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Intravenous Iron Preparations for Patients Undergoing Elective Surgery: A 2022 Update

Rapid Review

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Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
CI	confidence interval
EQ-5D	European Quality of Life – 5 Dimension Questionnaire
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICU	intensive care unit
MA	meta-analysis
NICE	National Institute for Health and Care Excellence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
RCT	randomized controlled trial
SR	systematic review

Key Messages

- For adults who are iron deficient before elective surgery, patients who received IV iron supplementation may have greater increases in hemoglobin and ferritin concentrations, similar or lower lengths of stay in hospital, and similar quality of life measures, functional outcomes, and rates of adverse events, compared to patients who did not receive IV supplementation. The findings were mixed for the rate of blood transfusions.
- For adults who are iron deficient before elective surgery, patients who received IV iron supplementation may experience similar changes in hemoglobin levels, quality of life scores, or number of adverse events when compared to patients who received oral iron supplementation. The findings were mixed regarding the risk of blood transfusions.
- No studies were found on the cost-effectiveness of IV iron preparation therapy for patients who are iron deficient undergoing elective surgery that met the criteria for this review.
- One guideline recommends the use of IV iron supplementation for patients with iron deficient anemia when surgery is less than 8 weeks away, patients are unable to tolerate or absorb oral iron supplementation, or for patient with suboptimal hemoglobin levels.

Context and Policy Issues

Pre-operative anemia is a common problem and can impact as much as 30% to 50% of patients presenting for surgery.[1,2] The WHO defines anemia as a hemoglobin level of less than 130 mg/mL in men and 120 mg/mL in non-pregnant women.[1] It is estimated that approximately 3% of Canadians have anemia and is most prevalent for people age 65 to 79.[3] The most common form of anemia is iron deficiency anemia, which can be acute or chronic, but becomes problematic when there are insufficient number of red blood cells to maintain oxygen demand.[1] This can be detrimental during surgery where blood loss may be high and may result in peri-operative blood transfusions and adverse post-operative outcomes such as inpatient complications, delayed hospital discharge, or mortality.[1,2]

A 2015 National Institute for Health and Care Excellence (NICE) guideline recommends that oral iron supplementation should be the first-line treatment option for patients with anemia undergoing surgery.[2,4] Oral iron supplementation is common and inexpensive, and can be an effective method of iron supplementation; however, oral iron can be poorly absorbed by the body and compliance with oral iron treatment is often low with only 20% to 40% of patients completing a full course of treatment.[2] Another common treatment option is peri-operative blood transfusion, but this can be associated with increased patient length of stay, morbidity, and mortality, and may be effected by a limited supply and increase demand of donated blood.[1] IV iron preparation (or supplementation) is an alternative treatment option for patients with iron deficiency undergoing elective surgery. IV iron is a method of iron supplementation administered directly to the patient and is often given to patients to correct anemia before surgery.[2] IV iron can be administered closer to the time of surgery because iron absorption is often more rapid compared to oral iron supplementation.[2] There are a number of common IV iron supplementations available to treat pre-operative anemia including ferric carboxymaltose, ferric derisomaltose (also known as iron isomaltoside), ferric gluconate, ferumoxytol, iron dextran, and iron sucrose.[5] The recommended doses for each type of IV iron supplementation varies, but can range from multiple doses at 125 mg to single doses at 2,000 mg.[5] IV iron

supplementations approved for use in Canada include ferric derisomaltose,[6] ferric gluconate,[7] ferumoxytol,[8] iron dextran,[9] and iron sucrose.[10]

The purpose of this report is to summarize the evidence related to clinical effectiveness, cost-effectiveness, and recommendations regarding IV iron preparations to support decisions involved in the use of this treatment for patients identified as iron deficient undergoing elective surgery. This report is an update to a previous CADTH report from 2019 that evaluated the use of IV iron preparations for the same population.[11]

Research Questions

1. What is the clinical effectiveness of IV iron preparations for patients identified as iron deficient undergoing elective surgery, including high blood loss surgery?
2. What is the cost-effectiveness of IV iron preparations for patients identified as iron deficient undergoing elective surgery, including high blood loss surgery?
3. What are the evidence-based guidelines regarding the use of IV iron preparations for patients identified as iron deficient undergoing elective surgery, including high blood loss surgery?

Methods

Literature Search Methods

The literature search strategy used in this report is an update of 1 developed for a previous CADTH report.[11] For the current report, a limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, Canadian and major international health technology agencies, as well as a focused internet search. No filters were applied to limit the retrieval by study type. The initial search was limited to English-language documents published between January 1, 2014 and February 28, 2019. For the current report, database searches were rerun on September 13, 2022 to capture any articles added to the databases since the initial search date. The search of major health technology agencies was also updated to include documents published since February 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. As an update to a previous CADTH report, articles were reviewed if they were made available since the previous search date and were not included in the 2019 CADTH report.[11] The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

The terms IV iron, IV iron preparation, IV iron supplementation are all used in the literature to describe the intervention of interest, but for the purpose of this report the term IV iron supplementation will be used consistently to summarize the findings from the literature.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, or they were duplicate publications. Economic evaluations and evidence-based guidelines were excluded if they were published before 2019, and health technology assessments, systematic reviews, RCTs, and non-randomized studies were excluded if they were published before 2021. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[12] for systematic reviews, the Downs and Black checklist[13] for randomized and non-randomized studies, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[14] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 465 citations were identified in the literature search. Following screening of titles and abstracts, 384 citations were excluded and 81 potentially relevant reports from the electronic search were retrieved for full-text review. Thirty-nine potentially relevant

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients identified as iron deficient undergoing elective surgery (i.e., any surgery scheduled in advance of the operation)
Intervention	IV iron preparations (e.g., iron isomaltoside, ferric carboxymaltose, iron sucrose, ferumoxytol, iron dextran, sodium ferric gluconate)
Comparator	Q1 to Q2: Blood transfusion, standard of care, saline, no treatment, no IV iron, placebo Q3: No comparator
Outcomes	Q1: Clinical Effectiveness (e.g., mortality and morbidity, length of hospital stay, comorbidities, need for blood transfusion, hemoglobin level, hemoglobin change, patient quality of life), safety (e.g., hypersensitivity, allergic reaction, rate of adverse events) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-years gained, incremental cost. cost per adverse event avoided) Q3: Recommendations related to the use of IV iron preparations for adult patients identified as iron deficient undergoing elective surgery
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 103 publications were excluded for various reasons, and 17 publications met the inclusion criteria and were included in this report, with 1 additional report included through a bibliographical hand-search. These comprised 6 systematic reviews (SRs), 4 randomized controlled trials (RCTs), 6 non-randomized studies, and 1 evidence-based guideline. Appendix 1 presents the PRISMA[15] flow chart of the study selection.

Summary of Study Characteristics

Six SRs[16-21] including 3 with meta-analysis (MA),[16,17,19] 4 RCTs,[22-25] 6 non-randomized studies,[26-31] and 1 evidence-based guideline[32] was included in this report.

Four SRs[16-18,20] had broader inclusion criteria than this report: 3 SRs[16-18] including 2 with MA[16,17] included a range of interventions related to iron supplementation including the use of oral iron supplementation. One SR included a study with an irrelevant comparator.[20] Only studies that fit the inclusion criteria for this report will be reported on.

Additional details regarding the characteristics of included publications are provided in Appendix 2, Tables 2 to 4. There was some overlap of studies included in the SRs, and the degree of overlap is summarized in Appendix 5, Table 15.

Study Design

All 6 SRs were published in 2021[18-21] or 2022.[16,17]The authors of 1 SR and MA included 10 RCTs published up to December 2020.[16] The authors of 1 SR and MA included 7 primary studies comprised of 2 RCTs and 5 non-randomized studies published up to February 2021.[17] The authors of 1 SR included 7 RCTs published up to December 2019.[18] The authors of 1 SR and MA included 10 RCTs published up to February 2019.[19] The authors of 1 SR included 10 RCTs published up to January 2021.[20] The authors of 1 SR included 9 primary studies comprised of 5 RCTs and 4 non-randomized studies published up to November 2020.[21] The primary study overlap between these SR is summarized in Appendix 5, Table 15. Eleven of the 30 primary studies were included in 2 or more SRs.

Three RCTs were published in 2022,[22-24] while 1 RCT was published in 2021.[25] One non-randomized study was published in 2022,[26] while 5 non-randomized studies were published in 2021.[27-31] Five of the non-randomized studies were retrospective cohort studies that used historical patient data in their analysis.[26-30] One non-randomized study was a multicenter prospective cohort study that used prospectively collected patient data.[31] When reported, patient follow-up time varied across studies depending on the outcome being reported, but ranged from 21 days to 3 months.

One evidence-based guideline[32] was identified that presented recommendations that were broader in scope than this report; however, recommendations related to the management of pre-operative anemia were presented. Recommendations were developed by 2 reviewers based on a systematic review of evidence.[32] In addition, 1 evidence-based guideline from NICE[33] was identified from the literature search but did not provide any specific recommendations related to the use of IV iron supplementation for patients identified as iron deficient undergoing elective surgery; therefore, no summary of can be provided. This evidence-based guideline did reference a recommendation from an evidence-based guideline from 2015[4] that was captured in the 2019 CADTH report.[11]

Country of Origin

The included SRs were conducted in the UK,[16] China,[17] the US,[18,20,21] and Canada.[19]

The included RCTs were conducted in Hong Kong,[22] Norway,[23] Egypt,[24] and Singapore.[25] The included non-randomized studies were conducted in Denmark,[26] Singapore,[27] the UK,[28,30] Canada,[29] and Germany.[31]

The included evidence-based guideline was conducted in Canada.[32]

Patient Population

Two SRs[16,21] included primary studies of adult patients undergoing elective abdominal surgery receiving pre-operative iron supplementation; however, 1 of these SRs[16] did not restrict on the type of iron supplementation, while the other SR specified including studies that focused on IV iron supplementation.[21] One SR included primary studies of patients who received iron supplementation undergoing surgery for colorectal cancer.[17] One SR included primary studies of adult patients who receive intra-operative or post-operative iron supplementation for elective total joint arthroplasty surgery.[18] Two SRs[19,20] included primary studies of adult patients who received IV iron supplementation and underwent any elective surgery. One of these SRs focused on pre-operative IV iron supplementation,[19] while the other did not specify.[20]

One RCT included adults with colorectal cancer undergoing elective curative tumour resection operation and anemia or iron deficiency.[22] One RCT included patients who severe aortic stenosis and iron deficiency.[23] One RCT included patients aged 52 to 67 with anemia scheduled for elective coronary artery bypass grafting.[24] One RCT included adult patients with iron deficiency or anemia scheduled for elective major abdominal surgery.[25]

Four non-randomized studies (3 retrospective cohort studies[27-29] and 1 prospective cohort study)[31] included adult patients undergoing any elective surgery but did specify that patients included in the study were either iron deficient and/or anemic. One non-randomized study included adult patients undergoing colorectal cancer surgery with iron deficiency anemia.[26] One non-randomized study included adult elective cardiac and aortic surgical patients with iron deficiency and anemia.[30]

The target population for the included evidence-based guideline was patients with comorbid condition, specifically anemia, hyperglycemia, and smoking, undergoing major surgery.[32] The authors did not specify a type of major surgery for the recommendations.

Interventions and Comparators

Consistent with the inclusion criteria for the current report, the identified SRs included primary studies examined the effectiveness of IV iron supplementation for patients identified as iron deficient undergoing elective surgery.[16-21] The type of IV iron supplementation included IV ferric carboxymaltose,[16-21] IV iron sucrose,[16,17,19,21] IV isomaltoside,[17,18] and unspecified IV iron.[16,19] IV iron supplementation was administered pre-operatively,[16,17,19-21] intra-operatively,[18] and/or post-operatively[17,18,20] at varied doses ranging from 100 mg to 2,000 mg. The comparators for the identified SRs included oral iron supplementation (usual care),[16-21] placebo,[16-21] and no treatment.[17,18,20,21]

Similarly, the identified RCTs examined to effectiveness various IV supplementation including IV iron isomaltoside or ferric derisomlatose,[22,23] and IV ferric carboxymaltose.[24,25]

IV supplementation for each RCT was given pre-operatively at various doses ranging from 1,000 mg to 2,000 mg.[22-25] The comparators for the identified RCTs included no treatment,[22] placebo,[23,24] or oral iron supplementation.[25] The non-randomized studies examined the effectiveness of various IV supplementation including IV ferric carboxymaltose,[26,27,31] IV iron isomaltoside,[28,30] and IV iron sucrose.[29] Each non-randomized study administer the IV iron supplementation pre-operatively at various doses ranging from 200 mg to 1,000 mg.[26-31] The comparators for the identified non-randomized studies included no treatment[26,28-31] and oral iron supplementation.[27,29]

The identified evidence-based guideline presented diagnostic and treatment algorithms for the management of pre-operative anemia which included a recommendation related to IV iron supplementation specifically.[32]

Outcomes

The identified SRs reported outcomes related to the clinical effectiveness of IV iron supplementation for patients identified as iron deficient undergoing elective surgery. Each SR reported outcomes related to patient hemoglobin levels, and safety and adverse events including mortality and infection.[16-21] Five SRs reported outcomes related to the incidence of blood transfusion.[16,17,19-21] Three SRs reported on patient quality of life outcomes,[18-20] and 2 of these SRs reported on hospital length of stay.[19,20] Additional clinical effectiveness outcomes were captured in the SRs, which included incidence of anemia,[18,19] measures of ferritin level,[19,20] and various measures of functional outcomes.[18]

Similarly, the identified RCTs and non-randomized studies reported outcomes related to the clinical effectiveness of IV supplementation for patients identified as iron deficient undergoing elective surgery. Each RCT[22-25] and 3 non-randomized studies reported outcomes related to patient hemoglobin levels.[26,28,29] Two RCTs[22,25] and 6 non-randomized studies[26-31] reported outcomes related to the incidence of blood transfusion. Each RCT[22-25] and 2 non-randomized studies[26,30] reported various outcomes related to safety and adverse events. In relations to safety and adverse event outcomes, 2 of the RCTs[23,24] and 4 non-randomized studies[26,28,30,31] reported mortality outcomes, while 3 RCTs[22-24] and 2 non-randomized studies reported infection related outcomes.[26,30] Three RCTs[22,23,25] reported outcomes related to quality of life measured by quality of recovery[22] and the European Quality of Life – 5 Dimensions questionnaire.[23,25] Three RCTs[22,24,25] and 4 non-randomized studies[26-28,31] reported outcomes related to length of patient recovery measured by length of hospital stay[22,24,26-28,31] or days alive at home.[22,25,26] Additional clinical effectiveness outcomes were captured from the identified RCTs and non-randomized studies including measures of ferritin level,[22,23,28] and measures of functional outcomes.[23]

The identified evidence-based guideline provided recommendations related to the use of IV iron supplementation for the management of pre-operative anemia for patients undergoing surgery.[32] The strength of recommendation and quality of evidence supporting the recommendation was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE).[32]

Summary of Critical Appraisal

An overview of the critical appraisal of the included studies is summarized below. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Tables 5 to 7.

Systematic Reviews

All 6 included SRs provided clearly defined research questions and inclusion criteria, included multiple databases in the literature searches, and provided adequate details of the included primary studies.[16-21] Four SRs stated that review methods were established before the review was conducted,[16,19-21] with 3 of the SRs providing PROSPERO registration numbers.[16,19,21] Each SR also indicated that literature search screening and study inclusion was conducted in duplicate,[16-21] but only 4 SRs indicated that additional handsearching of included or relevant studies was done.[16,17,19,20] Two SR indicated that no restrictions were included in the search methods,[17,19] while 3 SRs indicated that no restrictions on search time frame was included in their search.[16,18,20] Two SRs indicated that data extraction of primary studies was performed in duplicate,[17,19] while 1 study indicated that data extraction was performed by 1 author and checked by another author[21]; thus minimizing potential errors in data collection. Each SR assessed the risk of bias of the included primary studies using appropriate techniques,[16-21] while 4 SRs used appropriate techniques for assessing publication bias.[16,17,19,20] SRs with MA included appropriate methods of statistical combination and measurement of heterogeneity (e.g., Cochrane's Q-test and I^2 statistics).[16,17,19] Two SRs indicated that risk of bias was accounted for in the analysis,[19,20] while all 3 of the SRs with MA indicated that heterogeneity was accounted for and discussed in their findings.[16,17,19] Three SRs disclosed if any funding was received for the review,[17,20,21] and 5 SRs disclosed any potential conflict of interest implications for the review.[17-21]

Overall, none of the SRs provided justification for their exclusion criteria or a list of excluded studies,[16-21] while 5 of the SRs did not adequately justify the included study designs for the review.[16-19,21] SRs that included publication restrictions did not provided adequate details or justifications for restricting publication in their search.[16,18,20,21] This lack of detail may present issues in determining if bias may have impacted the authors selection of primary studies. Two SRs did not indicate if the review protocol was established in advance of conducting the review, presenting challenges in determining if there had been any post hoc deviations to the findings.[17,18] None of the SRs reported sources of funding for the included primary studies.[16-21] Three SRs did not provide adequate information related to the statistical analysis, presenting challenges in determining if appropriate statistical analyses were conducted for primary study outcomes.[18,20,21] Three SRs did not indicate if risk of bias was accounted for in their findings.[16,18,21] Finally, 3 SRs did not report if any funding was received for the review,[16,18,19] while 1 of these SRs did not report if there was any potential conflicts of interest which may impact the ability to determine if these review may have been impacted by any external influence.[16]

Randomized Controlled Trials

All 4 RCTs clearly defined the objective, outcomes, inclusion and exclusion criteria, interventions used, and characteristics of included patients.[22-25] Three of the RCTs indicated that the trial protocol had been registered before conducting the trial.[22,24,25] Each RCT clearly described the main findings and included appropriate measures of variability (standard deviation, mean difference, 95% confidence intervals[CI]) and exact P values when needed.[22-25] Each RCT used appropriate statistical tests to assess main outcomes and outcome measures were valid and reliable.[22-25] The patients who were recruited in each RCT and who participated in the trials were likely representative of the entire population from which they were recruited.[22-25] For 2 of the RCTs,[22,24] it is likely that the staff, places, and facilities used in the trial may have been representative of the treatment that majority of patients would likely receive; the level of detail related to staff, places, and facilities was insufficient and therefore unclear for 2 RCTs.[23,25] Three RCTs reported that no patients were lost to follow-up,[22,24,25]

and 1 RCT provided characteristics of any patients that were lost to follow-up.[23] Only 1 RCT blinded the patients, investigators, and data collectors to the treatment received,[23] while 2 RCT indicated that only those providing the treatment, the investigators, and data collectors were blinded to the treatment received by the patient.[22,24] One RCT indicated that patients were not blinded to the treatment for safety considerations.[22] One RCT did not provide details of patient blinding,[24] while another RCT indicated that neither the patients, investigators, or data collectors were blinded to treatment allocation.[25] Each RCT clearly described the randomization process,[22-25] while 3 studies clearly described randomization concealment strategies.[22-24] Because of the nature of the intervention, it was assumed that compliance to the intervention was reliable for each RCT.[22-25] Sufficient power calculations were used to determine adequate sample sizes for 3 RCT,[22-24] while 1 RCT did not provide details related to determining adequate sample size.[25] Each RCT provided information related to any funding received for the trial, and any potential conflicts of interest implications.[22-25]

Non-Randomized Studies

All 6 non-randomized studies clearly defined the objectives, outcomes, inclusion criteria, interventions used, and characteristics of included patients.[26-31] Four of the non-randomized studies received ethical approval,[26,27,29,30] while 1 non-randomized study registered the protocol before conducting their study.[31] Each non-randomized study clearly described the main findings including appropriate measures of variability (interquartile range, standard deviation, 95% CI) and exact P values when needed.[26-31] Each non-randomized study used appropriate statistical tests to assess main outcomes and outcome measures used were valid and reliable.[26-31] Five non-randomized studies used patient data from the same population over the same period of time for both intervention and comparator groups, and patient data was likely representative of the population from which they were recruited.[26-29,31] One non-randomized study identified principle confounders and accounted for possible confounding factors in the analysis using regression models.[29] Five non-randomized studies did not adequately identify principle confounders and it was not clear if confounding factors were accounted for in the analysis.[26-31] One non-randomized study indicated that sufficient power calculations were used to determine adequate sample size.[27] It is unclear if all important adverse events were captured in any of the non-randomized studies.[26-31] Due to the retrospective cohort study design of 5 non-randomized studies, it is unlikely that follow-up information was captured.[26-30] One non-randomized study that used a prospective cohort study design did not provide sufficient detail related to patient loss to follow up, and it was unclear if loss to follow-up was accounted for in the analysis.[31] Three non-randomized studies provided information related to any funding received for the study,[26,27,29] while 5 non-randomized studies declared any potential conflict of interest implications.[27-31]

Evidence-Based Guideline

The identified evidence-based guideline clearly described the overall objective and population to which the guideline is meant to apply, its target users, the systematic methods used to collect evidence, and the link between the recommendations and supporting evidence using GRADE.[32] The recommendations are easily identifiable, specific and unambiguous, and provide different options for conditions or health issues.[32] The evidence-based guideline, however, did not clearly describe the health questions covered in the guideline, did not clearly indicate if relevant professionals or the views and preferences of the target population were included in the guideline development, did not clearly indicate if additional health benefits were considered in the formulation of the recommendations, and did not clearly indicate if the guideline had been externally reviewed before its publication.[32] In addition, the evidence-based guideline did not provide criteria for evidence selection, the strengths and limitations

of the body of evidence, the methods formulating the evidence, or a procedure for updating the guideline.[32] This evidence-based guideline did not provide consideration for external applicability, and it is unclear if the guideline had been influenced by funding of competing interests.[32]

Summary of Findings

Clinical Effectiveness of IV Iron Preparations for Patients Identified as Iron Deficient Undergoing Elective Surgery

Six SRs[16-21] (3 with MA),[16,17,19] 4 RCTs,[22-25] and 6 non-randomized studies[26-31] were identified regarding the clinical effectiveness of IV iron preparations for patients identified as iron deficient undergoing elective surgery, including high blood loss surgery. Additional details are available in Appendix 4 by outcome: patient hemoglobin level (Table 8), blood transfusion occurrence (Table 9), quality of life (Table 10), days in hospital or recovery (Table 11), safety and adverse events (Table 12), and additional clinical outcomes (Table 13).

Three SRs with MA[16,17,19] were found to have some overlap between studies included in their analysis. A summary table outlining the degree of overlap between the SRs is included in Appendix 5. One SR with MA[16] in which each primary study was captured in another SR was included in this report because the MA presented a combined synthesis of outcomes not captured in other SRs included in this report. Similarly, findings from other SRs are presented for uniquely reported outcomes or primary studies that are not captured in any other included SR. Findings from included SRs with MA[16,17,19] are presented as combined measures of effects, and no attempt was made to present findings from individual studies included in each MA, thus the pooled estimates from separate SRs contain some of the same data. When applicable, findings are presented in relation to comparator as patients who did not receive IV iron supplementation or patients who received oral iron supplementation.

Patient Hemoglobin Level

When Compared to No Treatment or Placebo

Two SRs with MA found that patients who received IV iron supplementation showed statistically significantly higher concentrations of hemoglobin compared to those who did not receive IV iron supplementation.[16,17] Similarly, the third SR with MA found that patients who received IV iron supplementation showed a statistically significantly greater increase in hemoglobin concentrations compared to those who did not receive IV iron supplementation at post-treatment and over 4 weeks post-operatively.[19] One SR[18] included 4 primary RCT studies that reported on mean hemoglobin concentrations at various time points between patients who received IV iron supplementation and patients who did not; however, numerical findings and P values were not presented among studies for these outcomes. One included RCT reported that mean post-operative hemoglobin levels significantly favoured those who received IV iron supplementation.[18] One included RCTs reported that the change in pre-operative to post-operative hemoglobin levels was not significant for all patients, but 2 included RCTs reported that change in hemoglobin levels at post-operative day 30 significantly favoured those who received IV iron supplementation.[18] Two included RCTs reported the rate of anemia at post-operative day 30 was significantly lower for those who received IV iron supplementation.[18]

One SR[20] included 3 primary RCT studies not captured in a SR with MA that reported on measured of hemoglobin concentration at various time points between patients who received IV iron supplementation and patients who did not; however, statistical comparisons were

not presented for the studies. Two included RCTs consistently showed higher levels of hemoglobin concentrations for patients who received IV iron supplementation compared to patients who did not, however it is unclear whether these findings are statistically different.[20] One SR[21] included 3 primary studies (3 non-randomized studies) that reported on the mean change in hemoglobin concentration from iron deficiency diagnosis to surgical admission for patients who received IV iron supplementation compared to patients who did not. Three included primary studies showed that the change in hemoglobin concentration was statistically significantly larger for patients who received IV iron supplementation.[21]

Two RCTs reported the mean change in hemoglobin from baseline to before the time of surgery[22] or follow-up,[23] and reported that patients who received IV iron supplementation showed a statistically significantly greater change in hemoglobin compared to patients who did not receive IV iron supplementation.[22,23] One RCT reported the comparison of mean hemoglobin concentrations at various time points, including on admission, pre-operatively, post-operatively, 1 week after surgical discharge, and 4 weeks after surgical discharge for patients who received IV iron supplementation compared to placebo.[24] The RCT reported that patients who received IV iron supplementation showed statistically significantly higher hemoglobin concentrations pre-operatively and 4 weeks after surgical discharge, while a statistically significantly lower hemoglobin concentration was shown post-operatively.[24] The findings should be interpreted with caution because these only give a comparison of hemoglobin level at certain time points rather than comparing a change in hemoglobin levels over time. In addition, the RCT reported that patients who received IV iron supplementation had a statistically significantly lower incidence of anemia 4 weeks after surgical discharge compared to placebo.[24]

One retrospective cohort study reported that the mean change between baseline and pre-operative hemoglobin concentrations were higher for patients who received IV iron supplementation compared to patients who did not, but this change was not statistically significantly different.[26]

One retrospective cohort study compared mean hemoglobin levels at various time points across different patients groups, which included patients who were responsive to IV iron supplementation, patients who were unresponsive to IV iron supplementation, patients who did not received treatment, and patients who were not anemic.[28] The authors of this retrospective cohort study found that the change in mean hemoglobin concentrations were statistically significantly different from pre-assessment to pre-operative phase, while the change in mean hemoglobin concentrations were lowest among patients who did not received treatment from pre-operative to post-operative phase but the measure of statistical significance was not reported.[28]

When Compared to Oral Iron

One SR included 1 RCT that reported a lower level of hemoglobin concentration for patients who received IV iron supplementation compared to patients who received oral iron supplementation; however, it is unclear whether these findings are statistically different.[20]

One RCT reported that the mean rise in hemoglobin levels was not statistically significantly different between patients who received IV iron supplementation and those who received oral iron supplementation.[25]

One retrospective cohort study reported the change in hemoglobin concentration from referral to pre-operative for patients who received IV iron supplementation at 3 different

doses (1 to 300 mg, 301 mg to 600 mg, and > 600 mg), and patients who received oral iron supplementation.[29] The authors reported that patients who received IV iron supplementation at more than 600 mg showed a statistically significant increase in hemoglobin concentration from referral to pre-operative, while each other group showed an increase but was reported to be not significant.[29]

Blood Transfusion Occurrence

When Compared to No Treatment or Placebo

Three SRs with MA with some overlapping primary studies reported findings on the combined total number of blood transfusions received between patients who received IV iron supplementation and patients who did not.[16,17,19] A non-statistically significant finding from 1 SR with MA suggest that for patients who received pre-operative IV iron supplementation there may be little-to-no difference in risk of receiving a pre-operative blood transfusion when compared to patients who received no treatment [i.e., risk ratio (95% CI), 0.57 (0.30 to 1.09); P = 0.09].[16] However, this finding was based on a MA of 4 studies and there was a moderately high level of statistical heterogeneity (i.e., I^2 = 64%), and it is unclear whether this had an impact on the precision of this effect estimate.

One SR with MA reported that the risk of receiving a blood transfusion was statistically significantly lower for patients who received IV iron supplementation compared to patients who did not [i.e., 35% lower risk (95% CI, 52% to 12%); P = 0.005].[17] One SR with MA reported the risk of receiving a blood transfusion was statistically significantly lower for patients who did not receive IV iron supplementation in both a random and fixed effects model, respectively [i.e., 16% lower risk (95% CI, 29% to 1%); P = 0.04; 17% lower risk (95% CI, 30% to 2%); P = 0.03].[19]

One SR[20] included 5 primary RCT studies that reported the proportion of patients who received an allogenic blood transfusion for patients who received IV iron supplementation compared to patients who did not; however, statistical comparisons were not presented among studies. The proportion of patients who received an allogenic blood transfusion varied across individual studies, with 3 RCTs reporting a lower proportion of blood transfusions for patients who received IV iron supplementation while 2 RCTs reported higher proportions of blood transfusions for patients who received IV iron supplementation; however, it is unknown whether these difference are statistically significant.[20] One SR[21] included 3 non-randomized studies that reported the proportion of patients who received a blood transfusion and the amount of blood transfused between patients who received IV iron supplementation and those who did not. The proportion of patients who received a blood transfusion was not statistically, significantly different for 2 non-randomized studies, while 1 retrospective cohort study showed that a the proportion of patients who received a blood transfusion was statistically significantly lower for patients who received IV iron supplementation compared to patients who did not.[21] Similarly, the amount of blood transfused was not statistically significantly different for 1 retrospective cohort study, while 1 retrospective cohort study showed that the amount of blood transfused was statistically, significantly lower for patients who received IV iron supplementation compared to patients who did not.[21]

Two RCTs reported on the number of patients who received a red blood cell transfusion at various time points for patients who received IV iron supplementation compared to patients who did not.[22,25] One RCT found that the proportion of patients who received a red blood cell transfusion pre-operatively and post-operatively was lower for patients who received IV iron supplementation but was not shown to be statistically significant.[22]

One retrospective cohort study reported the median number of blood transfusion at various time points, and found that the group of patients who received IV iron supplementation had a higher proportion of blood transfusions at the pre-operative, day of surgery, and post-operative time points compared to the group of patients who did not receive IV iron; however, no statistical comparisons were reported, thus limiting the interpretation of these findings.[26] One retrospective cohort study found that the median number of red blood cell units transfused perioperatively was statistically significantly lower for patients who were responsive to IV iron supplementation compared to patients who received IV iron supplementation and were unresponsive or patients who were untreated.[28] One retrospective cohort study found that anemic patients who received IV iron supplementation had a statistically significantly higher number of blood transfusion events and median number of blood cell units transfused compared to patients who were not anemic and did not receive treatment; however, no statistically significant difference was found between anemic patients who received IV iron supplementation and anemic patients who did not receive IV iron supplmentation.[30] One prospective cohort study found that the mean total blood cell units transfused was highest among patients who are anemic and did not receive treatment compared to patients who are anemic, iron deficient, and received IV iron supplementation or patients who are not anemic and did not receive treatment; however, statistical comparisons were not presented among patient groups, thus limiting the interpretation of these findings.[31]

One retrospective cohort study showed that patients who received IV iron supplementation at the lowest dose (1 mg to 300 mg) had statistically significantly greater odds of receiving a blood transfusion compared to no treatment.[29] Patients who received IV supplementation at larger doses (301 mg to 600 mg, and > 600 mg) and oral iron supplementation reported that the odds of receiving a blood transfusion compared to no treatment was not statistically significantly different.[29]

When Compared to Oral Iron

One SR with MA also reported that the risk of blood transfusion between patients who received IV iron supplementation and patients who received oral iron supplementation was not statistically significantly different [i.e., risk ratio (95% CI), 0.88 (0.51 to 1.51); P = 0.63].[19]

One RCT that compared patients who received IV iron supplementation to oral iron supplementation found no statistically significant difference in the number of patients who received a blood transfusion from recruitment to discharge, pre-operatively, or post-operatively.[25] The RCT found a statistically significantly larger number of patients who received IV iron supplementation had blood transfusions intra-operative [i.e., 6 (46.2%) versus 1 (7.7%) respectively; P = 0.03].[25]

One retrospective cohort study reported the number of blood transfusions at various time points for patients who received IV iron supplementation compared to oral supplementation, and found that patients who received IV iron supplementation had a significantly lower number of intra-operative blood transfusions.[27] The authors found that number of transfusions received over the entire peri-operative period was not statistically significantly different between IV iron and oral iron supplementation.[27]

Quality of Life

When Compared to No Treatment or Placebo

One SR included 1 primary RCTs that reported quality of life outcomes using the European Quality of Life – 5 Dimension Questionnaire (EQ-5D).[18] The SR authors reported that for

the included RCT that the difference in EQ-5D scores between patients who receive IV iron supplementation and patients who did not was not significant, however, no numerical or statistical values were reported.[18] One SR with MA reported quality of life outcomes from 2 included RCTs, and the SR authors reported that the changes in quality of life outcomes were not statistically significant at 60-days post-hospital discharge and 4 weeks post-surgery for patients who received IV supplementation and patients who did not; however, the measurements were not reported.[19]

One SR included 3 primary RCTs that reported on various quality of life outcomes for patients who received IV iron supplementation compared to patients who did not; however, statistical significance findings were not presented among studies.[20] One included RCT reported that quality of life, physical, and mental scores from post-operative day 1 to week 12 were higher for patients who received IV iron supplementation compared to patients who did not.[20] One included RCT reported that mean fatigue and dyspnea scores were lower for patients who received IV iron supplementation compared to placebo.[20] One included RCT reported similar mean EQ-5D 5 level utility and health scores at 10 days, 8 weeks, and 6 months post-operative and similar multi-dimensional fatigue inventory scores for patients who receive IV iron supplementation compared to placebo.[20]

One RCT reported a lower median quality of recover score for patients who received IV iron supplementation compared to patients who did not; however, this was not statistically significantly different.[22] One RCT reported EQ-5D 3 level index and visual analogue scale scores at baseline and follow up and found no statistically, significant difference between patients who received IV iron supplementation and placebo.[23]

When Compared to Oral Iron

One SR included 1 RCT that reported quality of life outcomes using the EQ-5D and independence index score outcomes.[18] The SR authors reported that the difference in EQ-5D scores and independence index scores between patients who received IV iron supplementation and oral iron supplementation was not significant; however, no numerical or statistical values were reported.

One RCT reported no statistically significant difference in EQ-5D 3 level scores at baseline, 1 month, and 3-month follow-up for patients who received IV iron supplementation compared to oral iron supplementation.[25]

Days in Hospital or Recovery

When Compared to No Treatment or Placebo

One SR included 8 primary RCTs that reported mean or median length of stay in hospital for patients who received IV iron supplementation compared to patients who did not; however, statistical comparisons were not presented for the studies.[20] Each included RCT reported the same or a lower number of days spent in hospital for patients who received IV iron supplementation compared to patients who did not, but the lack of statistical comparisons limits the certainty in these findings.[20] One SR included 3 non-randomized studies (1 retrospective cohort studies, 1 retrospective and prospective cohort study, and 1 prospective cohort study) that reported the mean length of hospital stay for patients who receive IV iron supplementation compared to patients who did not.[21] Two included non-randomized studies reported no statistically significant difference in mean length of hospital stay between groups, while 1 retrospective and prospective cohort study reported a statistically significant lower number of days spent in hospital for patients who received IV iron supplementation.[21]

One RCT reported no statistically significant difference in median post-operative length of stay days and days at home within 30 days of surgery for patients who received IV iron supplementation compared to patients who did not.[22] One RCT reported that patients who received IV iron supplementation showed a statistically significantly lower length of hospital and ICU stay compared to placebo.[24]

One retrospective cohort study reported no statistically significant difference in median length of hospital stay days and days alive and out of hospital at 30 days and 90 days between patients who receive IV iron supplementation and those who did not.[26] One retrospective cohort study reported that the mean length of stay in days was statistically significantly higher among patients who received IV iron supplementation but were unresponsive to treatment compared to patients who were not anemic and did not receive treatment.[28] One prospective cohort study found that the mean length of hospital stay in days was lowest among patients who were not anemic and received no treatment compared to patients who were anemic, iron deficient and received IV iron supplementation, patients who were just iron deficient and received IV iron supplementation, and patients who were anemic and did not receive treatment; however, statistical comparisons were not presented among patient groups, thus limiting the interpretation of these findings.[31]

When Compared to Oral Iron

One RCT reported that patients who received IV iron supplementation compared to oral supplementation showed no statistically significant difference in mean days alive and out of hospital at 30 days, 3 months, and 6 months.[25]

One retrospective cohort study reported a statistically significantly lower mean length of hospital stay for patients who received IV iron supplementation compared to oral supplementation.[27]

Safety and Adverse Events

When Compared to No Treatment or Placebo

One SR included 2 primary RCTs that reported the rates of adverse events for patients who received IV iron supplementation compared to patients who did not; however, no statistical comparisons were presented among studies.[18] The rates of adverse events was similar for patients who received IV iron supplementation compared to patients who did not for both included RCTs, with 1 RCT reporting no adverse events for both groups.[18]

One SR with MA reported on the occurrence of serious adverse effects based on findings from 2 included primary studies, and the occurrence non-serious adverse effects based on the findings from 7 included primary studies.[19] The findings suggest that patients who received IV iron supplementation had no difference in risk of serious adverse effects compared to patients who did not receive IV iron supplementation [i.e., risk ratio (95% CI), 0.96 (0.44 to 2.10); P = 0.92].[19] The findings also suggested that patients who received IV iron supplementation had little-to-no difference in risk of non-serious adverse effects compared to patients who did not receive IV iron supplementation [i.e., risk ratio (95% CI), 1.13 (0.78 to 1.65); P = 0.52].[19]

One SR included 4 primary RCTs that reported the proportion of patients who experienced adverse events for patients who receive IV iron supplementation and patients who did not; however, no statistical comparisons were presented among studies.[20] Two included RCTs reported that a higher proportion of patients who received IV iron supplementation

experienced adverse events compared to placebo, while 2 included RCT reported that 0 patients who received IV iron supplementation experience adverse events.[20]

One RCT reported the number of patients who experienced any surgical complications, the grade of surgical complication, and hospital readmissions within 30 days and found no statistically significant difference in each outcome for patients who received IV iron supplementation compared to patients who did not.[22] One RCT reported that patients who received IV iron supplementation had a lower number of serious and non-serious adverse events compared to patients who received placebo.[23] One RCT reported the incidence of adverse cardiovascular events, prolonged ventilation, heart failure, and stroke for patient who receive IV iron supplementation compared to placebo.[24] Patients who received IV iron supplementation reported lower numbers for each outcome compared to placebo; however, the incidence for each outcomes was not significantly different.[24]

One retrospective cohort study reported the proportion of patients experiencing any complication, surgical complications, and medical complications for patient who received IV iron supplementation compared to patients who did not.[26] The authors found that the number of all complications and surgical complications was significantly higher for patients who received IV iron supplementation, and that the number of medical complications was higher for patients who received IV iron supplementation but was shown to be not statistically significant.[26]

One retrospective cohort study reported the number of cerebrovascular accidents, renal replacement procedures, and re-operations for patients who are anemic and received IV iron supplementation, patients who are anemic and did not receive IV supplementation, and patient who are not anemic.[30] Overall, patients who are anemic and received IV iron supplementation reported the highest relative proportion for each outcome across groups.[30]

One SR with MA,[19] and 1 SR[20] with 2 included primary RCTs not captured in a SR with MA reported the difference in risk and proportion of patients who died for patients who received IV iron supplementation compared to those who did not. The authors of the SR and MA reported little-to-no difference in the risk of mortality at 30-days post-operatively and more than 2 months post-hospital discharge.[19] The SR reported similar proportions of post-operative mortality across both included RCT for patients who received IV iron supplementation compared to patients who did not.[20] In addition, 2 RCTs,[23,24] 3 retrospective cohort studies,[26,28,30] and 1 prospective cohort study reported the number of deaths or mortality rate for patients who received IV iron supplementation compared to patients who did not. Generally, the number or rate of mortality was similar for each included primary study[23,24,26,28,30,31]; however, 1 retrospective cohort study found that the number of in-hospital mortality was statistically significantly lower for patient who were anemic and received IV iron supplementation compared to patients who were anemic and did not receive IV iron supplementation.[30]

One SR with MA[19] reported little-to-no difference in the risk of post-operative infection for patients who received IV iron supplementation compared to patients who did not.[19] Three RCTs[22-24] and 2 retrospective cohort studies[26,30] reported number or incidence of infections between patients who received IV iron supplementation and patients who did not. Generally, the number or incidence of infections were similar between groups and no statistically significant difference was found in any of the included primary studies.[22-24,26,30]

When Compared to Oral Iron

One RCT reported the number patients readmitted to hospital for 6 months follow-up was not statistically significantly different between patients who received IV iron supplementation and oral iron supplementation.[25]

Additional Clinical Outcomes

Functional Outcomes

One SR included 2 primary RCTs that reported functional outcomes for 6-Minute Walk Test scores and Functional Assessment of Cancer Therapy for patients with Anemia/Fatigue scores and the SR authors reported that the difference in both functional outcomes was not significant for patients who received IV iron supplementation and patients who did not, however, numerical findings were not reported.[18] One RCT reported the mean 6-Minute Walk Test distance between patients who received IV iron supplementation and placebo at baseline and follow-up and found the mean difference in distance between the groups was not statistically significantly different.[23]

Ferritin Levels

One SR and MA reported mean ferritin level differences at various time points.[19] The authors found that mean ferritin levels were significantly higher at post-treatment and pre-surgery, hospital discharge, and at 4 or more weeks post-operative for patients who received IV iron supplementation compared to patients who did not.[19] Two RCTs reported a significantly greater mean change in ferritin concentration from baseline to before surgery or follow-up for patients who received IV iron supplementation compared to patients who did not.[22,23,28]

Cost-Effectiveness of IV Iron Preparations for Patients Identified as Iron Deficient Undergoing Elective Surgery

No evidence was identified regarding the cost-effectiveness of IV iron preparations for patients identified as iron deficient undergoing elective surgery; therefore, no summary can be provided.

Guidelines Regarding the Use of IV Iron Preparations for Patients Identified as Iron Deficient Undergoing Elective Surgery

One evidence-based guideline was identified regarding the use of IV iron preparations for patients identified as iron deficient undergoing elective surgery, including high blood loss surgery.[32] Additional details are available in Appendix 4, Table 14.

The guideline recommends that IV iron supplementation may be appropriate for patients with iron deficient anemia in certain circumstances which includes less than 8 weeks until surgery, unable to tolerate or absorb oral iron supplementation, or hemoglobin levels under 100 g/L.[32] Evidence supporting this recommendation was from 1 SR, 4 RCTS, 1 prospective cohort study, and 2 retrospective cohort studies.[32] The strength of recommendation was considered strong and the quality of evidence was considered high.[32]

Limitations

The primary studies summarized in the 6 included SRs were of variable quality.[16-21] Three of the 4 RCTs included in 1 SR with MA were shown to have high risk of bias.[16] One SR with

MA reported that each primary study (2 RCTs and 5 non-randomized studies) had low risk of bias.[17] The risk of bias for the 7 RCTs included in 1 SR were reported to be varied, with 4 RCTs having low risk of bias, 1 RCT having high risk of bias, and 2 RCTs having unclear risk of bias.[18] Six of the 10 included RCTs for 1 SR with MA were reported to have unclear of high risk of bias.[19] One SR reported that each of the 10 included RCTs were considered to have high risk of bias largely due to a lack of blinding.[20] All 9 included studies for 1 SR were reported to have low risk of bias due to blinding and randomization in the RCTs and good comparability of cohorts in the non-randomized studies.[21] In addition, 3 included SR with MA reported a large degree of heterogeneity across primary studies for major outcomes related to hemoglobin concentration[16,17,19] and risk of blood transfusion.[16] There was also a large degree of overlap in primary studies included in the SRs, and this overlap should be considered when interpreting findings from SRs with MA.[16,17,19]

The evidence in this report may be limited by the clinical heterogeneity of the included publications. The type of IV iron supplementation, the time of administration, and the dose of supplementation varied across each included SR and primary study included in this report. In addition, the type of comparator varied across each study and some included studies described the comparator as a control, which may include more than 1 relevant comparator. The populations varied across each study, specifically in relation to the type of surgery that was provided which can be challenging to compare outcomes between surgery type. Because of the heterogeneity across each study in terms of intervention used and comparator, it may be challenging to determine the generalizability of the overall findings for outcomes related to clinical effectiveness of IV iron use in patients identified as iron deficient. The recommendation from the included evidence-based guideline did not specify the type, administration, or dose of IV iron supplementation; however, this may be dependent on the patient and type of surgery.

No evidence was identified regarding the cost-effectiveness of IV iron preparations for patients identified as iron deficient undergoing elective surgery, and no conclusion can be drawn related to funding considerations for this treatment.

One non-randomized study[29] and the included evidence-based guideline[32] was conducted in Canada. One SR and MA was conducted in Canada but included primary studies from a variety of countries.[19] Majority of the included evidence related to the clinical effectiveness of IV iron use for patients identified as iron deficient undergoing elective surgery were conducted in a variety of countries. Thus, it is unclear how generalizable the findings are to the Canadian context. This should be considered because the prevalence of iron deficiency, access to elective surgeries, and availability or type of IV iron supplementation may vary between countries, and therefore may have different implications depending on the population and cultural context.

Conclusions and Implications for Decision- or Policy-Making

This report included 6 SRs (3 with MA),[16-21] 4 RCTs,[22-25] 6 non-randomized studies,[26-31] and 1 evidence-based guideline related to the use of IV iron preparations for patients identified with iron deficiency undergoing elective surgery, including high blood loss surgery. No evidence

was identified regarding the cost-effectiveness of IV iron preparations for patients identified as iron deficient undergoing elective surgery.

Each of the included studies and evidence-based guideline specified that the population of interest included adult patients identified as anemic and/or iron deficient undergoing elective surgery.[16-32] Most of the included studies specified that IV iron treatment was administer pre-operatively,[16,19,21,22,24-30] while some studies indicated that IV iron was administered intra-operatively, post-operatively, or did not specify.[17,18,20,23,31,32] Each study indicated the specific type and dose of IV iron supplementation used, but this varied among studies. The type of IV iron supplementation included IV ferric carboxymaltose, iron sucrose, iron isomaltoside, or unspecified IV iron and doses ranged from 100 mg to 2,000 mg.

Based on the evidence summarized within this report, patients who received IV iron supplementation were reported to generally have greater increases in the change of hemoglobin levels at various time points of the surgical care compared to patients who did not receive IV iron supplementation.[16-24,26,28] Similar findings were present for patient ferritin levels.[19,22,23] The evidence also showed that patients who received IV iron supplementation had similar or lower lengths of hospital stay or days in recovery compared to patients who did not receive IV iron supplementation.[20-22,24,26,28,31] The evidence related to the number of patients who received a blood transfusion was mixed, with some studies reporting fewer blood transfusion occurrences while some studies reported no difference or more blood transfusion occurrences for patient who received IV iron supplementation compared to patients who did not.[16,17,19-22,26,28,30,31] Findings related to blood transfusion occurrences should be interpreted with caution due to measurements of imprecision and heterogeneity within studies, and a lack of statistical tests reported for some results. Because of these variations in findings, it is challenging to accurately draw conclusion on the impact of IV iron supplementation for blood transfusion occurrences. The evidence related to patient quality of life generally found outcomes for patients who received IV iron supplementation and patients who did not were similar for various quality of life measures.[18-20,22,23] Similarly, the evidence that reported on outcomes related to adverse events and safety was mixed but generally found no differences between patients who received IV iron supplementation and patients who did not for various outcomes.[18-20,22-24,26,30] In addition, evidence related to the number or rate of mortality[19,20,23,24,26,28,30,31] and the number or incidence of infection[19,22-24,26,30] generally found similar or no difference in patients who received IV iron supplementation compared to patients who did not. Outcomes related to patient function also showed no difference in patients who receive IV iron supplementation and patients who did not.[18,23]

In general, the studies summarized in this report suggest that when compared to oral iron supplementation, those who were treated with IV iron supplementation had no difference in hemoglobin levels,[20,25,29] quality of life scores,[18,25] or the number of adverse events.[25] The findings related to mean length of stay were mixed with 1 study reporting no difference,[25] or lower lengths of stay when comparing IV iron to oral iron supplementation.[27] The findings were mixed regarding the risk of blood transfusions at various time points, with studies reporting no differences,[19,25,27] increases,[25] and decreases[27] when comparing IV iron to oral iron supplementation,

The evidence-based guideline was conducted in Canada for patients with comorbid condition, specifically anemia, hyperglycemia, and smoking, undergoing major surgery.[32] This guideline provided a strong recommendation for the use of IV iron supplementation for patients with iron deficient anemia in circumstances where surgery is less than 8 weeks away, patients are

unable to tolerate or absorb oral iron supplementation, or for patient with hemoglobin levels under 100 g/L.[32]

The previous 2019 CADTH report reported on similar outcomes related to hemoglobin concentration, blood transfusion occurrences, and adverse events including infections and mortality.[11] The findings from this report are generally consistent with those outlined in the previous CADTH report, with IV iron supplementation being favoured for hemoglobin concentration control and mixed results found for the need for blood transfusion and mortality between IV iron supplementation compared to no treatment.[11] These clinical findings may be challenging to compare between reports due to the volume and level of evidence that informed the findings in the 2019 CADTH report, which included 1 SR and 3 non-randomized studies, while the clinical evidence in this report is informed by 6 SRs (3 with MA), 4 RCTs and 6 non-randomized studies. The 2019 CADTH report also included 1 economic evaluation and an evidence-based guideline, which was used to inform an updated guideline identified (but not included) in this report.[11]

The limitations for the included literature (e.g., variable quality of primary studies included in the SRs, clinical heterogeneity of the included studies, the overall quality of the included studies, lack of cost-effectiveness literature, and limited Canadian context) should be considered when interpreting the findings of this report. The evidence from this report is meant to build from the literature that was identified in the 2019 CADTH report,[11] and provide decision-makers with the updated and relevant evidence related to the use of IV iron preparations for patients identified as iron deficient undergoing elective surgery. Further research that is specific to the Canadian context is needed to adequately assess the clinical effectiveness and cost-effectiveness of IV iron preparation and inform recommendations that are relevant to Canadian users.

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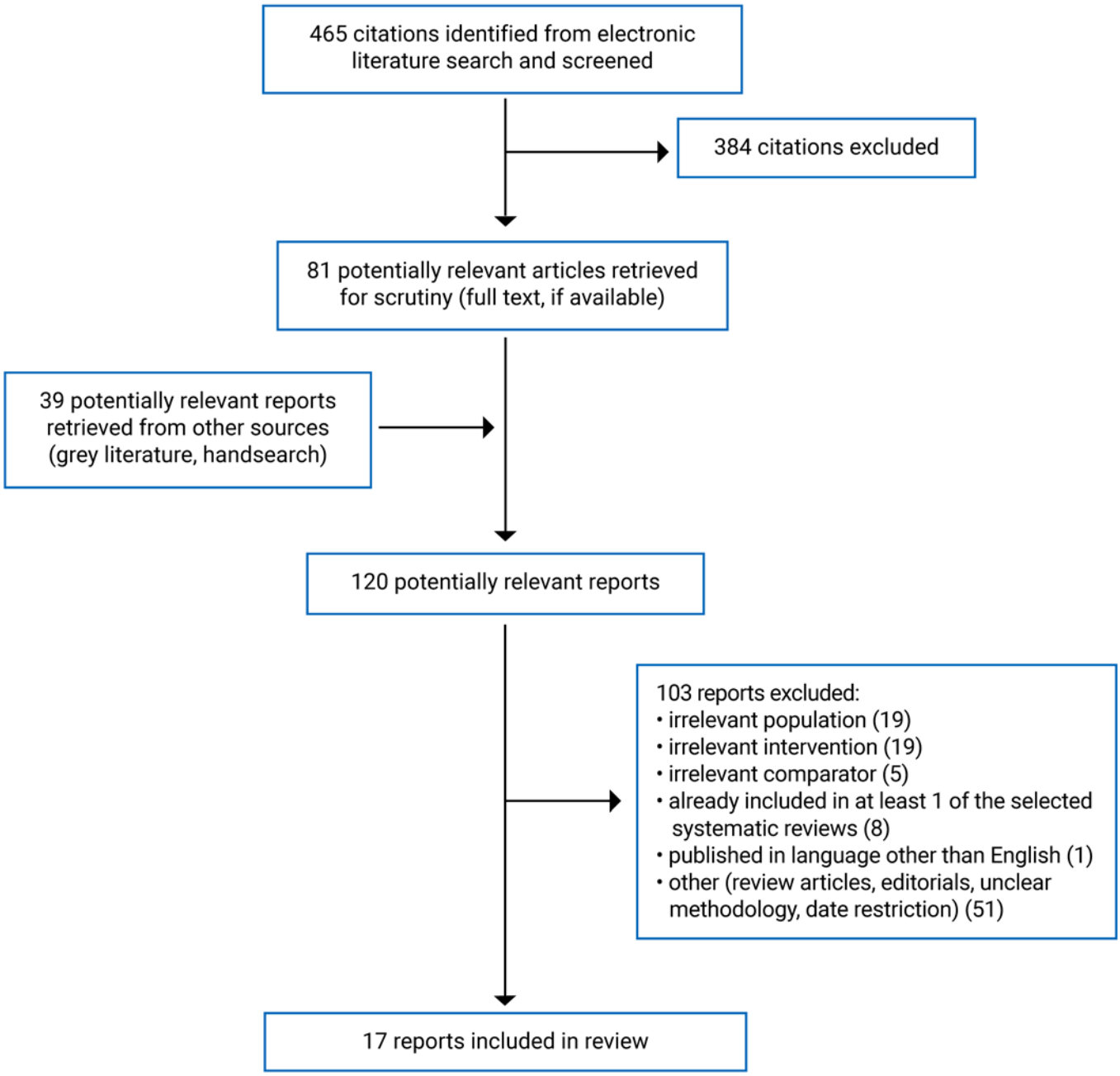
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study design, last search date and numbers of relevant primary studies included	Population characteristics	Relevant intervention(s) and comparator(s)	Relevant clinical outcomes, length of follow-up
Meyer et al. (2022)[16] UK **Funding source:** NR	**Study design:** SR with MA **Last search date:** December 2020 **Number of included studies:** 4 RCTs	**Eligibility criteria:** Studies that included patients who received pre-operative iron supplementation undergoing abdominal surgery **Total number of patients included:** 312 **Sample size (range):** 45 to 135	**Interventions (dose):** • IV iron (1,000 mg) • IV ferric carboxymaltose (15 mg/kg) • IV iron sucrose (600 mg) **Comparators**: Placebo or usual care (undefined)	**Outcomes:** • Risk of blood transfusion • Death from randomization to post-operative day 30 • Hemoglobin concentration at administration **Follow-up:** NR
Tang et al. (2022)[17] China **Funding source:** No funding	**Study design:** SR with MA **Last search date:** February 2021 **Number of included studies:** 7 (2 RCTs and 5 non-randomized studies)	**Eligibility criteria:** Studies that included patients who received iron supplementation undergoing surgery for colorectal cancer **Total number of patients included:** 879 **Sample size (range):** 45 to 318	**Interventions (dose):** • Pre-operative IV iron sucrose (600 mg) • Post-operative IV iron saccharose (100 to 200 mg) • Pre-operative IV iron carboxymaltose or iron isomaltoside (1,000 to 2,000 mg) • Pre-operative IV iron sucrose (2 doses of 500 mg) or iron isomaltoside (1,000 mg or 20 mg/kg if bodyweight under 50 kg) **Comparators**: No treatment; IV placebo; usual care (undefined)	**Outcomes:** • Change in hemoglobin concentration • Number of patients needed blood transfusion • Iron-related adverse events **Follow-up:** NR
Chaudhry et al. (2021)[18] US **Funding source: NR**	**Study design:** SR **Last search date:** December 2019	**Eligibility criteria:** Studies that included patients aged 18 years or older who received intra-operative or post-operative iron	**Interventions (dose):** • Post-operative IV ferric carboxymaltose (700 to 1,000 mg)	**Outcomes:** • Change in hemoglobin levels • Rate of post-operative anemia

Study citation, country, funding source	Study design, last search date and numbers of relevant primary studies included	Population characteristics	Relevant intervention(s) and comparator(s)	Relevant clinical outcomes, length of follow-up
	Number of included studies: 7 RCTs	supplementation for elective TJA surgery **Total number of patients included:** 646 **Sample size (range):** 58 to 122	• Intra-operative IV ferric carboxymaltose (1,000 mg) • Intra-operative IV iron isomaltoside (≤ 20 mg/kg) **Comparators:** Oral iron supplementation; placebo; no treatment	• Rate of adverse events • Post-operative QoL and functional outcomes **Follow-up:** Varied by individual study or was NR
Elhenawy et al. (2021)[19] Canada **Funding source:** NR	**Study design:** SR with MA **Last search date:** February 2019 **Number of included studies:** 10 RCTs	**Eligibility criteria:** Studies that included adult patients who received pre-operative IV iron supplementation for elective surgery **Total number of patients included:** 1039 **Sample size (range):** 56 to 203	**Interventions (dose):** • IV ferric carboxymaltose (1,000 mg) • IV iron sucrose (2 doses of 300 mg) • IV ferric carboxymaltose (15 mg/kg or up to 1,000 mg) • IV iron sucrose (3 doses of 100 mg pre- and post-operative) • IV iron (20 mg/kg or up to 1,000 mg) • IV iron sucrose (3 doses of 200 mg) • IV iron sucrose (100 mg per dose for 4 weeks as needed) • IV iron sucrose (200 mg) **Comparators:** Placebo; usual care (undefined); oral iron supplementation	**Outcomes:** • Allogeneic blood transfusion exposure • Change in hemoglobin levels • Ferritin levels • Iron-deficiency anemia • Adverse events • Mortality • Infection • Hospital length of stay • QoL **Follow-up:** Varied by study but ranged from hospital discharge to 3 months post-hospital discharge
Jones et al. (2021)[20] US **Funding source:** Peloton Advantage, LLC funded by American Regent, Inc.	**Study design:** SR **Last search date:** January 2021 **Number of included studies:** 10 RCTs	**Eligibility criteria:** Studies that included adult patients who underwent elective surgery and received IV iron supplementation **Total number of patients included:** 1975 **Sample size (range):** 44 to 481	**Interventions (dose):** • Post-operative IV ferric carboxymaltose (700 to 1,000 mg) • Pre-operative IV ferric carboxymaltose (15 mg) and post-operative IV ferric carboxymaltose (0.5 mg per 1 ml blood loss) • Post-operative IV ferric	**Outcomes:** • Change in hemoglobin concentration • Serum ferritin • Proportion of patient who received blood transfusion • Adverse events

Study citation, country, funding source	Study design, last search date and numbers of relevant primary studies included	Population characteristics	Relevant intervention(s) and comparator(s)	Relevant clinical outcomes, length of follow-up
			carboxymaltose (15 mg/kg or maximum 1,000 mg) • Pre-operative IV ferric carboxymaltose (1,000 mg/week or 2,000 mg during trial) • Pre-operative IV ferric carboxymaltose (1 to 2 doses of 1,000 mg for patients <50 kg or 500 mg for patients ≥50 kg) • Pre-operative IV ferric carboxymaltose (maximum 1,000 mg) **Comparators:** Placebo; usual care, oral iron supplementation; no treatment	• Mortality • Hospital length of stay • QoL **Follow-up:** Varied by individual study or was NR
Moon et al. (2021)[21] US **Funding source:** No funding	**Study design:** SR **Last search date:** November 2020 **Number of included studies:** 9 (5 RCTs and 4 non-randomized studies)	**Eligibility criteria:** Studies that included adult patients who underwent elective abdominal surgery and received pre-operative IV iron supplementation **Total number of patients included:** 1817 **Sample size (range):** 60 to 487	**Interventions (dose):** • IV ferric carboxymaltose (1 dose of 1,000 mg) • IV iron sucrose (2 doses of 300 mg) • IV ferric carboxymaltose (3 doses of 1,000 mg) • Pre-operative IV ferric carboxymaltose (1,000 mg) and post-operative IV ferric carboxymaltose (0.5 mg/L blood loss) • IV iron sucrose (dose unspecified) • IV iron sucrose or ferric carboxymaltose (dose unspecified) • IV ferric carboxymaltose (1,000 to 2,000 mg) • IV iron sucrose (500 mg) or IV iron	**Outcomes:** • Risk of blood transfusion • Number of transfusion episodes • Change in hemoglobin levels • Mortality **Follow-up:** Varied by individual study or was NR

Study citation, country, funding source	Study design, last search date and numbers of relevant primary studies included	Population characteristics	Relevant intervention(s) and comparator(s)	Relevant clinical outcomes, length of follow-up
			isomaltoside (1,000 mg) **Comparators:** Placebo; oral iron supplementation; no treatment	

IV = intravenous; kg = kilogram; MA = meta-analyses; mg = milligram; ml = milliliter; NR = not reported; QoL = quality of life; RCT = randomized controlled trial; SR = systematic review; TJA = total joint arthroplasty.

Note: This table has not been copy-edited.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design and objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Randomized Controlled Trials				
Fung et al. (2022)[22] Hong Kong **Funding source:** No funding	**Study design:** RCT **Objective:** To determine the effects of IV iron isomaltoside for iron deficiency treatment in individuals scheduled for colorectal surgery	**Eligibility criteria:** Adults diagnosed with colorectal cancer listed for elective curative tumour resection operation with anemia or iron deficiency **Number of participants:** 40 (20 in iron therapy group and 20 in control group) **Mean age (SD):** 68.4 (6.8) iron therapy group; 69.8 (12.6) control group **Number of males (%):** 15 (75%) iron therapy group; 9 (45%) control group	**Intervention (dose):** IV iron isomaltoside (20 mg/kg up to 1,000 mg infused for 30 minutes) 3 weeks before surgery **Comparator**: No treatment	**Outcomes:** • Changes in hemoglobin concentration • Changes in ferritin concentration • Blood transfusion during peri-operative period • Surgical complications • Post-operative length of stay • Quality of recovery **Follow-up:** 30 days after surgery for quality of recovery measurement
Kvaslerud et al. (2022)[23] Norway **Funding source:** Pharmacosmos provided medication and the study grant	**Study design:** RCT **Objective:** To evaluate whether IV iron could provide benefits for iron deficient patients with severe aortic stenosis after TAVI	**Eligibility criteria:** Patients who had severe aortic stenosis and iron deficiency **Number of participants:** 104 (51 received intervention and 53 received a placebo) **Mean age, years (SD):** 80 (7.8) intervention group; 79.2 (6.5) control group **Number of males (%):** 28 (55%) intervention group; 32 (60%) control group	**Intervention (dose):** IV ferric derisomaltose (20 mg/kg or maximum dose of 2,000 mg) **Comparator**: Placebo (IV saline solution)	**Outcomes:** • 6-minute walk distance • Quality of life **Follow-up:** 3 months post-operative

Study citation, country, funding source	Study design and objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Shokri et al. (2022)[24] Egypt **Funding source:** No funding	**Study design:** RCT **Objective:** To evaluate the effects of pre-operative IV iron use in patients undergoing elective coronary artery bypass grafting	**Eligibility criteria:** Patients aged 52 to 67 with anemia scheduled for elective coronary artery bypass grafting and eligible to receive IV iron **Number of participants:** 80 (40 received intervention and 40 received a placebo) **Mean age, years (SD):** 58.35 (4.44) intervention group; 60.8 (4.79) control group **Number of female (%):** 22 (55%) intervention group; 15 (37.5%) control group	**Intervention (dose):** IV ferric carboxymaltose (single dose of 1,000 mg) 7 days before surgery **Comparator:** Placebo (100 ml of saline solution) 7 days before surgery	**Outcomes:** • Incidence of anemia • Hemoglobin level at admission • Length of stay • Post-operative complications • Adverse events • Mortality **Follow-up:** 4 weeks post discharge
Thin et al. (2021)[25] Singapore **Funding source:** Khoo Pilot Award from Duke-NUS Medical School. Vifor Pharma provided the investigational product medication doses.	**Study design:** RCT **Objective:** To determine the feasibility to compare the pre-operative treatment of iron deficiency with IV iron therapy versus oral iron therapy in patients undergoing elective major abdominal surgery	**Eligibility criteria:** Patients adults aged 21 years and older with iron-deficiency anemia, scheduled for elective major abdominal surgery, presenting between one and 4 weeks of their planned surgery, and who can receive the study intervention at least 7 days before the date of surgery **Number of participants:** 26 (13 received intervention and 13 received a placebo) **Mean age, years (SD):** 59.2 (12.4) intervention group; 55.2 (23.3) control group **Number of female (%):** 10 (76.9%) intervention group; 8 (61.5%) control group	**Intervention (dose):** IV ferric carboxymaltose (single dose of 15 mg/kg up to 1,000 mg) **Comparator (dose):** Oral iron (ferrous fumarate 200 mg twice daily until 1 day before surgery)	**Outcomes:** • Change in full blood count and anemia panel • Adverse events • Complications • Mortality • Health-related QoL **Follow-up:** 30 days for complications and mortality outcomes

Study citation, country, funding source	Study design and objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Non-randomized Studies				
Ploug et al. (2022)[26] Denmark **Funding source:** Supported by grants from "The region of Southern Denmark", "The University of Southern Denmark, SDU" and from Pharmacosmos.	**Study design:** Retrospective cohort study **Objective:** To investigate the efficacy of pre-operative IV iron treatment in everyday clinical practice in a series of consecutive iron deficient anemic patients undergoing elective surgery for colorectal cancer	**Eligibility criteria:** Patients undergoing colorectal cancer surgery and who were diagnosed with iron deficiency anemia at the time of the colorectal cancer diagnosis. **Number of participants:** 170 (122 received iron therapy and 48 did not receive iron therapy) **Mean age, years (range):** 75 (70 to 82) treatment group; 74.5 (63.5 to 82.5) no treatment group **Number of female (%):** 54 (44.3%) treatment group; 26 (54.2%) no treatment group	**Intervention (dose):** IV ferric derisomaltose (20 mg/kg) **Comparator:** No treatment	**Outcomes:** • Change in hemoglobin concentration • Peri-operative transfusion rate • Postoperative complications • Hospital length of stay • Days alive and out of hospital **Follow-up:** • 30 days for complications • 30 to 90 days for days alive and out of hospital
Abdullah et al. (2021)[27] Singapore **Funding source:** Funded by department funds from the Department of Anaesthesiology, Singapore General Hospital	**Study design:** Retrospective cohort study **Objective:** To compare the incidence of blood transfusion and hospital length of stay between anemic patients who received IV iron pre-operatively to undergoing elective surgery versus standard care	**Eligibility criteria:** Patients who had undergone elective surgeries requiring general anesthesia or regional anesthesia, except for transplant, burns and cardiac surgery, and who were diagnosed with iron deficiency anemia and were prescribed pre-operative IV iron therapy **Number of participants:** 7696 (89 received IV iron therapy and 7607 received oral iron therapy) **Mean age, years (SD):** 55.2 (15.3) in IV iron therapy group; 58 (16.2) in oral iron therapy group **Number of female (%):** 68 (76.4%) in	**Intervention (dose):** IV ferric carboxymaltose (15 mg/kg up to 1,000 mg **Comparator:** Oral iron therapy (dose not specified)	**Outcomes:** • Incidence of transfusion • Average unit of blood transfused • Hospital length of stay **Follow-up:** NA (chart review)

Study citation, country, funding source	Study design and objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		IV iron therapy group; 5483 (72.1%) in oral iron therapy group		
Evans et al. (2021)[28] UK **Funding source:** NR	**Study design:** Retrospective cohort study **Objective:** To analyze data from patients undergoing elective cardiac surgery to assess the impact of intravenous iron on pre-operative hemoglobin and transfusion	**Eligibility criteria:** Patients with iron deficiency anemia at surgical pre-assessment were considered for intravenous iron as an outpatient **Number of participants:** 447 (75 were anemic and received treatment; 72 were anemic and did not receive treatment; and 300 were not anemic) **Mean age, years (SD):** 71 (11) in the treated anemic group; 72 (8) in the anemic untreated group; 68 (11) in the non-anemic group **Number of male (%):** 48 (64%) in the treated anemic group; 32 (44%) in the anemic untreated group; 228 (76%) in the non-anemic group	**Intervention (dose):** IV iron isomaltoside (20 mg/kg) **Comparator:** No treatment	**Outcomes:** • Transfusion requirements • Length of stay • In-hospital mortality **Follow-up:** 30-day mortality
Peel et al. (2021)[29] Canada **Funding Source:** The University of Toronto Quality in Utilization, Education and Safety Research Program as part of a Canadian Blood Services Project Grant	**Study design:** Retrospective cohort study **Objective:** To determine optimal treatment strategies for using iron therapy for pre-operative anemia in adults undergoing cardiac surgery	**Eligibility criteria:** Patients with anemia schedules for a procedure with a high transfusion rate, all major high blood loss surgeries, and bleeding disorder or signed refusal of blood products **Number of participants:** 532 (84 IV iron therapy; 207 oral iron therapy; 71 epoetin therapy; 92 dual therapies; 78 no treatment) **Mean age, years (SD):** 68 (13) IV iron therapy; 67 (12) oral iron therapy; 71 (8) epoetin therapy; 70 (12) dual therapy; 68 (10) no treatment	**Intervention (dose):** IV iron sucrose (200 to 300 mg) **Comparator:** Oral iron (ferrous fumarate), epoetin alfa, no treatment	**Outcomes:** • Improved hemoglobin levels • Likelihood of transfusion **Follow-up:** NA (chart review)

Study citation, country, funding source	Study design and objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Number of female (%): 41 (48%) IV iron therapy; 77 (68%) oral therapy; 34 (48%) epoetin therapy; 53 (58%) dual therapy; 24 (31%) no treatment		
Quarterman et al. (2021)[30] UK **Funding source:** NR	**Study design:** Retrospective cohort study **Objective:** To evaluate outcomes of patients undergoing elective cardiac surgery who attended a pre-operative anemia clinic for the diagnosis and treatment of iron deficiency anemia	**Eligibility criteria:** Elective cardiac and aortic surgical patients with proven iron deficiency and anemia **Number of participants:** 2864 (190 received treatment; 581 did not receive treatment; 2093 not anemic) **Mean age, years (range):** 71 (63 to 77) received treatment; 73 (67 to 78) did not receive treatment; 69 (61 to 75) not anemic **Number of female (%):** 104 (54.7%) received treatment; 280 (48.2%) did not receive treatment; 409 (19.5%) not anemic	**Intervention (dose):** Iv iron isomaltoside (single dose of 1,000 mg or 20 mg/kg) **Comparator:** No treatment	**Outcomes:** • Number of blood transfusions • In-hospital mortality • Infections • Adverse events • Complications **Follow-up:** NA (chart review)
Triphaus et al. (2021)[31] Germany **Funding source:** NR	**Study design:** Prospective cohort study **Objective:** To evaluate the outcomes of iron deficient anemic patients with and without iron supplementation compared to non-anemic patients	**Eligibility criteria:** Adults undergoing major surgery were screened for iron deficiency anemia between 2015 and 2018 and grouped based on anemia and treatment status **Number of participants:** 1728 (184 patients with iron deficiency anemia and received treatment; 55 patients without anemia but iron deficiency and received treatment; 461 with anemia and no treatment; 1028 without anemia and no treatment) **Mean age, years (SD):** 63.3 (16.1) iron deficient anemic who received	**Intervention (dose):** IV ferric carboxymaltose (500 mg or 1,000 mg) **Comparator:** No treatment	**Outcomes:** • Transfusion rate • Change in hemoglobin level • IV iron-related adverse event • In-hospital mortality • Hospital length of stay **Follow-up:** 21-day postoperative follow-up for hemoglobin level analysis

Study citation, country, funding source	Study design and objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		treatment; 59.5 (15.7) not anemic but iron deficient and received treatment; 65.6 (14.2) anemic with no treatment; 63.6 (13.2) not anemic and no treatment **Number of female (%):** 73 (39.5%) iron deficient anemic who received treatment; 29 (52.7%) not anemic but iron deficient and received treatment; 111 (24.1%) anemic with no treatment; 307 (29.9%) not anemic and no treatment		

IV = intravenous; kg = kilogram; mg = milligram; ml = milliliter; NA = not applicable; NR = not reported; QoL = quality of life; RCT = randomized controlled trial; SD = standard deviation; TAVI = transcatheter aortic valve implementation.

Note: This table has not been copy-edited.

Table 4: Characteristics of Included Guidelines

Intended users, target population	Relevant intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Greenberg et al. (2021)[32]						
Intended users: Surgeons caring for patients scheduled to undergo major elective surgery **Target population**: Patients with comorbid conditions (specifically anemia, hyperglycemia, and smoking) undergoing major surgery	Present diagnostic and treatment algorithms for the management of pre-operative anemia including iron supplementation	• Postoperative hemoglobin and ferritin levels • Hospital length of stay days • Frequency of transfusion • Safety (mortality and adverse events)	A systematic review was undertaken which included multiple database searches (Ovid MEDLINE[R] Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE[R] Daily and Ovid MEDLINE[R]) from 1946 to time of review	Strength of recommendation[a] and quality of evidence[b] was assessed using GRADE	Recommendations were developed by 2 reviewers	NR

GRADE = Grading of Recommendations Assessment, Development and Evaluation; NR = not reported.

[a]Strength of recommendation was assessed using a combination of quality of supporting evidence described as a "balance between desired and undesired effects, how wise the proposed use of resources is, and variability of individual preferences and values."[32] Strength of recommendation was "strong" or "weak".

[b]Quality of evidence was based on how likely further research is to change confidence in the estimate of effect. Classified in 4 levels: "high", "moderate", "low", or "very low".

Note: This table has not been copy-edited.

Appendix 3: Critical Appraisal of Included Publications

Note that this table has not been copy-edited.

Table 5: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[12]

Strengths	Limitations
Meyer et al. (2022)[16]	
• The research question and inclusion criteria were clearly defined • Review methods were established before review was conducted (PROSPERO: CRD42021228806) • Review authors did screen multiple databases and references of relevant review articles • Literature screening was conducted by 2 independent review authors • Search timeframe was not restricted • Review authors provided adequate detail of included studies • Risk of bias was assessed for all included studies using the RoB2 Cochrane Collaboration's tool for assessing risk of bias in RCTs • Combination of results were assessed using pooled relative risk, risk difference and mean difference obtained using models with random effects • Heterogeneity was assessed using the Q-test and quantified using the I^2 value, and heterogeneity was discussed • Publication bias was assessed using funnel plots	• Review authors did not justify included study designs or exclusion criteria • Justification for publication restrictions were not provided (Non-RCTs study design, English only) • Unclear if data extraction was performed in duplicate • List of excluded studies and justification for exclusion was not provided • Review authors did not report on sources of funding for included studies • Potential impact of risk of bias for individual studies on the results on the meta-analysis was not assessed • Review authors did not report if they had any conflicts of interest or received any funding
Tang et al. (2022)[17]	
• The research question and inclusion criteria were clearly defined and included PICO components • Review authors did screen multiple databases and reference of included and relevant studies • Literature screening was conducted by 2 independent review authors • No publication restrictions were included in the search • Data extraction was conducted by 2 independent review authors • Review authors provided adequate detail of included studies • Risk of bias was assessed for all included studies using the Cochrane Collaboration tool for RCTs and the Newcastle-Ottawa score for non-randomized studies • Combinations of results were assessed using relative risk and mean difference while considering heterogeneity within and between studies • Heterogeneity was assessed using the chi-square test and I^2 • Publication bias was assessed using funnel plots	• Unclear if review protocol was registered in advance • Review authors did not justify included study designs or exclusion criteria • List of excluded studies was not provided • Review authors did not report on sources of funding for included studies

Strengths	Limitations
• The review authors reported receiving no funding or potential conflict of interest	
Chaudhry et al. (2021)[18]	
• The research question and inclusion criteria were clearly defined • Review authors did screen multiple databases • Literature search screening was conducted by 2 independent review authors • Search timeframe was not restricted • Review authors provided adequate detail of included studies • Risk of bias was assessed using Cochrane RoB tools for RCTs • Review authors disclosed any potential conflicts of interest	• Unclear if review protocol was registered in advance • Review authors did not justify included study designs or exclusion criteria • Justification for publication restrictions were not provided (non-RCT study designs, English studies only) • Unclear if authors searched references or any additional sources of information • Unclear if data extraction was performed in duplicate • List of excluded studies was not provided • Description of statistical analyses was not provided • Risk of bias was not accounted for in the interpretation of discussion of results • Publication bias was not assessed • Review authors did not report on funding sources of included studies • Review authors did not report if they received any funding
Elhenawy et al. (2021)[19]	
• The research question and inclusion criteria were clearly defined • Review methods were established before review was conducted (PROSPERO: CRD42015016771) • Review authors did screen multiple databases and reference of included and relevant studies • No publication restrictions were included in the search • Literature search screening was conducted by 2 independent review authors • Data extraction was conducted by 2 independent review authors • Review authors provided adequate detail of included studies • Risk of bias was assessed using Cochrane RoB tools • Combinations of results were assessed using risk ratios and mean difference while considering heterogeneity within and between studies • The Cochrane's Q-test was used to calculate the statistical heterogeneity among studies • Overall quality of evidence was determined using GRADE which included an assessment of publication bias • Potential impact of risk of bias for individual studies on the results on the meta-analysis was assessed • Review authors did disclose any potential conflicts of interest	• Review authors did not justify included study designs or exclusion criteria • List of excluded studies was not provided • Review authors did not report funding sources of included studies • Review authors did not report if they received any funding

Strengths	Limitations
Jones et al. (2021)[20]	
• The research question and inclusion criteria were clearly defined • Review methods were established before review was conducted • Review authors did screen multiple databases and reference of included and relevant studies • Literature search screening was conducted by 2 independent review authors • Search timeframe was not restricted • Review authors provided adequate detail of included studies • Risk of bias was assessed using Cochrane RoB tools • Overall quality of evidence was determined using GRADE which included an assessment of publication bias • Risk of bias was accounted for in the interpretation of discussion of results • The review authors reported funding source and potential conflict of interest	• Review authors did not justify exclusion criteria • List of excluded studies was not provided • Unclear if data extraction was performed in duplicate • Unclear if additional restrictions were included in the literature search (e.g., language) • Description of statistical analyses was not provided • Review authors did not report funding sources of included studies
Moon et al. (2021)[21]	
• The research question and inclusion criteria were clearly defined • Review methods were established before review was conducted (PROSPERO: 160868) • Review authors did screen multiple databases • Literature search screening was conducted in duplicate with multiple authors • Data extraction was performed by one author and checked by another author • Review authors provided adequate detail of included studies • Risk of bias was assessed for all included studies using the Cochrane Collaboration tool for RCTs and the Newcastle-Ottawa score for non-randomized studies • The review authors reported receiving no funding or potential conflict of interest	• Review authors did not justify included study designs or exclusion criteria • Justification for publication restrictions were not provided (Potential time frame restrictions, English studies only) • Unclear if authors searched references or any additional sources of information • List of excluded studies was not provided • Unclear if publication bias was assessed • Description of statistical analyses was not provided • Risk of bias was not accounted for in the interpretation of discussion of results • Review authors did not report funding sources of included studies

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; RCT = randomized controlled trial; RoB = risk of bias.

Table 6: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[13]

Strengths	Limitations
Randomized Controlled Trials	
Fung et al. (2022)[22]	
• The objective, outcomes, inclusion and exclusion criteria, interventions, and patient characteristics were clearly defined in the introduction and methods • The trial protocol was registered • The main findings are clearly described with appropriate measures of variability (95% CI) and exact P values unless < 0.001 • Patients who were recruited and who participated may have been representative of the entire population from which they were recruited • No patients appear to have been lost to follow-up • The staff, places, and facilities may have been representative of the treatment majority of the patients received • Those providing treatment, the investigators and the data collectors were blinded to the treatment received for each participant • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Intention to treat approach was used • Patients from intervention and comparator groups were recruited from the same population over the same period of time • Randomization process and concealment was clearly described • Sufficient power calculations were used to determine adequate sample size • Authors declared receiving no funding or conflicts of interest	• It is unclear if all important adverse events were reported • Patients were not blinded to the treatment received due to the nature and safety of the intervention • It is unclear if analysis was adjusted for different lengths of follow-up
Kvaslerud et al. (2022)[23]	
• The objective, outcomes, inclusion and exclusion criteria, interventions, and patient characteristics were clearly defined in the introduction and methods • The main findings are clearly described with appropriate measures of variability (95% CI) and exact P values unless < 0.001 • Characteristics of patients lost to follow-up was described • Patients who were recruited and who participated may have been representative of the entire population from which they were recruited • Patients, investigators, and data collectors were blinded to treatment	• It is unclear if trial protocol was registered • It is unclear if all important adverse events were reported • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • It is unclear if there were any protocol deviations • It is unclear if analysis was adjusted for different lengths of follow-up or if lost to follow-up would have affected the results

Strengths	Limitations
• Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Intention to treat approach was used • Patients from intervention and comparator groups were recruited from the same population over the same period of time • Randomization process and concealment was clearly described • Sufficient power calculations were used to determine adequate sample size • Authors declared funding and potential conflicts of interest	
Shokri et al. (2022)[24]	
• The objective, outcomes, inclusion and exclusion criteria, interventions, and patient characteristics were clearly defined in the introduction and methods • The trial protocol was registered • The main findings are clearly described with appropriate measures of variability (mean difference with standard deviation) and exact P values unless < 0.001 • No patients appear to have been lost to follow-up • Patients who were recruited and who participated may have been representative of the entire population from which they were recruited • The staff, places, and facilities may have been representative of the treatment majority of the patients received and treatment was provided by the same surgical team • Those providing treatment, the investigators and the data collectors were blinded to the treatment received for each participant • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Intention to treat approach was used • Patients from intervention and comparator groups were recruited from the same population over the same period of time • Randomization process and concealment was clearly described • Sufficient power calculations were used to determine adequate sample size • Authors declared receiving no funding or conflicts of interest	• It is unclear if all important adverse events were reported • It is unclear if patients were blinded to the treatment received • It is unclear if there were any protocol deviations • It is unclear if analysis was adjusted for different lengths of follow-up

Strengths	Limitations
Thin et al. (2021)[25]	
• The objective, outcomes, inclusion and exclusion criteria, interventions, and patient characteristics were clearly defined in the introduction and methods • The trial protocol was registered • The main findings are clearly described with appropriate measures of variability (standard deviation) and exact P values • No patients appear to have been lost to follow-up • Patients who were recruited and who participated may have been representative of the entire population from which they were recruited • Randomization process was clearly described • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Patients from intervention and comparator groups were recruited from the same population over the same period of time • Authors declared funding and potential conflicts of interest	• It is unclear if all important adverse events were reported • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • Patients, those administering the treatment, investigators, or data collectors were not blinded to the treatment allocation • It is unclear if randomization was concealed to individuals or investigators • It is unclear if analysis was adjusted for different lengths of follow-up • It is unclear if power calculations were conducted to establish adequate sample size • It is unclear if there were any protocol deviations
Non-Randomized Studies	
Ploug et al. (2022)[26]	
• The objective, outcomes, inclusion and exclusion criteria, interventions, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval • The main findings are clearly described with appropriate measures of variability (interquartile range) and exact P values unless < 0.001 • Patient data used may have been representative of the entire population from which they were recruited • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Patient data from intervention and comparator groups were from the same population over the same period of time • Authors declared study funding sources	• It is unclear if all important adverse events were reported • Principle confounders between comparison group was not clearly outlined • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • Patient loss to follow-up was likely not captured due to study design (retrospective cohort study) • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in analysis • It is unclear if sufficient power calculations were used to determine adequate sample size • Authors did not declare any potential conflicts of interest
Abdullah et al. (2021)[27]	
• The objective, outcomes, inclusion and exclusion criteria, interventions, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval	• It is unclear if all important adverse events were reported • Patient loss to follow-up was likely not captured due to study design (retrospective cohort study) • It is unclear if the staff, places, and facilities may have

Strengths	Limitations
• A propensity matched case-control approached was used, which may help control for confounding factors • The main findings are clearly described with appropriate measures of variability (standard deviation) and exact P values unless < 0.001 • Patient data used may have been representative of the entire population from which they were recruited • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Patient data from intervention and comparator groups were from the same population over the same period of time • Sufficient power calculations were used to determine adequate sample size • Authors declared funding and potential conflicts of interest	been representative of the treatment majority of the patients received • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in the analysis despite the study design approach (propensity matched case-control)
Evans et al. (2021)[28]	
• The objective, outcomes, inclusion criteria, interventions, and patient characteristics were clearly defined in the introduction and methods • The main findings are clearly described with appropriate measures of variability (interquartile range, standard deviation, and 95% CI) and exact P values unless < 0.001 • Patient data used may have been representative of the entire population from which they were recruited • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Patient data from intervention and comparator groups were from the same population over the same period of time • Authors declared potential conflicts of interest	• It is unclear if the study received ethical approval • Patient exclusion criteria was not clearly defined • It is unclear if all important adverse events were reported • Patient loss to follow-up was likely not captured due to study design (retrospective cohort study) • Principle confounders between comparison group was not clearly outlined • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in analysis • It is unclear if sufficient power calculations were used to determine adequate sample size • Authors did not report study funding sources
Peel et al. (2021)[29]	
• The objective, outcomes, inclusion and exclusion criteria, interventions, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval • Missing data variable in >25% of patient data was removed from modelling • Principle confounders were identified, and regression models were used to account for possible confounding factors in the analysis	• It is unclear if all important adverse events were reported • Patient loss to follow-up was likely not captured due to study design (retrospective cohort study) • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if sufficient power calculations were used to determine adequate sample size

Strengths	Limitations
• The main findings are clearly described with appropriate measures of variability (standard deviation and 95% CI) and exact P values unless < 0.0001 • Patient data used may have been representative of the entire population from which they were recruited • The staff, places, and facilities may have been representative of the treatment majority of the patients received • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Patient data from intervention and comparator groups were from the same population over the same period of time • Authors declared funding and potential conflicts of interest	
Quarterman et al. (2021)[30]	
• The objective, outcomes, inclusion criteria, interventions, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval • The main findings are clearly described with appropriate measures of variability (interquartile range) and exact P values unless < 0.001 • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Patient data from intervention and comparator groups were from the same population over the same period of time • Authors declared potential conflicts of interest	• Patient exclusion criteria was not clearly defined • It is unclear if all important adverse events were reported • Patient loss to follow-up was likely not captured due to study design (retrospective cohort study) • Principle confounders between comparison group was not clearly outlined • It is unclear is patient data used may have been representative of the entire population from which they were recruited because of a change in administration policy after the study was complete • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in analysis • It is unclear if sufficient power calculations were used to determine adequate sample size • Authors did not report study funding sources
Triphaus et al. (2021)[31]	
• The trial protocol was registered • The objective, outcomes, inclusion criteria, and interventions were clearly defined in the introduction and methods • Patient characteristics were available in supplemental information • The main findings are clearly described with appropriate measures of variability (interquartile range and standard deviation) and exact P values	• Patient exclusion criteria was not clearly defined • It is unclear if all important adverse events were reported • It is unclear if patient loss to follow up was accounted for in the analysis and characteristics of any patients lost to follow up were not clearly described • Principle confounders between comparison group was not clearly outlined • It is unclear is patient data used may have been

Strengths	Limitations
• Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Authors declared potential conflicts of interest	representative of the entire population from which they were recruited because recruitment was done using multiple centres • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in analysis • It is unclear if sufficient power calculations were used to determine adequate sample size • It is unclear if patient data from intervention and comparator groups were from the same population over the same period of time • Authors did not report study funding sources

Table 7: Strengths and Limitations of Guidelines Using AGREE II[14]

Item	Greenberg et al. (2021)[32]
Domain 1: scope and purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Unclear
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: stakeholder involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Unclear
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Unclear
6. The target users of the guideline are clearly defined.	Yes
Domain 3: rigour of development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	No
9. The strengths and limitations of the body of evidence are clearly described.	No
10. The methods for formulating the recommendations are clearly described.	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Unclear
12. There is an explicit link between the recommendations and the supporting evidence.	Yes

Item	Greenberg et al. (2021)[32]
13. The guideline has been externally reviewed by experts prior to its publication.	Unclear
14. A procedure for updating the guideline is provided.	No
Domain 4: clarity of presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: applicability	
18. The guideline describes facilitators and barriers to its application.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	No
Domain 6: editorial independence	
22. The views of the funding body have not influenced the content of the guideline.	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	No

AGREE II = Appraisal of Guidelines for Research and Evaluation II.

Appendix 4: Main Study Findings

Note that this table has not been copy-edited.

Table 8: Summary of Findings by Outcome — Patient Hemoglobin Level

Study citation and design	Study findings
Meyer et al. (2022)[16] SR and MA (Based on 3 included studies)	**Hemoglobin concentration at time of admission** Combined total concentration for patients who received pre-operative IV iron = 258 g/dl Combined total concentration for no treatment = 256 g/dl Mean difference (95% CI) = 0.81 (0.30 to 1.33); P = 0.002; I^2 = 60%
Tang et al. (2022)[17] SR and MA (Based on 3 included studies)	**Effect of iron therapy on hemoglobin concentrations (units not specified)** Combined total concentration for patients who received IV iron therapy = 123 Combined total concentration for control group = 213 Mean difference (95% CI) = 0.29 (0.02 to 0.56); P = 0.04; I^2 = 77%
Chaudhry et al. (2021)[18] SR (1 RCT, Na et al. 2011)	**Mean pre-operative hemoglobin levels** IV iron therapy group = 12 g/dl Control group = 12 g/dl **Mean postoperative hemoglobin levels** POD 1, 2, 3, 2 week and 6-week follow-up significantly favours the intervention; POD 5 was not significant
Chaudhry et al. (2021)[18] SR (1 RCT, Bisbe et al. 2014)	**Mean pre-operative hemoglobin levels** IV iron group = 14 g/dl Oral iron group = 14 g/dl **Mean follow-up hemoglobin levels (SD)** IV iron group = 12 g/dl (1.2) Oral iron group = 11 g/dl (1.1) **Pre- to postoperative change in hemoglobin** POD 30 change was not significant for all patients; Subset analysis of pre-operative low iron or severe postoperative anemia was significant favouring IV iron therapy (1.9 g/dl vs 1.2 g/dl pre-operative low iron subset; 2.4 g/dl vs 1.1 g/dl severe postoperative anemia subset) **Mean postoperative hemoglobin levels** POD 1, 4 and 30 was not significant for all patients; Subset analysis of pre-operative low iron or severe postoperative anemia was significant favouring IV iron therapy **Rate of anemia at final follow-up** POD 30 significantly favours IV iron therapy group (58% IV iron vs 76% oral iron)
Chaudhry et al. (2021)[18] SR (1 RCT, Park et al. 2019)	**Mean pre-operative hemoglobin levels** IV iron group = 12 g/dl Placebo group = 13 g/dl **Mean follow-up hemoglobin levels (SD)** IV iron group = 13 g/dl (1.3)

Study citation and design	Study findings
	Placebo group = 13 g/dl (1.1) **Pre- to postoperative change in hemoglobin** POD 1 and 5 change was not significant for all patients; POD 30 change was significant favouring IV iron group (0.3 g/dl vs -0.8 g/dl) **Mean postoperative hemoglobin levels** POD 1, 5 and 30 was not significant between groups
Chaudhry et al. (2021)[18] SR (1 RCT, Yoo et al. 2019)	**Mean pre-operative hemoglobin levels** IV iron group = 14 g/dl Control group = 13 g/dl **Mean follow-up hemoglobin levels (SD)** IV iron group = 13 g/dl (0.9) Control group = 12 g/dl (1.0) **Mean postoperative hemoglobin levels** POD 1 and 7 was not significant for all patients; POD 30 was significant favouring the IV iron group **Rate of anemia at final follow-up** POD 30 significantly favours IV iron therapy group (34% IV iron vs 62% control group)
Elhenawy et al. (2021)[19] SR and MA	**Change in hemoglobin levels at post-treatment (random effects model based on 7 included studies)** Combined total hemoglobin level for patients who received IV iron therapy = 298 g/L Combined total hemoglobin level for placebo or standard of care group = 282 g/L Mean difference (95% CI) = 7.15 (2.26 to 12.04); P = 0.004; I^2 = 79% **Direct comparison between IV iron and oral iron therapy for change in hemoglobin levels at post-treatment (random effects model based on 5 included studies)** Combined total hemoglobin level for patients who received IV iron therapy = 224 g/L Combined total hemoglobin level for patients who received oral iron therapy = 225 g/L Mean difference (95% CI) = 7.63 (1.41 to 13.86); P = 0.02; I^2 = 87% **Change in hemoglobin levels at > 4 weeks postoperative follow-up (random effects model based on 4 included studies)** Combined total hemoglobin level for patients who received IV iron therapy = 227 g/L Combined total hemoglobin level for placebo or standard of care group = 282 g/L Mean difference (95% CI) = 6.46 (3.10 to 9.81); P = 0.0002; I^2 = 33%
Jones et al. (2021)[20] SR (1 RCT, Khalafallah et al. 2016)	**Mean change in hemoglobin from postoperative day 1 to postoperative week 12 (SD)**[a] IV iron group = 3.2 g/dl (0.16) Standard of care group = 2.81 g/dl (0.18)
Jones et al. (2021)[20] SR (1 RCT, Kim et al. 2017)	**Increase in hemoglobin level from baseline to postoperative week 12**[a] IV iron group = 3.3 g/dl Placebo = 1.6 g/dl

Study citation and design	Study findings
Jones et al. (2021)[20] SR (1 RCT, Padmanabhan et al. 2019)	**Change in mean hemoglobin level between enrollment and surgical admission (SD)[a]** IV iron group = 1.3 g/dl (0.9) Oral iron group = 4.4 g/dl (0.9)
Moon et al. (2021)[21] SR (1 retrospective cohort study, Wilson et al. 2018)	**Mean change in hemoglobin from iron deficiency anemia diagnosis to admission** IV iron group = 1.05 g/dl Control group = 0.16 g/dl P < 0.0001
Moon et al. (2021)[21] SR (1 retrospective and prospective cohort study, Calleja et al. 2015)	**Mean change in hemoglobin from iron deficiency anemia diagnosis to admission** IV iron group = 1.5 g/dl Control group = 0.5 g/dl P < 0.0001
Moon et al. (2021)[21] SR (1 prospective cohort study, Kam et al. 2020)	**Mean change in hemoglobin from iron deficiency anemia diagnosis to admission** IV iron group = 1.9 g/dl Control group = 0.6 g/dl P < 0.001
Fung et al. (2022)[22] RCT	**Mean change in hemoglobin from baseline to before surgery (95% CI)** IV iron group = 7.9 g/L (3.2 to 12.3) Control group = 1.7 g/L (-1.9 to 5.3) P = 0.040
Kvaslerud et al. (2022)[23] RCT	**Mean hemoglobin from baseline to follow-up (SD)** Mean IV iron group hemoglobin at baseline = 13.3 g/L (1.2); Mean IV iron group hemoglobin at follow-up = 13.7 g/L (1.4) Mean placebo group hemoglobin at baseline = 13.3 g/L (1.3); Mean placebo group hemoglobin at follow-up = 13.1 g/L (1.5) Mean difference (95% CI) = 0.6 g/L (0.1 to 1.0); P = 0.015
Shokri et al. (2022)[24] RCT	**Mean hemoglobin levels on admission between IV iron group and placebo group (SD)** IV iron group = 9.53 g/dl (0.84) Placebo group = 9.77 g/dl (0.74) P = 0.103 **Mean pre-operative hemoglobin levels between IV iron group and placebo group (SD)** IV iron group = 12.76 g/dl (0.88) Placebo group = 10.03 g/dl (0.83) P < 0.001 **Mean postoperative hemoglobin levels between IV iron group and placebo group (SD)** IV iron group = 9.1 g/dl (0.63) Placebo group = 7.55 g/dl (0.6) P < 0.001 **Mean hemoglobin levels 1 week after discharge between IV iron group and placebo group (SD)**

Study citation and design	Study findings
	IV iron group = 10.35 g/dl (0.89) Placebo group = 10.18 g/dl (0.85) P = 0.397 **Mean hemoglobin levels 4 weeks after discharge between IV iron group and placebo group (SD)** IV iron group = 12.44 g/dl (0.71) Placebo group = 11.26 g/dl (1.13) P < 0.001 **Incidence of anemia 4 weeks after discharge between IV iron group (N = 40) and placebo group (N = 40), n (%)** IV iron group = 13 (32%) Placebo group = 32 (80%) P < 0.001
Thin et al. (2021)[25] RCT	**Mean rise in hemoglobin level between IV iron group and oral iron group (SD)** IV iron group = 0.2 g/dl (1.6) Oral iron group = 0.8 g/dl (0.7) P = 0.3
Ploug et al. (2022)[26] Retrospective cohort study	**Change between baseline and pre-operative hemoglobin levels for IV iron group and control group (range)** IV iron group = 0.64 g/dl (0.32 to 1.61) Control group = 0.48 g/dl (0.81 to 2.09) P = 0.94
Evans et al. (2021)[28] Retrospective cohort study	**Comparison of mean hemoglobin levels at pre-assessment phase (SD)** IV treatment responsive group = 120 g/l^{-1} (7) IV treatment unresponsive group = 114 g/l^{-1} (9) Untreated anemic group = 121 g/l^{-1} (7) Non-anemic group = 146 g/l^{-1} (10) P < 0.001 **Comparison of mean hemoglobin levels at pre-surgery phase (SD)** IV treatment responsive group = 137 g/l^{-1} (8) IV treatment unresponsive group = 120 g/l^{-1} (7) Untreated anemic group = 119 g/l^{-1} (10) Non-anemic group = 143 g/l^{-1} (11) P < 0.001 **Comparison of mean hemoglobin levels at post-surgery phase (SD)** IV treatment responsive group = 111 g/l^{-1} (17) IV treatment unresponsive group = 104 g/l^{-1} (11) Untreated anemic group = 106 g/l^{-1} (15) Non-anemic group = 115 g/l^{-1} (16)

Study citation and design	Study findings
	P < 0.001 **Change in mean hemoglobin levels from pre-assessment to pre-operative phase (95% CI)** IV treatment responsive group = 17 g/l^{-1} (13 to 21) IV treatment unresponsive group = 6 g/l^{-1} (3 to 8) Untreated anemic group = -2 g/l^{-1} (-4 to 0) Non-anemic group = -2 g/l^{-1} (-3 to -1) P < 0.001 **Change in mean hemoglobin levels from pre-operative to postoperative phase (95% CI)** IV treatment responsive group = -26 g/l^{-1} (-31 to -19) IV treatment unresponsive group = -16 g/l^{-1} (-20 to -12) Untreated anemic group = -13 g/l^{-1} (-16 to -9) Non-anemic group = -29 g/l^{-1} (-31 to -27) P = NR
Peel et al. (2021)[29] Retrospective cohort study	**Change in hemoglobin level between referral and pre-operative level for each relevant group (95% CI)** IV iron 1 to 300 mg group = 2.49 g/L (-0.68 to 5.66); P = 0.1238 IV iron 301 to 600 mg group = 1.48 g/L (-1.73 to 4.69); P = 0.3646 IV iron > 600 mg group = 9.80 g/L (6.17 to 13.42); P < 0.0001 Oral iron group = 1.62 g/L (-0.85 to 4.08); P = 0.1974

CI = confidence interval; dl = deciliter; EPO = erythropoietin; g = grams; L = liter; MA = meta-analysis; mg = milligram; NR = not reported; POD = postoperative day; SD = standard deviation; SR = systematic review; vs = versus.

[a]Statistical significance between groups was not provided by Jones et al. (2021)

Table 9: Summary of Findings by Outcome — Blood Transfusion Occurrence

Study citation and design	Study findings
Meyer et al. (2022)[16] SR and MA (Based on 4 included studies)	**Pre-operative allogenic blood transfusion** Combined total number of transfusion events for patients who received pre-operative IV iron = 334 Combined total number of transfusion events for no treatment = 317 Risk difference (95% CI) = -0.13 (-0.27 to 0.01); P = 0.07; I^2 = 65% Risk ratio (95% CI) = 0.57 (0.30 to 1.09); P = 0.09; I^2 = 64%
Tang et al. (2022)[17] SR and MA (Based on 5 included studies)	**Number of patients receiving blood transfusion** Combined number of transfusion events for patients who received IV iron therapy = 289 Combined number of transfusion events for control group = 429 Risk ratio (95% CI) = 0.65 (0.48 to 0.88); P = 0.005; I^2 = 0%
Elhenawy et al. (2021)[19] SR and MA	**Number of patients receiving blood transfusion (random effects model based on 8 studies)** Combined number of transfusion events for patients who received IV iron therapy = 445 Combined number of transfusion events for placebo or standard of care group = 428

Study citation and design	Study findings
	Risk ratio (95% CI) = 0.84 (0.71 to 0.99); P = 0.04; I^2 = 0% **Number of patients receiving blood transfusion (fixed effects model based on 8 studies)** Combined number of transfusion events for patients who received IV iron therapy = 445 Combined number of transfusion events for placebo or standard of care group = 428 Risk ratio (95% CI) = 0.83 (0.70 to 0.98); P = 0.03; I^2 = 0% **Direct comparison between IV iron and oral iron therapy for number of blood transfusions (random effects model based on 3 studies)** Combined number of transfusion events for patients who received IV iron therapy = 139 Combined number of transfusion events for patients who received oral iron therapy = 144 Risk ratio (95% CI) = 0.88 (0.51 to 1.51); P = 0.63; I^2 = 37%
Jones et al. (2021)[20] SR (1 RCT, Brisbe et al. 2014)	**Proportion of patients receiving an allogenic blood transfusion, n/N (%)[a]** IV iron group = 3/59 (5.1%) Oral iron group = 2/62 (3.2%)
Jones et al. (2021)[20] SR (1 RCT, Khalafallah et al. 2016)	**Proportion of patients receiving an allogenic blood transfusion, n/N (%)[a]** IV iron group = 1/103 (0.1%) Standard of care group = 5/98 (5.1%)
Jones et al. (2021)[20] SR (1 RCT, Kim et al. 2017)	**Proportion of patients receiving an allogenic blood transfusion, n/N (%)[a]** IV iron group = 3/218 (1.4%) Placebo group = 4/219 (1.8%)
Jones et al. (2021)[20] SR (1 RCT, Padmanabhan et al. 2019)	**Proportion of patients receiving an allogenic blood transfusion, n/N (%)[a]** IV iron group = 16/20 (80%) Oral iron group = 12/20 (60%)
Jones et al. (2021)[20] SR (1 RCT, Park et al. 2019)	**Proportion of patients receiving an allogenic blood transfusion, n/N (%)[a]** IV iron group = 2/29 (6.9%) Placebo group = 4/29 (12.8%)
Moon et al. (2021)[21] SR (1 retrospective cohort study, Laso-Morales et al. 2017)	**Proportion of patients receiving a transfusion (%)** IV iron group = 17% Control group = 16% P = NS **Mean amount of blood transfused per patient (unit not specified)** IV iron group = 0.4 Control group = 0.3 P = NS
Moon et al. (2021)[21] SR (1 retrospective and prospective cohort study, Calleja et al. 2015)	**Proportion of patients receiving a transfusion (%)** IV iron group = 9.9% Control group = 38.7%

Study citation and design	Study findings
	P < 0.001 **Mean amount of blood transfused per patient (unit not specified)** IV iron group = 0.2 Control group = 0.8 P < 0.001
Moon et al. (2021)[21] SR (1 prospective cohort study, Kam et al. 2020)	**Proportion of patients receiving a transfusion (%)** IV iron group = 1.42% Control group = 0.55% P = 0.076
Fung et al. (2022)[22] RCT	**Number of patients receiving pre-operative red blood cell transfusion, n (%)** IV iron group = 1 (5%) Control group = 3 (15%) P = 0.605 **Number of patients receiving postoperative red blood cell transfusion, n (%)** IV iron group = 1 (5%) Control group = 4 (20) P = 0.342
Thin et al. (2021)[25] RCT	**Number of patients who received red blood cell transfusion from recruitment to discharge, n (%)** IV iron group = 6 (46.2%) Oral iron group = 6 (46.2%) P = 1.0 **Number of patients who received red blood cell transfusion pre-operatively, n (%)** IV iron group = 0 Oral iron group = 3 (23.1%) P = 0.07 **Number of patients who received red blood cell transfusion intra-operatively, n (%)** IV iron group = 6 (46.2%) Oral iron group = 1 (7.7%) P = 0.03 **Number of patients who received red blood cell transfusion post-operatively, n (%)** IV iron group = 2 (15.4%) Oral iron group = 4 (30.8%) P = 0.4
Ploug et al. (2022)[26] Retrospective cohort study	**Median number of red blood cell transfusions between IV iron group (N = 122) and control group (N = 48), n (%)** IV iron group = 55 (45%) Control group = 19 (40%)

Study citation and design	Study findings
	Median number of pre-operative red blood cell transfusions between IV iron group (N = 122) and control group (N = 48), n (%) IV iron group = 29 (24%) Control group = 16 (33%) **Median number of the day of surgery red blood cell transfusions between IV iron group (N = 122) and control group (N = 48), n (%)** IV iron group = 13 (11%) Control group = 2 (4%) **Median number of postoperative day 1 to 30 red blood cell transfusions between IV iron group (N = 122) and control group (N = 48), n (%)** IV iron group = 24 (20%) Control group = 8 (17%)
Abdullah et al. (2021)[27] Retrospective cohort study	**Number of pre-operative transfusions received for 1:1 propensity matched IV iron group (N = 89) and oral iron group (N = 89), n (%)** IV iron group = 10 (11.2%) Oral iron group = 16 (18%) P = 0.289 **Number of pre-operative transfusions received for 1:2 propensity matched IV iron group (N = 89) and oral iron group (N = 178), n (%)** IV iron group = 10 (11.2%) Oral iron group = 30 (16.9%) P = 0.303 **Number of intra-operative transfusions received for 1:1 propensity matched IV iron group (N = 89) and oral iron group (N = 89), n (%)** IV iron group = 18 (20.2%) Oral iron group = 33 (37.1%) P = 0.02 **Number of intra-operative transfusions received for 1:2 propensity matched IV iron group (N = 89) and oral iron group (N = 178), n (%)** IV iron group = 18 (20.2%) Oral iron group = 72 (40.4%) P = 0.002 **Number of post-operative transfusions received for 1:1 propensity matched IV iron group (N = 89) and oral iron group (N = 89),n (%)** IV iron group = 20 (22.5%) Oral iron group = 15 (16.9%) P = 0.451 **Number of post-operative transfusions received for 1:2 propensity matched IV iron group (N = 89) and oral iron group (N = 178), n (%)** IV iron group = 20 (22.5%) Oral iron group = 28 (15.7%)

Study citation and design	Study findings
	P = 0.237 **Number of transfusions received over entire peri-operative period for 1:1 propensity matched IV iron group (N = 89) and oral iron group (N = 89), n (%)** IV iron group = 37 (41.6%) Oral iron group = 34 (38.2%) P = 0.759 **Number of transfusions received over entire peri-operative period for 1:2 propensity matched IV iron group (N = 89) and oral iron group (N = 178), n (%)** IV iron group = 37 (41.6%) Oral iron group = 73 (41%) P = 1.00
Evans et al. (2021)[28] Retrospective cohort study	**Median number of red blood cell units transfused perioperatively by group (range)** IV treatment responsive group = 0 (0 to 15) IV treatment unresponsive group = 2 (0 to 13); P < 0.001 vs non-anemic group; P = 0.013 vs treatment responsive group Untreated anemic group = 2 (0 to 16); P < 0.001 vs non-anemic group; P = 0.038 vs treatment responsive group Non-anemic group = 0 (0 to 17)
Peel et al. (2021)[29] Retrospective cohort study	**Odds of receiving a transfusion for each relevant group compared to no treatment, OR (95% CI)** IV iron 1 to 300 mg group = 2.32 (1.10 to 4.93); P = 0.0280 IV iron 301 to 600 mg group = 0.77 (0.39 to 1.50); P = 0.4422 IV iron > 600 mg group = 0.97 (0.49 to 1.95); P = 0.9401 Oral iron group = 0.84 (0.49 to 1.45); P = 0.5317 **Count of red blood cell units transfused for each relevant group, count ratio[b] (95% CI)** IV iron 1 to 300 mg group = 1.36 (0.91 to 2.03); P = 0.1305 IV iron 301 to 600 mg group = 0.84 (0.54 to 1.31); P = 0.4414 IV iron > 600 mg group = 0.66 (0.40 to 1.10); P = 0.1151 Oral iron group = 0.66 (0.47 to 0.94); P = 0.0196
Quarterman et al. (2021)[30] Retrospective cohort study	**Number of patients receiving red blood cell transfusion from each group, n (%)** Anemic and received IV iron treatment group (N = 190) = 114 (60%) Anemic and did not receive IV iron treatment or not iron deficient group (N = 581) = 368 (63.3%); P = 0.41 vs IV iron treatment group Not anemic group (N = 2093) = 548 (26.2%); P < 0.001 vs IV iron treatment group **Median number of red blood cell units received for each group (range)** Anemic and received IV iron treatment group (N = 190) = 1 (0 to 17) Anemic and did not receive IV iron treatment or not iron deficient group (N = 581) = 1 (0 to 13); P = 0.29 vs IV iron treatment group Not anemic group (N = 2093) = 0 (0 to 31); P < 0.001 vs IV iron treatment group

Study citation and design	Study findings
Triphaus et al. (2021)[31] Prospective cohort study	**Mean total red blood cell units transfused for each group (SEM)** Anemic, iron deficient and IV iron treatment group = 2 (0.3) Iron deficient and IV iron treatment group = 1.4 (0.4) Anemic and no treatment group = 2.5 (0.2) Not anemic and no treatment group = 1 (0.1)

CI = confidence interval; EPO = erythropoietin; IV = intravenous; MA = meta-analysis; N = number; NR = not reported; NS = not significant; OR = odds ratio; SEM = standard error mean; SR = systematic review; vs = versus.

[a]Statistical significance between groups was not provided by Jones et al. (2021)

[b]Count ratio represents how many times more red blood cell units are transfused for each variable group.

Table 10: Summary of Findings by Outcome — Quality of Life

Study citation and design	Study findings
Chaudhry et al. (2021)[18] SR (1 RCT, Brisbe et al. 2014)	**EQ-5D score** Difference in EQ-5D score between IV iron group and oral iron group was not significant **Independence index score** Difference in independence index score between IV iron group and oral iron group was not significant
Chaudhry et al. (2021)[18] SR (1RCT, Yoo et al. 2019)	**EQ-5D score** Difference in EQ-5D score between IV iron group and control group was not significant
Elhenawy et al. (2021)[19] SR with MA (1 RCT, Bernabeu-Wittel et al. 2016)	**SF36v2 at 60 days post-hospital discharge reassessment for IV iron therapy versus control** Results showed statistically non-significant changes between groups (measurements NR)
Elhenawy et al. (2021)[19] SR with MA (1 RCT, Froessler et al. 2016)	**SF36 at 4 weeks post-surgery reassessment for IV iron therapy versus control** Results showed statistically non-significant changes between groups (measurements NR)
Jones et al. (2021)[20] SR (1 RCT, Khalafallah et al. 2016)	**SF36 scores from postoperative day 1 to postoperative week 12[a]** IV iron group = 13.4 Standard of care group = 9.1 **Physical scores from postoperative day 1 to postoperative week 12[a]** IV iron group = 13.4 Standard of care group = 7.9 **Mental scores from postoperative day 1 to postoperative week 12[a]** IV iron group = 13.3 Standard of care group = 9.9
Jones et al. (2021)[20] SR (1 RCT, Kim et al. 2017)	**Mean fatigue scores at week 3 (95% CI)[a]** IV iron group = 30 (26.8 to 33.1) Placebo = 34.6 (31.3 to 37.9) **Mean dyspnea scores at week 12 (95% CI)[a]**

Study citation and design	Study findings
	IV iron group = 9.5 (7.2 to 11.8) Placebo = 14.2 (11.3 to 17.1)
Jones et al. (2021)[20] SR (1 RCT, Richards et al. 2019)	**Mean EQ-5D-5L Utility scores at 10 days, 8 weeks, and 6 months postoperative (SD)[a]** IV iron group = 0.80 (0.20); 0.79 (0.20); 0.82 (0.22) Placebo group = 0.81 (0.21); 0.77 (0.21); 0.82 (0.21) **Mean EQ-5D-5L Health scores at 10 days, 8 weeks, and 6 months postoperative (SD)[a]** IV iron group = 70.6 (20.5); 70.7 (19.4); 75.0 (18.4) Placebo group = 73.8 (19.6); 71.1 (19.5); 76.2 (19.2) **Mean MFI scores at 10 days, 8 weeks, and 6 months postoperative (SD)[a]** IV iron group = 53.2 (18.4); 52.9 (17.1); 48.8 (18.9) Placebo group = 50.5 (18.9); 53.9 (17.7); 47.4 (19.1)
Fung et al. (2022)[22] RCT	**Median QOR-15 score (range)** IV iron group = 107 (100 to 124) Control group = 115 (103 to 125) P = 0.547
Kvaslerud et al. (2022)[23] RCT	**Mean EQ-5D3L index scores between IV iron group and placebo group at baseline and follow-up (range)** Mean IV iron group scores at baseline = 0.83 (0.77 to 0.93); Mean IV iron group scores at follow-up = 0.91 (0.82 to 0.97) Mean placebo group scores at baseline = 0.81 (0.74 to 0.93); Mean placebo group scores at follow-up = 0.91 (0.78 to 0.97) Mean difference (95% CI) = -0.001 (-0.4 to 0.4); P = 0.97 **Mean EQ-5D VAS scores between IV iron group and placebo group at baseline and follow-up (range)** Mean IV iron group scores at baseline = 67 (50 to 80); Mean IV iron group scores at follow-up = 70 (48 to 84) Mean placebo group scores at baseline = 50 (40 to 73); Mean placebo group scores at follow-up = 75 (60 to 85) Mean difference (95% CI) = -7.8 (-16.5 to 0.86); P = 0.077
Thin et al. (2021)[25] RCT	**Mean EQ-5D-3L score at baseline between IV iron group (N = 15) and oral iron group (N = 15) (SD)** IV iron group = 70.3 (22) Oral iron group = 73 (8) P = 0.6 **Mean EQ-5D-3L score at 1 month follow-up between IV iron group (N = 13) and oral iron group (N = 11) (SD)** IV iron group = 70.4 (21.8) Oral iron group = 84.5 (12.1) P = 0.07 **Mean EQ-5D-3L score at 3-month follow-up between IV iron group (N = 13) and oral iron group**

Study citation and design	Study findings
	(N = 11) (SD) IV iron group = 80 (18.4) Oral iron group = 85.9 (10.7) P = 0.4

CI = confidence interval; EQ-5D = European Quality of Life – 5 Dimensions Questionnaire; EQ-5D-3L = European Quality of Life – 5 Dimension – 3 Levels; EQ-5D-5L = European Quality of Life – 5 Dimension – 5 Levels; IV = intravenous; MA = meta-analysis; MFI = Multidimensional Fatigue Inventory; NR = not reported; QOR-15 = 15-iten Quality of Recovery; RCT = randomized controlled trial; SD = standard deviation; SF36 = short form-36; SR = systematic review; VAS = visual analogue scale.

[a]Statistical significance between groups was not provided by Jones et al. (2021)

Table 11: Summary of Findings by Outcome — Days in Hospital or Recovery

Study citation and design	Study findings
Jones et al. (2021)[20] SR (1 RCT, Brisbe et al. 2014)	**Mean length of hospital stay, days (SD)[a]** IV iron group = 7.9 (1.7) Oral iron group = 7.6 (0.9)
Jones et al. (2021)[20] SR (1 RCT, Bernabeu-Wittel et al. 2016)	**Median length of hospital stay, days (range)[a]** IV iron group = 8 (6 to 11) IV iron + EPO group = 7 (5 to 10) Placebo group = 8 (6 to 10)
Jones et al. (2021)[20] SR (1 RCT, Froessler et al. 2016)	**Median length of hospital stay, days (range)[a]** IV iron group = 6 (1 to 19) No treatment group = 9 (1 to 23)
Jones et al. (2021)[20] SR (1 RCT, Khalafallah et al. 2016)	**Mean length of hospital stay, days (SD)[a]** IV iron group = 7.8 (10.3) Standard of care group = 11.6 (15.6)
Jones et al. (2021)[20] SR (1 RCT, Keeler et al. 2017)	**Median length of hospital stay, days (range)[a]** IV iron group = 6 (5 to 10) Oral iron group = 6 (4 to 9)
Jones et al. (2021)[20] SR (1 RCT, Kim et al. 2017)	**Mean length of hospital stay, days (SD)[a]** IV iron group = 10.7 (7.9) Placebo = 10.9 (13.8)
Jones et al. (2021)[20] SR (1 RCT, Padmanabhan et al. 2019)	**Median length of hospital stay, days (range)[a]** IV iron group = 7 (6 to 12) Oral iron group = 9 (6 to 14)
Jones et al. (2021)[20] SR (1 RCT, Richards et al. 2019)	**Median length of hospital stay, days (range)[a]** IV iron group = 9 (7 to 14) Placebo group = 9 (5 to 14)

Study citation and design	Study findings
Moon et al. (2021)[21] SR (1 retrospective cohort study, Laso-Morales et al. 2018)	**Mean length of stay (days)** IV iron group = 9 Control group = 9 P = NS
Moon et al. (2021)[21] SR (1 retrospective and prospective cohort study, Calleja et al. 2015)	**Mean length of stay (days)** IV iron group = 8.4 Control group = 10.9 P < 0.001
Moon et al. (2021)[21] SR (1 prospective cohort study, Kam et al. 2020)	**Mean length of stay (days)** IV iron group = 9 Control group = 8.5 P = NS
Fung et al. (2022)[22] RCT	**Median postoperative length of stay days (range)** IV iron group = 10 (5 to 19) Control group = 7 (5 to 10) P = 0.289 **Days at home within 30 days of surgery (range)** IV iron group = 20 (10 to 15) Control group = 23 (20 to 25) P = 0.461
Shokri et al. (2022)[24] RCT	**Length of hospital stay days between IV iron group and placebo group (SD)** IV iron group = 4.33 (1) Placebo group = 8.68 (1.1) P < 0.001 **ICU stay days between IV iron group and placebo group (SD)** IV iron group = 1.28 (0.45) Placebo group = 2.23 (0.95) P < 0.001
Thin et al. (2021)[25] RCT	**Mean total DAOH within 30 days between IV iron group and oral iron group (SD)** IV iron group = 19.3 (8.9) Oral iron group = 18.6 (10.2) P = 0.9 **Mean total DAOH within 3 months between IV iron group and oral iron group (SD)** IV iron group = 75.2 (16.1) Oral iron group = 68.8 (26.9) P = 0.5 **Mean total DAOH within 6 months between IV iron group and oral iron group (SD)** IV iron group = 166.8 (14.5)

Study citation and design	Study findings
	Oral iron group = 270.7 (442) P = 0.4
Ploug et al. (2022)[26] Retrospective cohort study	**Median length of stay days between IV group and control group (range)** IV iron group = 4 (3 to 5) Control group = 3.5 (3 to 5.5) P = 0.74 **Median DAOH 30-day follow-up between IV iron group and control group (range)** IV iron group = 26 (23 to 27) Control group = 26 (24 to 27) P = 0.997 **Median DAOH 90-day follow-up between IV iron group and control group (range)** IV iron group = 86 (83 to 87) Control group = 86 (82 to 87) P = 0.79
Abdullah et al. (2021)[27] Retrospective cohort study	**Mean length of stay days for 1:1 propensity matched IV iron group (N = 89) and oral iron group (N = 89) (SD)** IV iron group = 8 (12.5) Oral iron group = 15.1 (23.6) P = 0.013 **Mean length of stay days for 1:2 propensity matched IV iron group (N = 89) and oral iron group (N = 178) (SD)** IV iron group = 8 (12.5) Oral iron group = 14.1 (23.3) P = 0.006
Evans et al. (2021)[28] Retrospective cohort study	**Median length of stay days for each group (range)** IV treatment responsive group = 9 (6 to 41) IV treatment unresponsive group = 11 (5 to 182); P < 0.001 vs non-anemic group Untreated anemic group = 10 (3 to 53) Non-anemic group = 8 (4 to 49)
Triphaus et al. (2021)[31] Prospective cohort study	**Mean length of hospital stay days for each group (SEM)** Anemic, iron deficient and IV iron treatment group = 13.9 (0.8) Iron deficient and IV iron treatment group = 14.9 (1.8) Anemic and no treatment group = 16.7 (0.7) Not anemic and no treatment group = 11.8 (0.3)

DAOH = days alive and out of hospital; EPO = erythropoietin; ICU = intensive care unit; IV = intravenous; MA = meta-analysis; NS = not significant; RCT = randomized controlled trial; SD = standard deviation; SR = systematic review.

[a]Statistical significance between groups was not provided by Jones et al. (2021)

Table 12: Summary of Findings by Outcome — Safety and Adverse Events

Study citation and design	Study findings
Chaudhry et al. (2021)[18] SR (1 RCT, Brisbe et al. 2014)	**Rate of adverse events** IV iron group = 33% Oral iron group = 32%
Chaudhry et al. (2021)[18] SR (1RCT, Yoo et al. 2019)	**Rate of adverse events** IV iron group = 0% Control group = 0%
Elhenawy et al. (2021)[19] SR with MA (Based on 2 included study)	**Effects of IV iron therapy versus placebo or standard of care on the occurrence of associated serious adverse effects** Total IV iron group events = 85 Total placebo or standard of care group events = 91 Risk ratio (95% CI) = 0.96 (0.44 to 2.10); P = 0.92; I^2 = 0%
Elhenawy et al. (2021)[19] SR with MA (Based on 7 included studies)	**Effect of IV iron therapy versus placebo or standard of care on the occurrence of non-serious adverse effects (random effects model)** Total IV iron group events = 412 Total placebo or standard of care group events = 401 Risk ratio (95% CI) = 1.13 (0.78 to 1.65); P = 0.52; I^2 = 0%
Jones et al. (2021)[20] SR (1 RCT, Kim et al. 2017)	**Proportion of patients experiencing adverse events, n/N (%)**[a] IV iron group = 15/222 (6.8%) Placebo = 1/223 (0.4)
Jones et al. (2021)[20] SR (1 RCT, Padmanabhan et al. 2019)	**Proportion of patients experiencing adverse events, n/N (%)**[a] IV iron group = 0/20 Oral iron group = 3/20 (15%)
Jones et al. (2021)[20] SR (1 RCT, Park et al. 2019)	**Proportion of patients experiencing adverse events, n/N (%)**[a] IV iron group = 0/29 Placebo group = NR
Jones et al. (2021)[20] SR (1 RCT, Richards et al. 2019)	**Proportion of patients experiencing adverse events, n/N (%)**[a] IV iron group = 11/237 (5%) Placebo group = 5/237 (5%)
Fung et al. (2022)[22] RCT	**Number of patients experiencing any surgical complications, n (%)** IV iron group = 11 (55%) Control group = 8 (40%) P = 0.342 **Number of patients experiencing surgical complication grade 0, 1, 2, or 3** IV iron group = 9;7;3;1 Control group = 12;6;2;0 P = 0.636 **Hospital readmission within 30 days, n (%)**

Study citation and design	Study findings
	IV iron group = 1 (5%) Control group = 1 (5%) P = 1.00
Kvaslerud et al. (2022)[23] RCT	**Number of adverse events between IV iron group (N = 73) and Placebo group (N = 75)** IV iron group = 53 Placebo group = 66 **Number of serious adverse events between IV iron group (N = 73) and Placebo group (N = 75)** IV iron group = 37 Placebo group = 49
Shokri et al. (2022)[24] RCT	**Incidence of adverse cardiovascular events between IV iron group (N = 40) and placebo group (N = 40), n (%)** IV iron group = 5 (12.5%) Placebo group = 7 (17.5%) P = 0.531 **Incidence of prolonged ventilation between IV iron group (N = 40) and placebo group (N = 40), n (%)** IV iron group = 2 (5%) Placebo group = 6 (15%) P = 0.136 **Incidence of heart failure between IV iron group (N = 40) and placebo group (N = 40), n (%)** IV iron group = 1 (2.5%) Placebo group = 3 (7.5%) P = 0.305 **Incidence of stroke between IV iron group (N = 40) and placebo group (N = 40), n (%)** IV iron group = 0 Placebo group = 1 (2.5%) P = 0.314
Thin et al. (2021)[25] RCT	**Number of patients readmitted during 6-month follow-up between IV iron group (N = 13) and oral iron group (N = 12), n (%)** IV iron group = 4 (30.8%) Oral iron group = 4 (33.3%) P = 0.9
Ploug et al. (2022)[26] Retrospective cohort study	**All complications rate between IV iron group (N = 122) and control group (N = 48), n (%)** IV iron group = 31 (25%) Control group = 4 (8%) P = 0.01 **All surgical complications rate between IV iron group (N = 122) and control group (N = 48), n (%)** IV iron group = 24 (20%) Control group = 4 (8%)

Study citation and design	Study findings
	P = 0.05 **All medical complications rate between IV iron group (N = 122) and control group (N = 48), n (%)** IV iron group = 10 (8%) Control group = 1 (2%) P = 0.13
Quarterman et al. (2021)[30] Retrospective cohort study	**Number of cerebrovascular accidents from each group, n (%)** Anemic and received IV iron treatment group (N = 190) = 7 (3.7%) Anemic and did not receive IV iron treatment or not iron deficient group (N = 581) = 11 (1.9%); P = 0.17 vs IV iron treatment group Not anemic group (N = 2093) = 24 (1.2%); P = 0.01 vs IV iron treatment group **Number of renal replacement therapy procedures from each group, n (%)** Anemic and received IV iron treatment group (N = 190) = 7 (6.7%) Anemic and did not receive IV iron treatment or not iron deficient group (N = 581) = 9 (1.6%); P = 0.08 vs IV iron treatment group Not anemic group (N = 2093) = 13 (0.6%); P < 0.001 vs IV iron treatment group **Number of re-operations from each group, n (%)** Anemic and received IV iron treatment group (N = 190) = 9 (4.7%) Anemic and did not receive IV iron treatment or not iron deficient group (N = 581) = 24 (4.1%); P = 0.72 vs IV iron treatment group Not anemic group (N = 2093) = 73 (3.5%); P = 0.36 vs IV iron treatment group
Mortality	
Elhenawy et al. (2021)[19] SR with MA	**Effect of IV iron therapy versus placebo or standard of care on 30-day mortality (random effects model based on 4 included studies)** Total IV iron group events = 303 Total placebo or standard of care group events = 284 Risk ratio (95%CI) = 1.10 (0.60 to 2.00); P = 0.76; I^2 = 0% **Effect of IV iron therapy versus placebo or standard of care on mortality ≥ 2 months post-hospital discharge (based on 2 studies)** Total IV iron group events = 164 Total placebo or standard of care group events = 155 Risk ratio (95% CI) = 1.18 (0.63 to 2.19); P = 0.60; I^2 = 0%
Jones et al. (2021)[20] SR (1 RCT, Padmanabhan et al. 2019)	**Proportion of postoperative mortality, n/N (%)**[a] IV iron group = 1/20 (5%)[b] Oral iron group = 0/29
Jones et al. (2021)[20] SR (1 RCT, Richards et al. 2019)	**Proportion of postoperative mortality, n/N (%)**[a] IV iron group = 12/238 (5%) Placebo group = 10/236 (4%)

Study citation and design	Study findings
Kvaslerud et al. (2022)[23] RCT	**Number of deaths between IV iron group (N = 73) and Placebo group (N = 75)** IV iron group = 2 Placebo group = 5
Shokri et al. (2022)[24] RCT	**Mortality rate between IV iron group (N = 40) and placebo group (N = 40), n (%)** IV iron group = 2 (5%) Placebo group = 3 (7.5%) P = 0.644
Ploug et al. (2022)[26] Retrospective cohort study	**30-day mortality rate between IV iron group (N = 122) and control group (N = 48), n (%)** IV iron group = 1 (1%) Control group = 0 P = 0.72 **90-day mortality rate between IV iron group (N = 122) and control group (N = 48), n (%)** IV iron group = 2 (2%) Control group = 3 (6%) P = 0.14
Evans et al. (2021)[28] Retrospective cohort study	**Number of deaths for each group, n (%)** IV treatment responsive group (N = 24) = 0 IV treatment unresponsive group (N = 51) = 1 (2%) Untreated anemic group (N = 72) = 3 (6%); P = 0.012 vs non-anemic group Non-anemic group (N = 300) = 3 (1%)
Quarterman et al. (2021)[30] Retrospective cohort study	**Number of in-hospital mortality from each group, n (%)** Anemic and received IV iron treatment group (N = 190) = 3 (1.6%) Anemic and did not receive IV iron treatment or not iron deficient group (N = 581) = 14 (2.4%); P = 0.78 vs IV iron treatment group Not anemic group (N = 2093) = 17 (0.8%); P = 0.23 vs IV iron treatment group
Triphaus et al. (2021)[31] Prospective cohort study	**Mortality rate for each group, n (%)** Anemic, iron deficient and IV iron treatment group (N = 184) = 7 (3.8%) Iron deficient and IV iron treatment group (N = 55) = 3 (5.5%) Anemic and no treatment group (N = 461) = 27 (5.9%) Not anemic and no treatment group (N = 1028) = 31 (3%)
Infection	
Elhenawy et al. (2021)[19] SR with MA (Based on 2 included studies)	**Effect of IV iron therapy versus placebo or standard of care on postoperative infection occurrence (random effects model)** Total IV iron group events = 143 Total placebo or standard of care group events = 132 Risk ratio (95% CI) = 0.64 (0.30 to 1.40); P = 0.27; I^2 = 0%

Study citation and design	Study findings
Fung et al. (2022)[22] RCT	**Number of patients experiencing infection, n (%)** IV iron group = 6 (30%) Control group = 4 (20%) P = 0.465
Kvaslerud et al. (2022)[23] RCT	**Number of infections during IV treatment between IV iron group (N = 73) and Placebo group (N = 75)** IV iron group = 5 Placebo group = 6
Shokri et al. (2022)[24] RCT	**Incidence of infection between IV iron group (N = 40) and placebo group (N = 40), n (%)** IV iron group = 3 (7.5%) Placebo group = 5 (12.5%) P = 0.456
Ploug et al. (2022)[26] Retrospective cohort study	**All infectious complications rate between IV iron group (N = 122) and control group (N = 48), n (%)** IV iron group = 10 (8%) Control group = 1 (2%) P = 0.14
Quarterman et al. (2021)[30] Retrospective cohort study	**Number of sternal wound infections from each group, n (%)** Anemic and received IV iron treatment group (N = 190) = 7 (3.7%) Anemic and did not receive IV iron treatment or not iron deficient group (N = 581) = 16 (2.8%); P = 0.51 vs IV iron treatment group Not anemic group (N = 2093) = 42 (2%); P = 0.12 vs IV iron treatment group

CI = confidence interval; EPO = erythropoietin; IV = intravenous; MA = meta-analysis; N = number; NR = not reported; RCT = randomized controlled trial; SR = systematic review; vs = versus.

[a]Statistical significance between groups was not provided by Jones et al. (2021)

[b]Mortality in this population was due to unrelated causes.

Table 13: Summary of Findings by Outcome — Additional Clinical Outcomes

Study citation and design	Study findings
Functional outcomes	
Chaudhry et al. (2021)[18] SR (1 RCT, Brisbe et al. 2014)	**6MWT score** Difference in 6MWT score between IV iron group and oral iron group was not significant
Chaudhry et al. (2021)[18] SR (1RCT, Yoo et al. 2019)	**FACT-An score** Difference in FACT-An score between IV iron group and control iron group was not significant
Kvaslerud et al. (2022)[23] RCT	**Mean 6MWT distance between IV iron group and placebo group at baseline and follow-up (SD)** Mean IV iron group baseline distance = 355 m (113); Mean IV iron group follow-up distance = 375 m (132) Mean placebo group baseline distance = 367 m (129); Mean placebo group follow-up distance = 384 m (128) Mean difference (95% CI) = 2 m (-21 to 25); P = 0.86

Study citation and design	Study findings
Ferritin Levels	
Elhenawy et al. (2021)[19] SR with MA (Based on 3 included studies)	**Ferritin level comparison at post-treatment and pre-surgery between IV iron and placebo or standard of care** Mean difference (95% CI) = 94.09 ng/ml (51.57 to 136.61); P < 0.0001 **Ferritin level comparison at hospital discharge between IV iron and placebo or standard of care** Mean difference (95% CI) = 547.77 ng/ml (36.61 to 1058.94); P = 0.04 **Ferritin level comparison > 4 weeks postoperative between IV iron and placebo or standard of care** Mean difference (95% CI) = 347.57 ng/ml (290.92 to 404.21); P < 0.0001 **Ferritin level comparison at post-treatment and pre-surgery between IV iron and oral iron therapy** Mean difference (95% CI) = 106.12 ng/ml (32.46 to 179.78); P = 0.005
Fung et al. (2022)[22] RCT	**Mean change in ferritin concentration from baseline to before surgery between IV iron therapy and control** Mean difference (95% CI) = 296.8 ng/L (200.6 to 393.2); P < 0.001
Kvaslerud et al. (2022)[23] RCT	**Mean ferritin level from baseline to follow-up (SD)** Mean IV iron group ferritin level at baseline = 74.3 µg/L (57); Mean IV iron group ferritin level at follow-up = 361 µg/L (221) Mean placebo group ferritin level at baseline = 69 µg/L (52); Mean placebo group ferritin level at follow-up = 79 µg/L (86) Mean difference (95% CI) = 276 µg/L (216 to 336); P < 0.001

6MWT = 6-minute walk test; CI = confidence interval; FACT-An = Functional Assessment of Cancer Therapy for patients with Anemia/Fatigue; IV = intravenous; l = liter; m = meters; MA = meta-analysis; ml = milliliter; µg = microgram; ng = nanogram; NR = not reported; RCT = randomized controlled trial; SR = systematic review.

Table 14: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Greenberg et al. (2021)[32]	
"Intravenous iron infusions may be appropriate for patients with IDA in certain circumstances (i.e., < 8 wk until surgery, unable to tolerate/absorb oral iron formulation, hemoglobin level < 100 g/L)."[ref] Evidence supporting this recommendation was from 1 SR, 4 RCTs, 1 prospective cohort study, and 2 retrospective cohort studies.	**Strength of recommendation:** Strong **Quality of evidence:** High

IDA = iron deficient anemia; RCT = randomized controlled trial; SR = systematic review.

Appendix 5: Overlap Between Included Systematic Reviews

Note that this table has not been copy-edited.

Table 15: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Primary study citation	Meyer (2022)[16]	Tang (2022)[17]	Chaudhry (2021)[18]	Elhenawy (2021)[19]	Jones (2021)[20]	Moon (2021)[21]
Kam et al. ***Int J Colorectal Dis.*** 2020; 35(3): 521-527	—	Yes	—	—	—	Yes
Richards et al. ***Lancet*** 2020; 396: 1353-1361	Yes	—	—	—	Yes	—
Lee et al. ***J Obstet Gynaecol Res.*** 2019; 45 (4): 858-864	—	—	—	—	Yes	—
Padmanabhan et al. ***Interact Cardiovasc Thorac Surg.*** 2019; 28 (3): 447-454	—	—	—	—	Yes	—
Park et al. ***J Clin Med*** 2019; 8:1674	—	—	Yes	—	Yes	—
Yoo et al. ***SSRN*** 2019	—	—	Yes	—	—	—
Wilson et al. **Transfusion** 2018; 58 (3): 795-803	—	Yes	—	—	—	Yes
Keeler et al. ***Br J Surg*** 2017; 104 (3): 214-21	—	—	—	Yes	Yes	Yes
Kim et al. ***JAMA* 2017;** 317 (20): 2097-2104	—	—	—	—	Yes	—
Laso-Morales et al. ***Transfusion*** 2017; 57 (12): 3040-8	—	—	—	—	—	Yes
Wilson et al. ***Surg Oncol.*** 2018; 27 (2): 192-199	—	Yes	—	—	—	—
Bernabeu-Wittel et al. ***Transfusion*** 2016; 56 (9): 2199-211	—	—	—	Yes	Yes	—
Calleja et al. ***Int J Colorectal Dis.*** 2016; 31 (3): 543-51	—	—	—	—	—	Yes
Froessler et al. ***Ann. Surg.*** 2016; 264 (1): 41-46	Yes	—	Yes	Yes	Yes	Yes
Khalafallah et al. ***Lancet Haematol.*** 2016; 3 (9): e415-425	—	—	—	—	Yes	—
Shah et al. ***Natl J Commun Med.*** 2016; 7(1): 60-3	—	—	—	Yes	—	—
Johansson et al. ***Vox Sang*** 2015; 109 (3): 257-66	—	—	—	Yes	—	—
Bisbe et al. ***Br J Anaesth*** 2014; 113: 402-409	—	—	Yes	—	Yes	—

Primary study citation	Meyer (2022)[16]	Tang (2022)[17]	Chaudhry (2021)[18]	Elhenawy (2021)[19]	Jones (2021)[20]	Moon (2021)[21]
Garrido-Martin et al. ***Interact Cardiovasc Thoracic Surg.*** 2012; 15 (6): 1013-8	—	—	—	Yes	—	—
Titos-Acros et al. ***World J Surg.*** 2012; 36 (8): 1893-1897	—	Yes	—	—	—	—
Na et al. ***Transfusion (Paris)*** 2011; 51: 118-124	—	—	Yes	—	—	—
Serrano-Trenas et al. ***Transfusion*** 2011; 51 (1): 97-104	—	—	—	Yes	—	—
Edwards et al. ***Br. J. Surg*** 2009; 96 (10): 1122-1128	Yes	Yes	—	Yes	—	Yes
Kim et al. ***Acta Haemotal*** 2009; 121 (1): 37-41	—	—	—	Yes	—	Yes
Lidder et al. ***Ann. R Coll.*** 2007; 89 (4): 418-421	Yes	Yes	—	—	—	—
Mundy et al. ***J Bone Joint Surg Br*** 2005; 87: 213-217	—	—	Yes	—	—	—
Okuyama et al. ***Surg today.*** 2005; 35 (1): 36-40	—	Yes	—	—	—	—
Sutton et al. ***J Bone Joint Surg Br*** 2004; 113: 402-409	—	—	Yes	—	—	—
Weatherall et al. ***ANZ J Surg*** 2004; 74: 1049-1051	—	—	Yes	—	—	—
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