failure), regardless of their ejection fraction. Two promising studies, the German FAIR HF2 and the American Heart FID trials, are focusing on the long-term effect of supplementation on cardiovascular mortality up to more than 2 years and HHF and walking test at 6 min and at 6 months. We look forward to these results.

Acknowledgement

None.

Conflict of Interest

No conflict of Interest.

Appendix

Appendix 1

Section and Topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	Page 1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3

Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 4

Appendix 2

Section and Topic	Item #	Checklist item	Location where item is reported
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 4/6
Study characteristics	17	Cite each included study and present its characteristics.	Page 5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 5

Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 5
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 5
	23b	Discuss any limitations of the evidence included in the review.	Page 6
	23c	Discuss any limitations of the review processes used.	Page 6
	23d	Discuss implications of the results for practice, policy, and future research.	Page 7
Other Information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 7
Competing interests	26	Declare any competing interests of review authors.	Page 7
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 7

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