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Clinical effects of preoperative i.v. iron infusion in patients with colorectal cancer and iron-deficiency anemia

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Clinical effects of preoperative i.v. iron infusion in patients with colorectal cancer and iron-deficiency anemia

[Kliniska effekter av preoperativ järninfusion till patienter med kolorektal cancer och järnbristanemi]

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1. Abstract

Background: Preoperative iron deficiency anemia is common in patients with colorectal cancer. Traditionally, anemic patients are given oral iron substitution before colorectal cancer surgery, but this strategy has recently been questioned since intravenous (i.v.) iron substitution compounds have become available. The aim of this HTA was to evaluate the evidence for this new strategy.

Question at issue: Does preoperative iron infusion reduce mortality, risk for tumour recurrence, risk of perioperative complications, need for reoperation, or the need for blood transfusions, and does it improve health-related quality of life or reduce length of hospital stay, as compared with conventional treatment (placebo infusion, no treatment or oral iron substitution), in patients planned for operative treatment of colorectal cancer with a haemoglobin level below 115 g/l?

Method: A systematic literature search was performed in Medline, Embase, the Cochrane Library and several HTA-databases. After a systematic exclusion process, ten articles (four RCTs, five cohort studies and one SR) remained for quality assessment. The SR did not contain any relevant new information and was therefore only commented on.

Results:

Mortality was reported in one RCT and one retrospective cohort study. In the RCT, the control treatment was oral iron substitution, and in the cohort study no iron treatment. At five years, no significant effects of preoperative iron substitution i.v. were seen in either study. However, the 95% CI for the HR is wide, not excluding clinically important differences.

Conclusion: There may be little or no difference in mortality after preoperative i.v. iron infusion compared with oral iron substitution. (GRADE ⊕⊕◯◯**).** It is uncertain whether there is any difference between i.v. iron treatment and no iron treatment**.** Very low certainty of evidence (GRADE ⊕◯◯◯).

Tumour recurrence was reported in the same two articles as mortality. No significant differences between the groups were seen. However, the 95% CI for the HR is wide, not excluding clinical important differences.

Conclusion:There may be little or no difference in tumour recurrence after preoperative i.v. iron infusion compared with oral iron substitution. (GRADE ⊕⊕◯◯**).** It is uncertain whether there is any difference in tumour recurrence between i.v. iron treatment and no iron treatment. Very low certainty of evidence (GRADE ⊕◯◯◯).

Complications to the iron infusion per se were reported in two RCTs which for this purpose should be regarded as case series due to lack of meaningful controls. A few cases of headache, rash and symptomatic hypotension were seen. The outcome was not assessed according to GRADE.

The number of administered red blood transfusions (‘**need for transfusions**’) were reported in two RCTs and four cohort studies. One RCT used placebo infusion as control, and the other RCT had oral iron as control. All cohort studies had ‘no i.v. iron’ as reference treatment. Two of them used historical controls and two used retrospective data. In the RCTs, no significant differences were seen (p=0.335 and 0.470). Two cohort studies reported a reduction in transfusions and two did not see any significant difference.

Conclusion: It is uncertain whether there is any difference in need for transfusions between i.v. iron substitution and placebo or oral iron. (GRADE ⊕◯◯◯).

Peri- and postoperative complications were reported in two RCTs (control oral iron substitution) and three cohort studies (control no i.v. iron). In the RCTs and two out of three cohort studies, no significant differences in complication rates were seen.

Conclusion: It is uncertain whether there is any difference in peri- or postoperative complications between i.v. iron treatment and oral iron substitution or non-i.v. treatment (GRADE ⊕◯◯◯).

Health-related quality of life was reported in one RCT, using oral iron treatment as control. There were small improvements in the i.v. iron group in 'Functional assessment of cancer therapy-anemia subscale' and 'anemia trial outcome' indexes, p=0.001, and p=0.002.

Conclusion: It is uncertain whether there is any difference in health-related quality of life between i.v. and oral iron substitution (GRADE ⊕◯◯◯).

Length of hospital stay was presented in one RCT and one controlled cohort study. In the RCT the control treatment was placebo infusion and in the cohort study no i.v. iron treatment. No significant differences were seen in either study.

Conclusion: It is uncertain whether there is any difference in length of hospital stay between i.v. iron treatment and oral iron substitution or no i.v. iron treatment (GRADE ⊕◯◯◯).

General concluding remark:

Robust scientific evidence to evaluate the effect of i.v. iron compounds in CRC patients is lacking. Even if no evidence was demonstrated that treatment of this patient group with i.v. iron compounds improves major clinical outcomes, as compared to either no treatment or oral iron substitution, the 95% CI:s are wide. One therefore cannot exclude clinically important differences. Low or very low certainty of evidence.

2. Svensk sammanfattning – Swedish summary

Bakgrund: Anemi (blodbrist) är vanligt vid tjocktarmscancer, beroende på att tumören ofta blöder vilket ger upphov till järnbrist. Inför operation försöker man ofta ge patienten ett bättre blodvärde, eftersom detta förväntas göra patienten bättre rustad för att klara operationen. Traditionellt har järntillförseln skett i form av tabletter, men detta har två nackdelar: det tar tid, som regel ett par veckor, innan blodvärdet stiger, och biverkningar – framförallt förstoppning – är vanliga. Nya järnberedningar har nu utvecklats som kan ges intravenöst (i.v.) och som ger en snabbare påfyllning av järndepåerna, och dessa har nu på sina håll börjat införas i rutinsjukvård.

Frågeställning: Vid planerad koloncancerkirurgi och vid ett preoperativt blodvärde (Hb) under 115g/l, reducerar i.v. järntillförsel mortalitet, risk för återkomst av tumören, komplikationsrisk eller behovet av blodtransfusioner, eller förbättrar det livskvaliteten eller förkortar det vårdbehovet, jämfört med ingen behandling eller behandling med järntabletter?

Metod: En systematisk litteratursökning gjordes i databaserna Medline, Embase, the Cochrane Library och olika HTA-databaser. De förbestämda utfallsmåtten var mortalitet, tumörrecidiv, komplikationer, transfusionsbehov, livskvalitet och vårdtid. Vi identifierade 10 relevanta artiklar: fyra randomiserade kontrollerade studier och fem kontrollerade kohortstudier samt en systematisk översikt utan relevant tilläggsinformation.

Resultat: Studierna visade inga signifikanta skillnader i dödlighet eller återfall av tumören vid jämförelse mellan intravenös infusion och järn i form av tabletter. För övriga utfall, såsom behov av blodtransfusion, komplikationer och livskvalitet gick det inte att göra någon bedömning. Evidensstyrkan enligt GRADE-systemet bedömdes som låg eller mycket låg (GRADE ⊕⊕◯◯ eller ⊕◯◯◯).

Slutsatser: Tillförlitligt vetenskapligt stöd saknas för att besvara frågan. Parenteral järntillförsel till anemiska patienter inför koloncancerkirurgi kan ge liten eller ingen skillnad i mortalitet (GRADE ⊕⊕◯◯) och risk för tumörrecidiv (GRADE ⊕⊕◯◯) jämfört med järntabletter, men osäkerheten är stor. Det är vidare osäkert huruvida det påverkar behovet av blodtransfusioner (GRADE⊕◯◯◯), risken för komplikationer (GRADE⊕◯◯◯), livskvalitet ⊕◯◯◯) eller sjukhusvistelsetid (⊕◯◯◯), jämfört med ingen behandling eller järntabletter

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers and is ended with a concluding summary.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, May 26th 2021.

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Wallerstedt, Susanna	MD, Professor
Wartenberg, Constanze	Psychologist, PhD

DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of findings

Outcomes	Study design Number of studies	Relative effect (95% CI)	Absolute effect	Certainty of evidence GRADE*
Mortality	1 RCT (n=110)	HR for OS at 5 years: 0.82 (direction favours oral iron) (95% CI: 0.44 to 1.54), p= 0.522	<u>RCT</u> *Overall survival (OS)* I: 3 years: 78% (64 to 86%) C: 3 years: 82% (69 to 91%) n.s. I: 5 years: 63% (48 to 75) C: 5 years: 71% (57 to 82) n.s.	Low [1] ⊕⊕◯◯ (based on RCT, comparison i.v. iron vs oral iron)
	1 Cohort (n=320)		<u>Cohort</u> *OS (with propensity score adjustment):* I: mean OS 58 months C: data and p-value not stated *5-year OS* I: 64.3% (based on data from10 patients) C: not explicitly stated, estimated 70% (based on data from 25 patients) p-value (based on 1, 3 and 5-year data): 0.456	Very low [2] ⊕◯◯◯ (based on cohort, comparison i.v. iron vs no i.v. iron)
Tumour recurrence	1 RCT (n=110)	*Disease-free survival (DFS)* 5 years: HR 1.08 (direction favours i.v. iron) (95% CI: 0.61 to 1.92), p= 0.79	*Disease-free survival (DFS)* I: 3 years, 68% (95% CI: 54 to 80) C: 3 years, 66% (95% CI: 52 to 78%) I: 5 years 60% (95% CI: 47-73%) C: 5 years 55% (95% CI 41-69%) p=0.804	Low [1] ⊕⊕◯◯ (based on RCT, comparison i.v. iron vs oral iron)
	1 Cohort (n=320)	*Time to recurrence* HR 0.99 (95% CI: 0.52 to 1.88), p = 0.962 *DFS 5 years* HR=0.79 (CI 0.61-1.92) p=0.79	*Time to recurrence*: I: median 13.8 months, IQR 10.3-28.1 C: median 13.3 months, IQR 8.0-19.8 p=0.275 *DFS* I: mean DFS 58 months C: not stated! I: 5 year DFS: 83.4% C: not explicitly stated, estimated: 78% p=0.240	Very low [2] ⊕◯◯◯ (based on cohort, comparison i.v. iron vs no i.v. iron)

Complications to the iron infusion	2 RCTs, in this context case series (n=116+60)	NA	RCT 1: I: Postinfusion headache (n=3), rash (n=1) RCT 2: I: Symptomatic hypotension that did not require treatment (n=2)	Not assessed according to GRADE system
Need for transfusion	3 RCTs (n= 110+60+66) 4 Cohorts (n= 266+100+322+318)	Cohort 4: Need for postoperative transfusion (multivariable): OR: 0.54 (95% CI: 0.24 to 1.21), p=0.14 Need for postop transfusion (univariable): OR: 0.47 (95% CI: 0.23 to 0.99), p=0.04	RCT 1: Comparison responders vs. non-responders only, therefore not included in analysis RCT 2: I: 2/34, C: 5/26, p=0.335 RCT 3: I: 10/55, C: 14/61, p=0.470 Cohort 1: I: 9.9%, C: 38.7%, p<0.001 Cohort 2: I: 8/38 (21%), C: 30/62 (48%), p=0.006 Cohort 3: I: mean 0.3 (SD±0.8) units C: mean 0.4 (SD±1.2) units, n.s.	Very low [3] ⊕◯◯◯
Peri- and postoperative complications	2 RCTs n=116+116 (same patients in both studies?) 3 Cohorts (n=111+155 +232+90+94 +224)		RCT 1: No difference in complication severity (p=0.995), and rate (p=0.305). RCT 2: Infectious complications: Day 7: I: 28%, C: 16% (p=0.112) Day 28: I: 40%, C: 25% (p=0.091) Cohort 1: *Complications in total* I: 22.5% (n=111) C: 25.5% (n=155), n.s. (all comparisons n.s.)	Very low [4] ⊕◯◯◯

		Cohort 3: *Complications with i.v. iron* OR: 0.91 (95% CI: 0.50 to1.68) p=0.77	Cohort 2: *Infectious complications* I: 42/232 (18%), C: 26/90 (29%), p=0.018 (all other comparisons n.s.)	
Need for reoperation	No studies found			
Health-Related Quality of Life (n=61+55)	1 RCT	NA	*FACT-AN* Anaemia total score I: median 168 (IQR: 160–174) C: median 151 (IQR: 132–170), p=0.005 *SF36* General health I: median 77 (IQR: 65–86) C: median 62 (IQR: 50–77), p=0.002 Mental component summary I: mean 57 (SD±6) C: mean 51 (SD±10), p=0.001	Very low [5] ⊕◯◯◯
Length of hospital stay (n=34+26+ 232+90)	1 RCT 1 Cohort		RCT: I: 10 days (median) C: 8 days (median), p=0.273 Cohort: I: Mean, 9 (SD±6) days C: Mean, 9 (SD±5) days, p=0.889	Very low [6] ⊕◯◯◯

Footnotes: DFS: disease-free survival; FACT-AN: Functional Assessment of Cancer Therapy – Anaemia questionnaires. HRQoL: Health-Related Quality of Life; NA: Not applicable for this outcome; OR: Odds Ratio; OS: overall survival; SF36: Short Form 36 (transformed to 0–100 scale).

Downgraded due to: [1] very serious imprecision; [2] very serious imprecision and some uncertainty regarding study limitations; [3] some study limitations, serious inconsistency and serious imprecision; [4] serious study limitations and very serious imprecision; [5] very serious study limitations (open study, multiple measurements, selective reporting) and serious imprecision, [6]some study limitations and very serious imprecision.

[*] Certainty of evidence (GRADE)

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

CrC	Colorectal cancer
DFS	Disease free survival (DFS).
ERAS	Enhanced Recovery After Surgery
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluation (GRADE)
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
HTA	Health technology assessment
I.v.	Intravenous
NA	Not applicable (for this outcome)
OR	Odds Ratio
OS	Overall survival
RBCT	Red-Blood-Cell-Transfusion
RCT	Randomised controlled trial
SF36	Short Form 36 (transformed to 0–100 scale).
VGR	Region Västra Götaland
WHO	The World Health Organization

5. Background

Disease/disorder of interest and its degree of severity

Iron deficiency anemia in patients planned for operation of colorectal cancer.

Prevalence and incidence

Anemia in patients with cancer is common and this is particularly the case in patients with colorectal cancer. A tumor in the colon or rectum is often bleeding slowly, sometimes without the appearance of visible blood in the stools, and this happens in almost all patients with colorectal cancer. The resulting anemia is due to iron-deficiency. In fact, iron-deficiency anemia can be regarded as a common marker of colorectal cancer and may be the only visible sign of the disease (Schneider et al., 2018). A study from 1998 showed that 21% of men and 26% of women with colorectal cancer had anemia with levels of hemoglobin lower than 100g/l (Sadahiro et al., 1998). Another study from Karolinska University hospital showed that 52% of consecutive patients with colorectal cancer had anemia defined according to WHO, below 120 g/l for women and 130 g/l for men (Mörner et al., 2017). A compensatory tachycardia at rest is common with Hb levels around 100 g/l but serious cardiovascular symptoms are rare in individuals with hemoglobin levels above 80 g/l.

The proportion of patients presenting with anemia may differ with tumour site in the colon and rectum. In one study, anemia was e.g. found in 74.7% (215/288) of the patients with cancer in the caecum or ascending colon, in 57.1% (48/84) in the transverse colon, in 40.0% (180/300) in the sigmoid and in 30.5% (114/374) in the rectum (Edna et al., 2012).

The World Health Organisation (WHO) has defined anemia as blood hemoglobin concentration lower than 120 g/l in women and 130 g/l for men, but it has been suggested in the literature that the classification of anemia should be adjusted for gender, age and even ethnicity. Others (e.g. Enhanced Recovery After Surgery, ERAS) argue that the gender differences should be ignored, and that the hemoglobin target should be 130 g/l for all individuals.

Preoperative anemia is generally associated with poorer outcome after surgery and this applies also for colorectal cancer patients more specifically, with e.g. less overall survival and disease-free survival shown for rectal cancer patients (Wilson et al., 2017). In a study from Karolinska University hospital, one accordingly found an association between preoperative anemia and increased mortality (Mörner et al., 2017). However, it should be stressed that this is an association only.

In Sweden, approximately 6,000 individuals are diagnosed with colorectal cancer annually. In 2019, 186 out of 270 (68%) of individuals with rectal cancer and 547 out of 797 (69%) with colon cancer were operated with tumour resection in Region Västra Götaland.

Present treatment

Studies show that in general terms, preoperative anemia is associated with inferior surgical results and hence historically preoperative iron-deficiency anemia has been sought after and treated by either oral iron substitution or by pre- or perioperative red-blood-cell-transfusion (RBCT). The negative effects of RBCTare well known and there are also several problems with oral iron substitution, e.g., a slow onset of the haemoglobin increase and frequent gastrointestinal side effects that generate handling problems in this particular patient group. To circumvent these drawbacks, i.v. iron-infusion has been recommended as the choice of treatment by some colorectal cancer units in Sweden (Busch et al., 1994). The i.v. iron substitution is generally given when the colorectal cancer is diagnosed at the gastroenterology department, or alternatively in association with a separate outpatient visit to a nurse some weeks before surgery. The visit will take approximately 30-40 minutes because of the risk of adverse events (anaphylaxis-like but not lethal reactions). Sometimes the patient has already been given oral iron treatment by the referring general practitioner and in view of the short time frame to surgery the surgeon rarely offers oral iron substitution.

Routine i.v. iron substitution is currently not implemented at Sahlgrenska University Hospital. Most patients at Sahlgrenska University Hospital operated for colorectal cancer therefore remain untreated for their iron deficiency anemia.

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

Since 2017 in Sweden, a standardised protocol (standardiserat vårdförlopp, SVF) guarantees patients with cancer diagnosis and treatment within a specified time frame, two weeks from diagnosis until start of treatment. For colorectal cancer patients the treatment is surgery or start of oncological treatment. This time frame makes it difficult to wait for an effect of oral treatment of iron deficiency, a treatment that is also often poorly tolerated by colorectal cancer patients who frequently develop nausea and sometimes even bowel obstruction due to their cancer.

In contrast to Sahlgrenska University Hospital, some other hospitals in the region (Kungälvs Sjukhus, Södra Älvsborgs Sjukhus, Norra Älvsborgs Länssjukhus and Skaraborgs Sjukhus Skövde) already routinely offer their patients i.v. iron substitution but the threshold level of hemoglobin used to determine the indication for infusion varies from 100 g/l in Alingsås to 120 g/l in NÄL. According to spokespersons from these hospitals, routines based on this algorithm seem to work well in daily practice.

Number of patients per year who undergo current treatment regimen

As stated in the preceding paragraph, strategies for treatment of preoperative iron deficiency differ between hospitals. In the Region Västra Götaland (VGR) in 2019, 733 patients were operated because of colorectal cancer. We have been unable to ascertain the relative number of patients currently given i.v. iron substitution.

Present recommendations from medical societies or health authorities

The recommendations regarding the perioperative care of colorectal patients have been guided by the recommendations given by the ERAS society. The interest in perioperative care started with an eight-item checklist called Fast-track. The checklist included reducing the duration of fasting before surgery, reducing the use of opioids, and going back to normal walking and eating habits directly after surgery. With the Fast-track check list, length of hospital stay was shown to be reduced for numerous types of surgeries (Kehlet and Wilmore, 2008).

The interest in perioperative care increased and today the ERAS society regularly updates their recommendations for several disciplines, amongst them colorectal surgery (Gustafsson et al., 2019). Studies suggest that adherence to the ERAS protocol by more than 70% significantly reduces morbidity, symptoms, readmissions and improves 5-year survival after colorectal surgery in a dose-response-like fashion (Gustafsson et al., 2016, Gustafsson et al., 2011). In the recent update of the ERAS guidelines the authors strongly recommend treatment of preoperative anemia and, due to side effects and low efficiency of oral treatment, they advocate i.v. iron to all patients with iron deficiency anemia with a hemoglobin value of less than 130 g/l. Karolinska University hospital has already implemented these guidelines.

In the literature, we also found a consensus/current opinion report by expert anaesthesiologists and surgeons, in which they recommend treating iron deficiency anemia below 130 g/l to avoid the risk of perioperative blood cell transfusion (Muñoz et al., 2017). The authors recommend oral iron treatment if it is tolerated by the patient and provided that there are more than six weeks until surgery. If surgery is within less than six weeks or if oral iron intake is not tolerated by the patients, they recommend i.v. iron substitution.

An alternative way of rapidly increasing hemoglobulin levels is red cell blood transfusion. Patient Blood Management is a strategy with the aim of optimising the transfusion of red blood cells that is amongst the

highest in the world in Sweden. Patient blood Management includes not only a restrictive transfusion strategy but also guidelines regarding preoperative treatment of iron deficiency anemia.
A recent article in the Swedish Medical Journal (Läkartidningen) actually recommends i.v. iron treatment for patients with a short time to surgery and to those at risk for gastrointestinal side effects when on oral treatment (Wikman et al., 2020).

6. Health Technology at issue: I.v. iron substitution in patients with anemia, planned for colorectal cancer surgery

As stated above, anemia due to occult bleeding occurs frequently in colorectal cancer and severe anaemia is an important risk factor in most types of surgery. Patients planned for colorectal surgery are therefore often eligible for iron substitution. Previously, this has been done by oral substitution and in some cases by preoperative blood transfusion. The haemoglobin level on which the therapeutic decision is based is not clearly defined. Recently, iron substitution regimens for i.v. use have been developed and marketed and their use has been advocated for preoperative substitution of patients planned for colorectal surgery. Oral iron substitution necessitates a longer treatment period before haemoglobin levels increase and hence i.v. infusion of iron, associated with a faster increase of haemoglobin levels and better tolerance by the patients, might be of value to treat the anaemia within the short time period of 2 weeks or less before surgery.

I.v. administration of iron is associated with increased cost and work for the staff. It is also associated with adverse events, such as pseudoanaphylactic reactions, that need to be handled by adequately trained medical staff. Albeit worrisome for the staff, these reactions are not life threatening but need to be handled.

The aim of this HTA report is to assess the evidence for i.v. preoperative iron substitution in patients planned for colorectal surgery. We deliberately chose not to include increase in the blood haemoglobin level as an outcome, since this is a surrogate variable with unclear clinical consequences in these patients. Instead, we aimed to assess clinically important and measurable outcomes.

The haemoglobin threshold for anaemia in the nomination was 115 g/l, i.e. a value somewhat lower than the normally advocated thresholds for the diagnosis anaemia (120 g/l for women and 130 g/l for men, see above). We found no studies based on this particular threshold level. To handle this issue, we chose not to exclude studies solely on the basis of haemoglobin threshold levels and in Appendix 4 we explicitly state the threshold used in each individual study.

7. Objective

Does preoperative iron infusion reduce mortality, risk for tumour recurrence, risk of perioperative complications, need for reoperation, or the need for blood transfusions, and does it improve health-related quality of life or reduce length of hospital stay, as compared with conventional treatment (placebo infusion, no treatment or oral iron substitution), in patients planned for operative treatment of colorectal cancer with a haemoglobin level below 115 g/l?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Patients, 16 years or older, planned for operation of colorectal cancer, with iron deficiency and blood haemoglobin level below 115 g/l*
I	Preoperative iron infusion i.v.
C	Preoperative oral iron substitution, no i.v. iron infusion, placebo infusion, preoperative blood transfusion.
O	Critical for decision making Mortality Tumour recurrence Important for decision making Complications to the iron infusion Transfusions (during and after operation) Surgical complications Reoperation Health-related quality of life measured with validated instruments Less important for decision making Length of hospital stay

Limitations

* No exclusions solely on the basis of hemoglobin cutoff level.

8. Method

Systematic literature search (Appendix 1)

During October 2020, two medical librarians (authors TS, KM) performed systematic searches in Medline, Embase, the Cochrane Library and a number of HTA-databases. Reference lists of relevant articles were scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the identified abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all authors. All authors read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

The included studies were critically appraised using a checklist for assessment of randomised controlled trials, modified from the SBU by HTA-centrum, and a checklist for assessment of cohort studies, also modified from SBU by HTA-centrum. The included systematic review was not assessed for quality and is hence only commented on. The results and the assessed quality of each article have been summarised per outcome in Appendix 4. Data were extracted by at least two authors per outcome. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 8). The certainty of evidence was defined according to the GRADE system (Atkins et al, 2004; GRADE Working group).

Ongoing research

A search in Clinicaltrials.gov (2021-01-07) using the search terms (iron OR ferric OR ferrous OR ferinject OR monofer) AND (preoperative OR presurgical OR presurgery OR (pre OR prior OR before) AND (surgery OR operation OR operative OR procedure) AND (colorectal OR colon OR rectal OR rectum) identified 77 trials.

9. Results

Search results and study selection (Appendix 1)

The literature search identified 1,917 articles after removal of duplicates. After reading the abstracts 1,844 articles were excluded. Another 47 articles were excluded by two authors after reading the articles in full text. The remaining 26 articles were sent to all authors, and nine articles, four RCTs, and five non-randomised controlled observational studies (below called cohort studies) were finally included in the assessment (Appendix 2). In addition, one systematic review (SR) was commented on. Excluded articles, with reasons for exclusion, are listed in Appendix 3.

Included studies

This HTA report is based on four RCTs and five cohort studies. In addition, we identified one SR that was partially relevant to our topic. It did not add any new information and was not tabulated or assessed for quality and is only briefly commented on in the discussion.

All four RCTs were performed in the UK and three of them (Keeler et al., 2017, Keeler et al., 2019, Dickson et al., 2020) were based on the same patient cohort (n=116, recruited 2012-2014 and with varying follow-up times depending on outcomes). The reference treatment (C) in this patient cohort was oral iron substitution. The fourth RCT (Edwards 2009, n=60) focused on immediate postoperative care, within a time window of only 7 days (Edwards et al., 2009). The comparator was in this study placebo injection. The quality of the individual studies is tabulated in Appendix 4, under the respective outcome. Examples of problems with the three follow-up studies on the same patient group were lack of blinding and serious problems with precision.

Amongst the five cohort studies, three (Wilson et al., 2018a and 2018b and Laso-Morales et al., 2017) were retrospective cohort studies and two (Calleja et al., 2016 and Kam 2020) were prospective cohort studies with historical controls. The total number of studied patients was 1,306. In all studies the control treatment was 'no i.v. iron'. The quality of the individual studies is tabulated in Appendix 4, under the respective outcome. Frequently occurring problems were retrospective design, the use of historical controls, and lack of clarity regarding the control group.

Results per outcome

Preoperative i.v. iron substitution compared with either preoperative oral iron substitution, no treatment, or preoperative blood transfusion.

Outcomes, critical for decision-making

Mortality (Appendix 4:1)

Mortality was reported in one RCT comparing preoperative i.v. iron substitution with preoperative oral iron substitution (Dickson *et al*., 2020), and in one cohort study comparing preoperative i.v. iron substitution with no preoperative iron treatment (Wilson *et al*., 2018b). The certainty of evidence was hampered by very serious imprecision and non-blinding

The RCT reported no significant difference in overall survival at 5 years, with HR for OS 0.82 (direction favouring oral iron; 95% CI: 0.44 to 1.54, p= 0.522), between the groups with preoperative i.v. iron substitution and with preoperative oral iron substitution (Dickson *et al*., 2020).

The cohort study reported overall survival at three and five years of 73.1% and 64.3% (based on 10 patients) respectively in the cohort of individuals that received i.v. iron. Control data are not stated but can be estimated from Figure 1 in Wilson *et al*. (2018b). The authors reported no significant difference compared to the control group (p =0.456).

Conclusion: For the comparison i.v. versus oral treatment, there may be little or no difference in long-term overall survival. However, the 95% CI was wide, not excluding important clinical differences. Low certainty of evidence (GRADE ⊕⊕◯◯). For the comparison i.v. iron versus no i.v. iron, it is uncertain whether there is any difference (very low certainty of evidence, GRADE ⊕◯◯◯).

Tumour recurrence (Appendix 4:2)

Tumour recurrence was measured as time to recurrence or as Disease-free survival (DFS). There were two studies, one RCT and one cohort study, the same ones as those reported under the heading Mortality. (Dickson et al., 2020 and Wilson et al., 2018b). In the RCT the control group received oral iron and in the cohort study no i.v. iron. The certainty of evidence in both studies was down-graded due to very serious imprecision and some study limitations (open design with unclear presentation of data and a to some extent subjective outcome).

The RCT reported no significant difference in disease-free survival at five years, with HR: 1.08 (95% CI: 0.61 to 1.92), p= 0.79, between the groups with preoperative i.v. iron substitution and with preoperative oral iron substitution (Dickson et al., 2020).

The cohort study (Wilson et al., 2018b) reported disease-free survival (propensity scores to correct for baseline asymmetry). Without showing any actual numbers (figure only), the authors present DFS data of 87% and 83% after 3 and 5 years in the i.v. cohort and state that this was not significantly different from the control group, p=0.240.

They also report data regarding time to recurrence: with i.v. iron treatment 13.8 months (IQR 10.3-28.1) as compared to 13.3 months (IQR 8.0-19.8) in the control group, p= 0.275.

Conclusion: Based on the RCT, preoperative i.v. iron substitution compared with.preoperative oral iron substitution may result in little or no difference in tumour recurrence in anemic patients planned for surgery due to colorectal cancer. However, the 95% CI was wide, not excluding important clinical differences. Low certainty of evidence (GRADE ⊕⊕◯◯).

Outcomes, important for decision-making

Complications to the iron infusion (Appendix 4:3)

Complications related to the iron infusion were only reported in two RCTs (Edwards et al., 2009, Keeler et al., 2017). Since the reference treatment was not relevant for this outcome, this can be regarded as a short case series and was therefore not graded.

Three cases of post infusion headache, one case of rash and two cases of symptomatic hypotension were reported in the group with preoperative i.v. iron substitution. The outcome was not reported for the oral iron substitution group.

Need for transfusion measured as administered transfusions (Appendix 4:4)

Need for transfusion was reported in three RCTs (two of which were based on the same patients) and four cohort studies. In one of the RCTs (Dickson et al., 2020), data were only reported for "responders" vs "non-responders", generating serious problems regarding generalisability. In the remaining two RCTs, one (Edwards et al., 2009) had placebo infusion as control and one (Keeler et al., 2017) no treatment. Amongst the four cohort studies, two were conducted in Spain (Calleja et al., 2016; Laso-Morales et al., 2017), one in Hongkong (Kam et al., 2020), and one in the Netherlands (Wilson et al., 2018a). The control was in all cases "no i.v. iron". The certainty of evidence was downgraded due to some study limitations, serious inconsistency, and serious imprecision.

The RCTs reported no significant differences in need for transfusion between preoperative i.v. iron substitution (2/34, p=0.335), compared with placebo (5/26) (Edwards et al., 2009), and between preoperative i.v. iron substitution (10/55, p=0.470), compared with preoperative oral iron substitution (14/61) (Keeler et al., 2017).

Amongst the cohort studies, Calleja et al. (2016) and Kam et al. (2020), reported significant reductions in need for transfusion between preoperative i.v. iron substitution, with 9.9% (n=111, p<0.001), and 21% (n=38, p=0.006), respectively, and without preoperative iron substitution, with 38.7%(n=155), and 48% (n=62), respectively. Laso-Morales et al. (2017) did not find any significant differences in need for transfusion between preoperative i.v. iron substitution, with a mean of 0.3 (SD±0.8) units, compared with no preoperative iron substitution, with a mean of 0.4 (SD± 1.2) units. Wilson et al. (2018a) observed no significant difference in the need for postoperative transfusion, compared with no preoperative iron substitution, with OR 0.54 (95% CI: 0.24 to 1.21, p=0.14) in a multivariable analysis, but in a univariable analysis a significant difference was found, with OR 0.47 (95% CI: 0.23 to 0.99, p=0.04).

Conclusion: It is uncertain whether the need for transfusion is affected by preoperative i.v. iron substitution in patients with operative treatment of colorectal cancer compared with no preoperative i.v. iron or preoperative oral iron substitution.
Very low certainty of evidence (GRADE ⊕◯◯◯).

Peri- and postoperative complications (Appendix 4:5)

Peri- and postoperative complications were reported in two RCTs (Keeler et al., 2017 and 2019) and three cohort studies (Calleja et al., 2016; Keeler et al., 2017; Laso-Morales et al., 2017; Wilson et al., 2018a). The certainty of evidence was downgraded due to serious study limitations and very serious imprecision.

One RCT (based on the same underlying patient cohort) reported no significant difference in complication severity (p=0.995) or complication rate (p=0.305), between the groups with preoperative i.v. iron substitution and with preoperative oral iron substitution.

In the other RCT (same patient group) 28% 7-day infectious complications were reported in the i.v. group and 16% in the oral iron group (p=0.112). The corresponding figures at day 28 were 40% vs 25% (p=0.091).

One cohort study reported no significant difference in complication rates, with 20% (n=111) in total, and 6.7% surgical complications, in the i.v. iron substitution group, compared with 16% (n=155) in total and 6.7% surgical complications in the group with no preoperative iron substitution (Calleja et al., 2016). Another cohort study reported a significantly lower rate of infection related complications in the group with preoperative i.v. iron substitution 42/232 (18%) compared with the group no preoperative iron substitution 26/90 (29%), p=0.018, (Laso-Morales et al., 2017). The cohort study by Wilson et al. (2018a) reported complications to preoperative i.v. iron substitution, with OR: 0.91 (95% CI: 0.50 to1.68), p=0.77, compared with no preoperative iron substitution.

Conclusion: It is uncertain whether the risk for complications is affected by preoperative i.v. iron substitution in patients with operative treatment of colorectal cancer compared with no preoperative i.v. iron or preoperative oral iron substitution.
Very low certainty of evidence (GRADE ⊕◯◯◯).

Need for reoperation

No study reported this outcome.

Health-related quality of life (HRQoL) (Appendix 4:6)

Data on health-related quality of life was reported in one RCT based on 55+66 patients, using oral iron treatment as control (Keeler et al., 2019). The certainty of evidence was downgraded due to serious study limitations (open study, multiple measurements, selective reporting) and serious imprecision.

Three sets of questionnaires were used but lack of detail made the amplitude of the effects very difficult to evaluate. There were small but significant improvements in the HRQoL aspects ‘Functional assessment of cancer therapy-anemia subscale’ and ‘anemia trial outcome’ indexes.

Regarding Functional Assessment of Cancer Therapy – Anaemia questionnaires (FACT-AN), significant differences were observed, in favour for preoperative i.v. iron substitution, regarding e.g.: ‘Anaemia subscale’ with median 71 (IQR: 66–77), p=0.002, vs. median 66 (IQR: 55–72); ‘Anaemia trial outcome index’, with median 121 (IQR: 113–124), p=0.003, vs. median 108 (IQR: 90–123); and ‘Anaemia total score’, with median 168 (IQR: 160–174), p=0.005, vs. median 151 (IQR: 132–170).

Amongst SF36 components, significant differences were observed in favour for preoperative i.v. iron substitution regarding: ‘Role limitation due to pain’, median 100 (IQR: 50–100, p=0.01), vs. median 25 (IQR: 0–100); ‘General health’, median 77 (IQR: 65–86, p=0.002), vs. median 62 (IQR: 50–77); ‘Vitality’, mean 72 (SD 16, p<0.01), vs. mean 59 (SD 19); ‘Social functioning’, median 100 (IQR: 88–100, p=0.03) vs. median 75 (IQR: 50–100); ‘Role limitation due to emotion’, mean 80 (SD 37, p=0.03), vs. mean 74 (SD 43); ‘Mental health’, median 92 (IQR: 88–92, p<0.01, vs. median 84 (IQR: 72–92); and ‘Mental component summary’, mean 57 (SD 6, p=0.001), vs. mean 51 (SD 10) (Keeler *et al*., 2017).

The authors transformed the original data by dividing incremental values with the standard deviation of basal values, generating three effect levels (ratio 0.2, 0.5 and 0.8 for small, moderate, and large effect, respectively). The effect sizes were generally small to moderate.

Conclusion: It is uncertain whether preoperative i.v. iron substitution affects health-related quality of life in anemic patients scheduled for operative treatment of colorectal cancer compared with preoperative oral iron substitution.
Very low certainty of evidence (GRADE ⊕◯◯◯).

Other outcomes

Length of hospital stay (Appendix 4:7)
Length of hospital stay was reported in one RCT (Edwards et al., 2009) and in one cohort study (Laso-Morales et al., 2017). The certainty of evidence was downgraded due to some study limitations and very serious imprecision.

In the RCT the length of hospital stay was not significantly different in the group receiving preoperative i.v. iron substitution, with median 10 days (p=0.273), compared with median eight days in the placebo group.

Likewise, in the cohort study, there was no significant difference in the length of hospital stay, between the groups with or without preoperative i.v. iron substitution, with mean nine (SD 6) days (p=0.889), and nine (SD 5) days, respectively (Laso-Morales et al., 2017).

Conclusion: It is uncertain whether the length of hospital stay is affected by preoperative i.v. iron substitution in patients with operative treatment of colorectal cancer compared with no preoperative i.v. iron substitution.
Very low certainty of evidence (GRADE ⊕◯◯◯).

10. Ethical consequences

Although no significant differences were found for the most important outcomes, mortality and tumour recurrence, when comparing i.v. and oral iron substitution, the 95% CI were wide, thus not excluding important clinical differences. When robust evidence is lacking more research is needed before decisions regarding broad introduction into routine health care can be made.

11. Organisation

Time frame for the putative introduction of the new health technology

The treatment to manage preoperative anaemia by iron-infusion is already established in several hospitals in VGR and can also be started at the Sahlgrenska University hospital within weeks after a decision. The staff is trained and the treatment is already offered and administered to other patient categories. It will however withdraw budget and nurse resources from other patient needs.

Present use of the technology in other hospitals in Region Västra Götaland

Despite considerable efforts, it has not been possible to establish how often i.v. iron is currently used for substitution in preoperative colonic cancer patients in the VGR. At Sahlgrenska University Hospital that handles a substantial portion of colonic cancer and in particular rectal cancers, this mode of treatment is not used routinely.

Consequences of the new health technology for personnel

The i.v.i.v. iron will be administered at the day care-outpatient clinic. It will require an extra 40 minute visit to the nurses that will administer the iron to watch for adverse events like extremely rare anaphylaxis-like reactions. The handling of these issues will also require additional education of new nurses.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

One indication for treating anemia in cancer patients is to improve the condition for the patient during the postoperative period. This particular aspect was studied in some of the identified articles but except for an article measuring health-related quality of life with validated scales, no obvious beneficial effects were seen. Moderate postoperative symptoms are usually managed in primary care.

12. Economic aspects

Present costs of currently used technologies

In year 2020, there were 733 patients operated for colorectal cancer in VGR. 100 iron tablets (amount needed for oral substitution) costs approximately 150 SEK. Assuming that 2/3 patients need iron substitution, the direct cost is 73,300 SEK/year.

Expected costs of the new health technology

The substance cost for i.v. iron administration varies between manufacturers from approx. 815 to 2,000 SEK/patient, which would give yearly costs between 400,000 and 980,000 SEK.

In addition, each patient will need approximately 40 minutes of day-care clinic service with an estimated cost of 2,000 SEK/hour, i.e., 1,333 SEK. This would give yearly costs of about 650,000 SEK.

The total cost of the new health technology would thus be between approximately 1,050,000 and 1,630,000 SEK/year.

Total change in costs

The net increase in cost per year in VGR will be between approximately 1 to 1.5 million SEK.

Possibility to adopt and use the new technology within the present budget

Implementation of the new technology within the present budget would require additional funding to the healthcare sector or it will imply that other healthcare services are displaced.

Available economic evaluations or cost advantages/disadvantages

None identified.

13. Discussion

Summary of main results: No robust evidence for a clinical benefit was found for any of the clinical outcomes, when comparing i.v.. iron infusion with oral iron . Although no differences were found, the confidence intervals were wide, thus not excluding clinically relevant effects.

Overall completeness and applicability of evidence

The quality of the underlying literature was poor, with major problems related to use of historical controls and imprecision due to too few patients in the randomised studies, making data where no significant differences were found difficult to interpret. There was also the issue of repeated use of the same patient cohort in different RCTs and with lack of appropriate blinding (the patient will know if they get oral or i.v. treatment). Moreover, the control situation differed between the RCTs (oral iron treatment) and the cohort studies (no i.v. iron treatment).

Based on low certainty of evidence, there may be little or no difference in overall long-term mortality, and tumour recurrence by preoperative i.v. iron substitution in patients with surgical treatment of colorectal cancer compared to oral iron (GRADE in both cases ⊕⊕◯◯). However, the 95% CIs was wide, suggesting that important clinical differences cannot be excluded.

Based on very low certainty of evidence, it is uncertain whether need for transfusion, postoperative complications, health-related quality of life during convalescence, or length of hospital stay are affected by preoperative i.v. iron substitution in patients with operative treatment of colorectal cancer (GRADE ⊕◯◯◯).

Agreements and disagreements with other studies and reviews

We identified only one systematic review addressing this topic (Borstlap et al., 2015). However, the topic of this review was the value of iron substitution in general, thus it was not designed to compare i.v. and oral iron substitution. The search strategy identified RCTs only and the search was conducted as early as October 2014, i.e. before i.v. iron substitution had been broadly introduced. It therefore did not add any relevant information.

Agreement and disagreements with recommendations

According to present routines at the colorectal cancer unit at Sahlgrenska University Hospital where a large number of colorectal cancer patients are being operated, iron-deficiency anemia is rarely treated before surgery, a strategy that stands in contrast to the ERAS guidelines (see Background). There is currently no formal recommendation regarding this issue in the VGR but all hospitals except Sahlgrenska University Hospital seem to routinely use i.v. iron substitution based on varying hemoglobin cutoff levels.

Implications for research

There is a strong need for more randomized controlled and prospective studies.

14. Future perspective

Scientific knowledge gaps

The scientific documentation of a clinical value of i.v. iron substitution in this patient group is weak and this needs to be rectified by additional well designed RCTs. The published studies include too few patients, and in the controlled cohort studies there are too many confounders to enable proper conclusions.

Ongoing research

A search in Clinicaltrials.gov (2021-01-07) using the search terms (iron OR ferric OR ferrous OR ferinject OR monofer) AND (preoperative OR presurgical OR presurgery OR (pre OR prior OR before) AND (surgery OR operation OR operative OR procedure)) AND (colorectal OR colon OR rectal OR rectum) identified 77 trials.

7 trials were regarded as relevant for the current topic (Appendix 5). Two of those have mortality as outcome, five have outcome transfusion rates, two have outcome HRQoL, two have outcome complications, one has outcome length of stay, and three have morbidity score as outcome . Five studies have passed expected completion date. None of these studies are published.

15. Participants in the project

The question was nominated by

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Declaration of interests

No conflict of interests has been declared by the participating professionals.

Project time

The HTA was accomplished during the period of 21st of September 2020 – 27th of October 2021.
Literature searches were made on 8th of October 2020.

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue:
Does preoperative iron infusion reduce mortality, risk for tumour recurrence, risk of perioperative complications, need for reoperation, or the need for blood transfusions, and does it improve health-related quality of life or reduce length of hospital stay, as compared with conventional treatment (placebo infusion, no treatment or oral iron substitution), in patients planned for operative treatment of colorectal cancer with a haemoglobin level below 115 g/l?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P	Patients, 16 years or older, planned for operation of colorectal cancer, with iron deficiency and blood hemoglobin level below 115 g/l*
I	Preoperative iron infusion i.v.
C	Preoperative oral iron substitution, no i.v. iron infusion, placebo infusion, preoperative blood transfusion.
O	<u>Critical for decision making:</u> Mortality Tumour recurrence <u>Important for decision making</u> Complications to the iron infusion Transfusions (during and after operation) Surgical complications Reoperation Health-related quality of life measured with validated instruments <u>Less important for decision making</u> Length of hospital stay * No exclusions solely on the basis of hemoglobin cutoff level

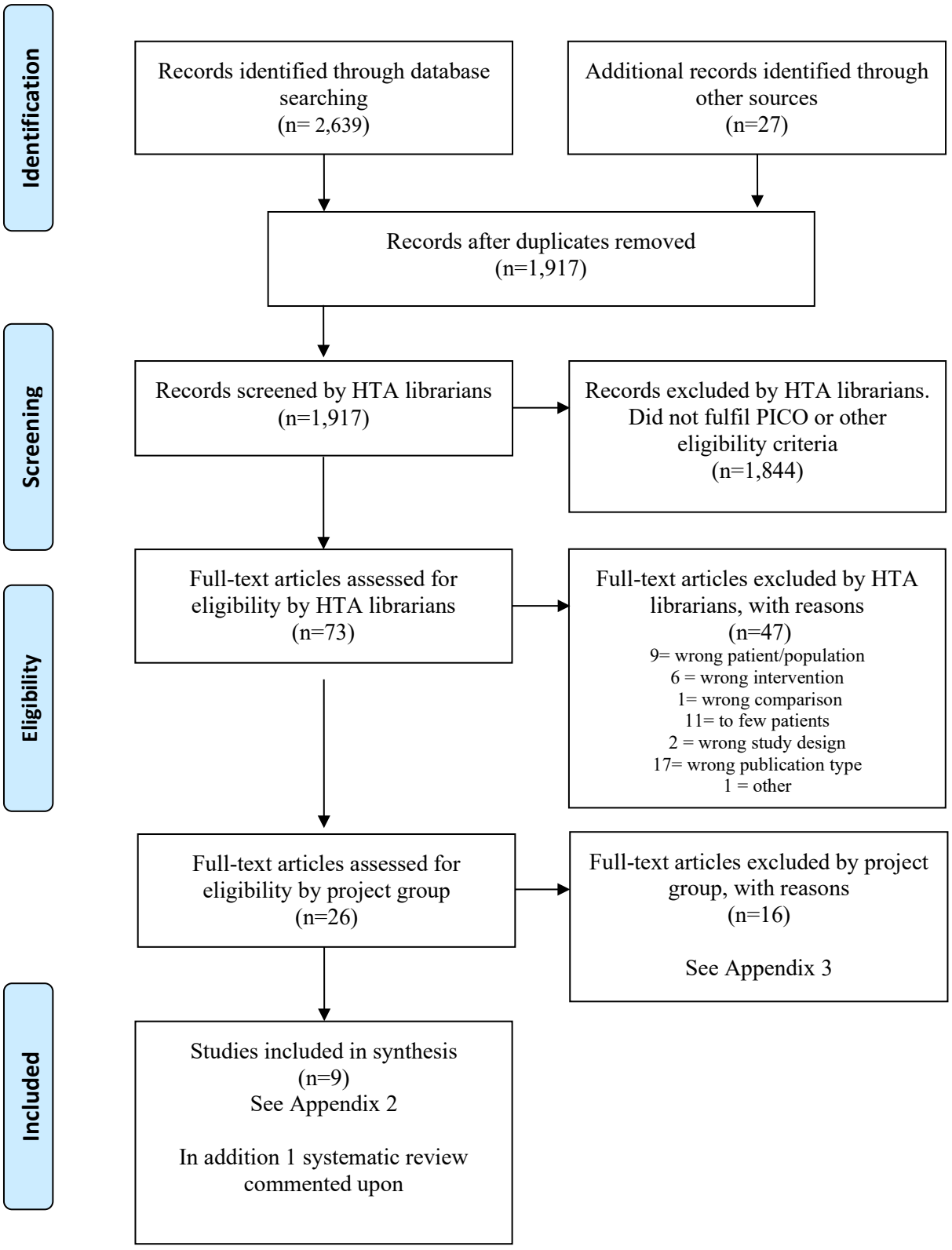
<u>Eligibility criteria</u>

Study design:
Systematic reviews from 2015
Randomised controlled trials
Non-randomised controlled observational studies, n>100
Case series regarding outcome complications, n>100

Language:
English, Swedish, Norwegian, Danish

Publication date: 2000-

Selection process – flow diagram



Modified from Moher et al., 2009

Search strategies

Database: Ovid MEDLINE(R) ALL 1946 to October 02, 2020 (Ovid)
Date: 8 Oct 2020
No. of results: 718

#	Searches	Results
1	exp Iron/	97074
2	exp Iron Compounds/	69818
3	(iron or ferric or ferrous or ferinject or monofer).ab,ti,kf.	210277
4	exp Hematinics/	62012
5	1 or 2 or 3 or 4	308838
6	(preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg* or ((pre or peri) adj (operat* or procedur* or surg*))).ti,ab,kf.	441289
7	((prior or before) adj3 (surg* or operat*)).ab,ti,kf.	115887
8	exp Preoperative Period/	7701
9	Preoperative Care/	62266
10	Perioperative Care/	14404
11	Perioperative Period/	3290
12	6 or 7 or 8 or 9 or 10 or 11	546676
13	exp Anemia/	161715
14	Iron/df [Deficiency]	5288
15	(anaemi* or anemi* or irondeficiency or iron-deficiency).ti,ab,kf.	166653
16	exp Blood Transfusion/	86119
17	transfusion.ti,ab,kf.	100316
18	13 or 14 or 15 or 16 or 17	359112
19	5 and 12 and 18	1050
20	limit 19 to yr="2000 -Current"	812
21	**limit 20 to (danish or english or norwegian or swedish)**	**718**

Database: Embase 1974 to 2020 October 07 (Ovid)
Date: 8 Oct 2020
No. of results: 1,745

#	Searches	Results
1	exp Iron/	159980
2	iron therapy/	8625
3	exp iron derivative/	4101
4	exp iron saccharate/	1427
5	exp iron isomaltose/	105
6	exp ferric carboxymaltose/	1331
7	exp antianemic agent/	123285
8	(iron or ferric or ferrous or ferinject or monofer).ab,kw,ti.	244843
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	400275
10	exp preoperative period/	325289
11	exp preoperative care/	39642
12	exp perioperative period/	51701
13	(preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg* or ((pre or peri) adj (operat* or procedur* or surg*))).ti,ab,kw.	617300

14	((prior or before) adj3 (surg* or operat*)).ab,ti,kw.	170943
15	10 or 11 or 12 or 13 or 14	882251
16	exp anemia/	360963
17	(anaemi* or anemi* or irondeficiency or iron-deficiency).ti,ab,kw.	220681
18	exp blood transfusion/	177400
19	transfusion.ti,ab,kw.	148385
20	16 or 17 or 18 or 19	589811
21	9 and 15 and 20	3446
22	limit 21 to yr="2000 -Current"	2947
23	limit 22 to (embase or medline)	1981
24	(animal not (animal and human)).sh.	1083685
25	23 not 24	1977
26	limit 25 to (article or article in press or conference paper or letter or note or "review")	1925
27	**limit 26 to (danish or english or norwegian or swedish)**	**1745**

Database: Cochrane Library (Wiley)
Date: 8 Oct 2020
No. of results: 176
Cochrane reviews: 4
Cochrane protocols: 0
Trials: 172
Editorials: 0
Special collections: 0
Clinical answers: 0
Other reviews: 0

ID	Search	Hits
#1	MeSH descriptor: [Iron] explode all trees	2544
#2	MeSH descriptor: [Iron Compounds] explode all trees	2391
#3	MeSH descriptor: [Hematinics] explode all trees	649
#4	(iron or ferric or ferrous or ferinject or monofer):ti,ab,kw (Word variations have been searched)	10592
#5	#1 OR #2 OR #3 OR #4	11855
#6	MeSH descriptor: [Preoperative Period] explode all trees	293
#7	MeSH descriptor: [Preoperative Care] this term only	4208
#8	MeSH descriptor: [Perioperative Care] this term only	989
#9	MeSH descriptor: [Perioperative Period] this term only	241
#10	((preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg* or ((pre or peri) next (operat* or procedur* or surg*)))):ti,ab,kw (Word variations have been searched)	59547
#11	(((prior or before) near/3 (surg* or operat*))):ti,ab,kw (Word variations have been searched)	23938
#12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	73364
#13	MeSH descriptor: [Anemia] explode all trees	5258
#14	((anaemi* or anemi* or irondeficiency or iron-deficiency)):ti,ab,kw (Word variations have been searched)	20739
#15	MeSH descriptor: [Blood Transfusion] explode all trees	3517
#16	(transfusion):ti,ab,kw (Word variations have been searched)	16425
#17	#13 OR #14 OR #15 OR #16	34725
#18	#5 AND #12 AND #17	337
#19	(clinicaltrials or trialsearch):so	333045
#20	**#18 NOT #19 with Cochrane Library publication date Between Jan 2000 and Dec 2020**	**176**

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
9 Oct 2020
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 27 new records.

Reference lists

Included studies:

Calleja JL, Delgado S, del Val A, Hervas A, Larraona JL, Teran A, et al. Ferric carboxymaltose reduces transfusions and hospital stay in patients with colon cancer and anemia. Int J Colorectal Dis. 2016;31(3):543-51. doi: https://dx.doi.org/10.1007/s00384-015-2461-x.

Dickson EA, Keeler BD, Ng O, Kumar A, Brookes MJ, Acheson AG, et al. Preoperative intravenous iron therapy and survival after colorectal cancer surgery: long-term results from the IVICA randomised controlled trial. Colorectal Dis. 2020;01:01. doi: https://dx.doi.org/10.1111/codi.15342.

Edwards TJ, Noble EJ, Durran A, Mellor N, Hosie KB. Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery. Br J Surg. 2009;96(10):1122-8. doi: https://dx.doi.org/10.1002/bjs.6688.

Kam PM, Chu CW, Chan EM, Liu OL, Kwok KH. Use of intravenous iron therapy in colorectal cancer patient with iron deficiency anemia: a propensity-score matched study. Int J Colorectal Dis. 2020;35(3):521-7. doi: https://dx.doi.org/10.1007/s00384-020-03508-y.

Keeler BD, Dickson EA, Simpson JA, Ng O, Padmanabhan H, Brookes MJ, et al. The impact of pre-operative intravenous iron on quality of life after colorectal cancer surgery: outcomes from the intravenous iron in colorectal cancer-associated anaemia (IVICA) trial. Anaesthesia. 2019;74(6):714-25. doi: https://dx.doi.org/10.1111/anae.14659.

Keeler BD, Simpson JA, Ng O, Padmanabhan H, Brookes MJ, Acheson AG, et al. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. Br J Surg. 2017;104(3):214-21. doi: https://dx.doi.org/10.1002/bjs.10328.

Laso-Morales M, Jerico C, Gomez-Ramirez S, Castellvi J, Viso L, Roig-Martinez I, et al. Preoperative management of colorectal cancer-induced iron deficiency anemia in clinical practice: data from a large observational cohort. Transfusion (Paris). 2017;57(12):3040-8. doi: https://dx.doi.org/10.1111/trf.14278.

Wilson MJ, Dekker JW, Bruns E, Borstlap W, Jeekel J, Zwaginga JJ, et al. Short-term effect of preoperative intravenous iron therapy in colorectal cancer patients with anemia: results of a cohort study. Transfusion (Paris). 2018a;58(3):795-803. doi: https://dx.doi.org/10.1111/trf.14456.

Wilson MJ, Dekker JWT, Buettner S, Harlaar JJ, Jeekel J, Schipperus M, et al. The effect of intravenous iron therapy on long-term survival in anaemic colorectal cancer patients: Results from a matched cohort study. Surg Oncol. 2018b;27(2):192-9. doi: https://dx.doi.org/10.1016/j.suronc.2018.03.005.

Systematic reviews, no appraisal done, only commented on:

Borstlap WA, Stellingwerf ME, Moolla Z, Musters GD, Buskens CJ, Tanis PJ, et al. Iron therapy for the treatment of preoperative anaemia in patients with colorectal carcinoma: a systematic review. Colorectal Dis. 2015;17(12):1044-54. doi: https://dx.doi.org/10.1111/codi.13110.

Excluded studies:

Alexander R, Alexander A, Surgenor S, J Williams E, F Nash G. Optimal iron replacement for colorectal cancer-induced anaemia. The Open Colorectal Cancer Journal. 2010;3(1). doi: https://doi.org/10.2174/1876820201003010027

Calvet X, Gene E, AngelRuiz M, Figuerola A, Villoria A, Cucala M, et al. Cost-minimization analysis favours intravenous ferric carboxymaltose over ferric sucrose or oral iron as preoperative treatment in patients with colon cancer and iron deficiency anaemia. Technol Health Care. 2016;24(1):111-20. doi: https://dx.doi.org/10.3233/THC-151074.

Drabinski T, Zacharowski K, Meybohm P, Ruger AM, Ramirez de Arellano A. Estimating the Epidemiological and Economic Impact of Implementing Preoperative Anaemia Measures in the German Healthcare System: The Health Economic Footprint of Patient Blood Management. Adv Ther. 2020;37(8):3515-36. doi: https://dx.doi.org/10.1007/s12325-020-01372-4.

Froessler B, Palm P, Weber I, Hodyl NA, Singh R, Murphy EM. The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery: A Randomized Controlled Trial. Ann Surg. 2016;264(1):41-6. doi: https://dx.doi.org/10.1097/SLA.0000000000001646.

Froessler B, Rueger AM, Connolly MP. Assessing the costs and benefits of perioperative iron deficiency anemia management with ferric carboxymaltose in Germany. Risk Manag Healthc Policy. 2018;11:77-82. doi: https://dx.doi.org/10.2147/RMHP.S157379.

Janssen TL, Steyerberg EW, van Gammeren AJ, Ho GH, Gobardhan PD, van der Laan L. Intravenous Iron in a Prehabilitation Program for Older Surgical Patients: Prospective Cohort Study. J Surg Res. 2020;257:32-41. doi: https://dx.doi.org/10.1016/j.jss.2020.07.059.

Jin L, Kapadia TY, Von Gehr A, Rosas E, Bird JB, Ramaswamy D, et al. Feasibility of a Preoperative Anemia Protocol in a Large Integrated Health Care System. Perm J. 2019;23. doi: https://dx.doi.org/10.7812/TPP/17-200.

Koo CH, Shin HJ, Cho H, Ryu JH. The Effect of Perioperative Intravenous Iron on Hemoglobin in Surgical Patients: A Meta-Analysis. J Surg Res. 2020;246:42-51. doi: https://dx.doi.org/10.1016/j.jss.2019.08.023.

Loughnane F, Muduma G, Pollock RF. Development of a Resource Impact Model for Clinics Treating Pre-Operative Iron Deficiency Anemia in Ireland. Adv Ther. 2020;37(3):1218-32. doi: https://dx.doi.org/10.1007/s12325-020-01241-0.

Meybohm P, Goehring MH, Choorapoikayil S, Fischer D, Rey J, Herrmann E, et al. Feasibility and efficiency of a preoperative anaemia walk-in clinic: secondary data from a prospective observational trial. Br J Anaesth. 2017;118(4):625-6. doi: http://dx.doi.org/10.1093/bja/aex024.

Ng O, Keeler BD, Mishra A, Simpson JA, Neal K, Al-Hassi HO, et al. Iron therapy for preoperative anaemia. Cochrane Database of Systematic Reviews. 2019;12:CD011588. doi: https://dx.doi.org/10.1002/14651858.CD011588.pub3.

Richards T, Baikady RR, Clevenger B, Butcher A, Abeysiri S, Chau M, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. Lancet. 2020;04:04. doi: https://dx.doi.org/10.1016/S0140-6736(20)31539-7.

Tang GH, Dhir V, Scheer AS, Tricco AC, Sholzberg M, Brezden-Masley C. Intravenous iron versus oral iron or observation for gastrointestinal malignancies: a systematic review. Eur J Gastroenterol Hepatol. 2019;31(7):799-808. doi: https://dx.doi.org/10.1097/MEG.0000000000001433.

Trentino KM, Mace HS, Symons K, Sanfilippo FM, Leahy MF, Farmer SL, et al. Screening and treating pre-operative anaemia and suboptimal iron stores in elective colorectal surgery: a cost effectiveness analysis. Anaesthesia. 2020;27:27. doi: https://dx.doi.org/10.1111/anae.15240.

Triphaus C, Judd L, Glaser P, Goehring MH, Schmitt E, Westphal S, et al. Effectiveness of Preoperative Iron Supplementation in Major Surgical Patients with Iron Deficiency: A Prospective Observational Study. Ann Surg. 2019;25:25. doi: https://dx.doi.org/10.1097/SLA.0000000000003643.

Wittkamp C, Traeger L, Ellermann I, Eveslage M, Steinbicker AU. Hepcidin as a potential predictor for preoperative anemia treatment with intravenous iron-A retrospective pilot study. PLoS ONE [Electronic Resource]. 2018;13(8):e0201153. doi: https://dx.doi.org/10.1371/journal.pone.0201153.

Other references:

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490-4. doi: https://dx.doi.org/10.1136/bmj.328.7454.1490.

Busch OR, Marquet RL, Hop WC, Jeekel J. Colorectal cancer recurrence and perioperative blood transfusions: a critical reappraisal. Semin Surg Oncol. 1994;10(3):195-9. doi: https://dx.doi.org/10.1002/ssu.2980100307.

[Checklist from SBU regarding cohort studies. (Modified) Version 2014]. [Internet]. [cited 2020 Nov 24] Available from: https://alfresco.vgregion.se/alfresco/service/vgr/storage/node/content/workspace/SpacesStore/ede81730-12c9-4917-bac9-3a0abb1268c1/Granskningsmall%20kohortstudier%20med%20kontrollgrupp.pdf?a=false&guest=true

[Checklist from SBU regarding randomized controlled trials]. (Modified) Version 2014]. [Internet]. [cited 2020 Nov 24] Available from: https://alfresco.vgregion.se/alfresco/service/vgr/storage/node/content/workspace/SpacesStore/122d27a7-a872-4932-8bac-378d1c3ecd34/Granskningsmall%20randomiserad%20kontrollerad%20pr%c3%b6vning%20RCT.pdf?a=false&guest=true

Edna TH, Karlsen V, Jullumstrø E, Lydersen S. Prevalence of anaemia at diagnosis of colorectal cancer: assessment of associated risk factors. Hepatogastroenterology. 2012;59(115):713-6. doi: https://dx.doi.org/10.5754/hge11479.

GRADE Working Group. [Internet]. [Place unknown]: GRADE Working Group, c2004-2020 [cited 2021 Feb 10]. Available from: http://www.gradeworkinggroup.org

Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch Surg. 2011;146(5):571-7. doi: https://dx.doi.org/10.1001/archsurg.2010.309.

Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O. Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. World J Surg. 2016;40(7):1741-7. doi: https://dx.doi.org/10.1007/s00268-016-3460-y.

Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS(®)) Society Recommendations: 2018. World J Surg. 2019;43(3):659-95. doi: https://dx.doi.org/10.1007/s00268-018-4844-y.

Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248(2):189-98. doi: https://dx.doi.org/10.1097/SLA.0b013e31817f2c1a.

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. doi: https://dx.doi.org/10.1371/journal.pmed.1000097.

Muñoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia. 2017;72(2):233-47. doi: https://dx.doi.org/10.1111/anae.13773.

Mörner ME, Edgren G, Martling A, Gunnarsson U, Egenvall M. Preoperative anaemia and perioperative red blood cell transfusion as prognostic factors for recurrence and mortality in colorectal cancer-a Swedish cohort study. Int J Colorectal Dis. 2017;32(2):223-32. doi: https://dx.doi.org/10.1007/s00384-016-2678-3.

Sadahiro S, Suzuki T, Tokunaga N, Mukai M, Tajima T, Makuuchi H, et al. Anemia in patients with colorectal cancer. J Gastroenterol. 1998;33(4):488-94. doi: https://dx.doi.org/10.1007/s005350050120.

Schneider C, Bodmer M, Jick SS, Meier CR. Colorectal cancer and markers of anemia. Eur J Cancer Prev. 2018;27(6):530-8. doi: https://dx.doi.org/10.1097/cej.0000000000000397.

Wikman A, Egenvall M, Jansson K, Jeppsson A, Lindgren S, Nilsson M, et al. Transfusionsstrategi – att ge blod på rätt indikation. Läkartidningen. 2020;5-6.

Wilson MJ, van Haaren M, Harlaar JJ, Park HC, Bonjer HJ, Jeekel J, et al. Long-term prognostic value of preoperative anemia in patients with colorectal cancer: A systematic review and meta-analysis. Surg Oncol. 2017;26(1):96-104. doi: https://dx.doi.org/10.1016/j.suronc.2017.01.005.

Project: HTA – Iron infusion
Appendix 2 – Characteristics of included studies

Author Year Country	Study Desig	Study Duration Upper Hb-limit	Study Groups; Intervention vs control (Initial actual Hb)	Patients (n)	Mean Age (years)	Men (%)	Outcome variables (relevant for PICO)
Dickson, 2020, UK	RCT	5-years < 110g/l for women, < 120g/l for men	I = Intravenous iron (mean Hb 102 g/l, 95% CI 4g/l) C = Oral iron (mean Hb 104g/l, CI 3 g/l) n.s.	I = 54 C = 56	I = 74.1 C = 75.2	I = 35 (65) C = 34 (61)	Mortality (survival) Cancer recurrence Need for transfusion Perioperative complications
Edwards, 2009, UK	RCT	7 days Anaemic subgroup: <125g/l in women, <135 g/l in males;	I = Intravenous iron (mean Hb 118; CI 2g/l) C = Placebo (mean Hb 124; CI 2 g/l) n.s.	I = 9 C = 9	Not stated	Not stated	Need for transfusion
Keeler, 2017, UK	RCT	2-3 months < 110g/l for women, < 120g/l for men	I = Intravenous iron (mean Hb 102 g/l, 95% CI 4g/l) C = Oral iron (mean Hb 104g/l, CI 3 g/l) n.s.	I = 55 C = 61	I = 73.9 C = 74.7	I = 35 (64) C = 37 (61)	Complications of drug Need for transfusion Perioperative complications
Keeler, 2019, UK	RCT	2-3 months < 110g/l for women, < 120g/l for men	For entire group: I= Intravenous iron: (Mean Hb 96; SD 13 g/l) C = Oral iron (Mean Hb 99; SD 11 g/l) n.s.	I=55 C=61 OPD data: I = 42 C = 50	For entire group: I = 73.8 (SD 8.9) C = 76.5 (SD 10.9)	For entire group: I = 35/55 C = 37/61	HRQoL after 2-3 months

Project: HTA – Iron infusion
Appendix 2 – Characteristics of included studies

Calleja, 2016, Spain	Cohort	30-days follow-up < 120g/l for women, < 130g/l for men	I = Intravenous iron (mean Hb 96 ;SD 14 g/l) C = No intravenous iron (mean Hb 100; SD 12 g/l) p<0.005	I = 111 C = 155	I = 72.9 C = 70.8	I = (57.3) C = (55.8)	Need for transfusions Perioperative complications
Kam, 2020, Hong Kong	Cohort	≥ 2 weeks M+F: 100 g/l before transfusion M+F: 120 g/l after transfusion	I = Intravenous iron (preop mean Hb 84;SD12 g/l) C = No intravenous iron (preop mean Hb 88; SD 11 g/l) p=0.117	I = 38 C = 62	I = 70.5 C = 69	I = 19 (50) C = 31 (50)	Complications of drug Need for transfusion
Laso-Morales, 2017, Spain	Cohort	30-days follow-up M+F: 130g/l	I = Intravenous iron (mean Hb 108; SD 15 g/d) C = No intravenous iron (mean Hb 120; SD 9 g/l) p=0.001	I = 232 C = 90	I = 71 C = 69	I = 135 (58) C = 45 (50)	Need for transfusion Length of hospital stay Perioperative complications (postoperative infection)
Wilson, 2018a, Netherlands	Cohort	30-days follow-up Females: 120 g/l; Males: 129g/l	I = Intravenous iron (mean Hb 63; SD 8 g/l) C = No intravenous iron (mean Hb 69; SD 7 g/l)	Total: I = 52 C = 153	I = 71.3 C = 74.3 p=0.09	% Males: I = 23/52 (44%) C = 93/153 (61%) p=0.04	Need for transfusion Perioperative complications

Wilson, 2018b, Netherlands	Cohort	5 years Females: 120 g/l; Males: 129g/l	I = Intravenous iron (mean Hb 60; range 55-70 g/l)) C = No intravenous iron (mean Hb 67, range 61-73 g/l) p<0.001	I = 102 C = 218	I = 75.0 C = 73.5	I = 54 (53) C = 120 (55)	Mortality (survival)

HRQOL=Health-Related Quality of Life

Project: HTA – Iron infusion
Appendix 3: Excluded articles

Author, year	Reason for exclusion
Alexander, 2010	Too few patients
Jin, 2019	Anemia handling protocol only, no data regarding colorectal surgery
Janssen, 2020	Type of operation not stated, data for CRC not stated.
Triphaus, 2019	Type of surgery not stated
Tang, 2019	Mixed surgery population
Ng, 2019	Mixed surgery population
Koo, 2020	Mixed surgery population
Richards, 2020	Mixed abdominal surgery, only 14% colorectal
Meybohm, 2017	Type of surgery not stated
Wittkamp, 2018	Type of surgery not stated
Trentino, 2020	Wrong outcome (cost)
Loughnane, 2020	Wrong outcome (cost)
Froesler, 2018	Mixed patient population, wrong outcome (cost)
Froesler, 2016	Type of surgery not stated (major abdominal)
Drabinski, 2020	Mixed patient population, unclear intervention, wrong outcome (cost)
Calvet, 2016	Wrong outcome (cost)

Project: HTA – Iron infusion
Appendix 4.1
Outcome variable: mortality/overall survival

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Hb inclusion level	Number of patients Actual Hb level	Withdrawals dropouts	Results		Comments	Directness *	Study limitations	Precision *
				Intervention	Control				
Dickson 2020 United Kingdom 7 centres	Follow-up of previous RCT (Keeler 2017) M: < 120 g/l F: < 110 g/l	110 (56 oral iron, 54 i.v. iron) I: Mean Hb 102 g/l, 95% CI +/- 4 g/l C: Mean Hb 104 g/l 95%CI +/-3 g/l	6 lost to follow up	Ferric carboxymaltose i.v. Dose according to anemia. > 2 weeks until surgery OS 3 years: 78% (64-86) OS 5 years: 63% (48-75) HR for OS at 5 years: 0.82 (95% CI 0.44-1.54), p= 0.522 (direction favours oral iron)	Ferrous sulphate orally 200mg twice daily > 2 weeks until surgery OS 3 years: 82% (69-91) OS 5 years: 71% (57-82)	Follow-up time 3 + 5 years.	+	?	-
Wilson 2018b Netherlands	Retrospective cohort M: 129 g/l F: 120 g/l	320 (218 no i.v. iron, 102 i.v. iron) Propensity score matching in 83+83 patients I: mean Hb 60; range 55-70 g/l C: mean Hb 67, range 61-73 g/l p<0.001	Not applicable	Carboxymaltose (Ferinject) or isomaltoside (monofer) 1000-2000 mg Mean OS (propensity score): 58 months p-value not stated 5 year OS (propensity score): 64.3% p=0.456	No iron treatment Mean OS (propensity score): not stated 5 year OS (propensity score) : not stated. Estimated from figure 70%	Outcome 5 year OS Propensity score matching to correct for baseline asymmetry *Very low initial Hb-level	?*	-	-

Project: HTA – Iron infusion
Appendix 4.2
Outcome variable: tumour recurrence/time to recurrence/DFS

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients Actual Hb level	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Dickson 2020 United Kingdom 7 centres	Follow-up of previous RCT (Keeler 2017) M: < 120 g/l F: < 110 g/l	110 (56 oral iron, 54 i.v. iron) I: 102 g/l, 95% CI 4g/l) C: 104g/l mean Hb 104g/l, CI 3 g/l	6 lost to follow up	Ferric carboxymaltose i.v. Dose according to anemia. > 2 weeks until surgery 2 regional and 15 distant 3 year DFS: 68%47-73) (95% CI: 54-80) 5-year DFS 60% (95% CI: 47–73) log rank p = 0.804 HR for DFS at 5 years: 1.08 (95% CI: 0.61-1.92), p= 0.79 HR for time to recurrence 0.99 (95% CI: 0.52-1.88) p = 0.962	Ferrous sulphate orally 200mg twice daily > 2 weeks until surgery 6 regional and 9 distant 3 year DFS: 66% (95% CI: 52-78%) 5-year DFS: 55% (95% CI: 41–69),	Follow-up time 3 + 5 years.	+	-	-

Project: HTA – Iron infusion
Appendix 4.2
Outcome variable: tumour recurrence/time to recurrence/DFS

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients Actual Hb level	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Wilson 2018b Netherlands	Retrospective cohort M: 129 g/l F: 120 g/l	320 (0 oral iron, 102 i.v. iron) Propensity score matching in 83+83 patients I: mean Hb 60; range 55-70 g/l)) C: mean Hb 67, range 61-73 g/l) p<0.001	Not applicable	Carboxymaltose (Ferinject) or isomaltoside (monofer) 1000-2000 mg Time to recurrence I: median 13.8 months, IQR 10.3-28.1 p=0.275 DFS I: mean DFS 58 months 5 year DFS (propensity score): I: 83.4% p=0.240	No iron treatment Time to recurrence C: median 13.3 months, IQR 8.0-19.8 5 year DFS (propensity score) : 5 year DFS (propensity score): C: not stated, estimated from figure: 78%	Outcome Time to recurrence/DFS Propensity score matching to correct for baseline asymmetry DFS C: mean DFS not stated *: Very low initial Hb-level	?*	-	-

Project: HTA – Iron infusion
Appendix 4:3
Outcome variable: Complications of intravenous iron infusion

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Hb level	Number of patients Actual Hb level	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Keeler, 2017, UK	RCT M: < 120 g/l F: < 110 g/l	I = 55 (mean Hb 102 g/l, 95% CI 4g/l) C = 61 (mean Hb 104g/l, CI 3 g/l)	I = 2 C = 4	Intravenous iron Postinfusion headache (n=3) Rash (n=1)	Oral iron		+	-	-
Edwards, 2009, UK	RCT M: < 135 g/l F: < 125 g/l	I =9 (mean Hb 118; CI 2g/l) C = 9 (mean Hb 124; CI 2 g/l)	I= 2 C=2	Intravenous iron Symptomatic hypotension immediately after the infusion that did not require treatment (n=2). No data for anemia group!	Oral iron		-	-	-

Project: HTA - Iron infusion
Appendix 4:4
Outcome variable: Need for transfusion

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Hb-level	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Dickson, 2020, UK 7k centres	Follow-up of previous RCT (Keeler 2017) M: < 120 g/l F: < 110 g/l	I = 54 C = 56	6 (study group not stated)	Ferric carboxymaltose i.v. Dose according to anemia. > 2 weeks until surgery	Ferrous sulphate orally 200mg twice daily > 2 weeks until surgery	Data given only for responders vs non-responders. therefore not included in GRADE-assessment of this outcome	-	-	-
Edwards, 2009, UK	RCT M: < 135 g/l F: < 125 g/l	I = 9 C = 9	I = 2 C = 2	Intravenous iron 2/9 p=0.335	Placebo 5/9		?	-	-
Keeler, 2017, UK	RCT M: < 120 g/l F: < 110 g/l	I = 55 C = 61	I = 2 C = 4	Intravenous iron 10/55 p=0.470	Oral iron 14/61		+	-	-
Calleja, 2016, Spain	Cohort (historic controls) M: < 130 g/l F: < 120 g/l	I = 111 C = 155	Not stated	Intravenous iron (Ferric carboxymaltose) 9.9% p<0.001 Open surgery 17.1% Laparoscopic surgery: 0%	No intravenous iron 38.7% Open surgery: 37.7% Laparoscopic: 25.4%		-	-	-

Project: HTA - Iron infusion
Appendix 4:4
Outcome variable: Need for transfusion

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Hb-level	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Kam, 2020, Hong Kong	Cohort (historic controls) M+F: 100 g/l before transfusion M+F: 120 g/l after transfusion	I = 38 C = 62	Not stated	Intravenous iron 8/38 (21%) p=0.006	No intravenous iron 30/62 (48%)		+	?	?
Laso-Morales, 2017, Spain	Cohort (retrospective) M+F: 130g/l	I = 232 C = 90	Not stated	Intravenous iron Mean 0.3 (SD±0.8) units, n.s.	No intravenous iron Mean 0.4 (SD±1.2) units		+	-	-
Wilson, 2018a, Netherlands	Cohort (retrospective) M: 129g/l F: 120g/l	I = 94 C = 224	Not stated	Intravenous iron Need for postop transfusion (multivariable): OR: 0.54 (95% CI: 0.24 to 1.21), p=0.14 (direction favours i.v. iron) Need for postop transfusion (univariable): OR: 0.47 (95% CI: 0.23 to 0.99) p=0.04	No intravenous iron		+	-	?

Project: HTA-Iron infusion
Appendix 4:5
Outcome variable: Peri- and postoperative complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Hb-level	Number of patients Initial Hb	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Dickson, 2020, UK	RCT M: < 120 g/l F: < 110 g/l	I = 54 (mean Hb 102 g/l, 95% CI 4g/l) C = 56 (mean Hb 104g/l, CI 3 g/l) n.s.	6 (study group not stated)	Intravenous iron Complications not stated	Oral iron		+	+	-
Edwards, 2009, UK	RCT M: < 135 g/l F: < 125 g/l	I = 9 C = 9	I = 2 C = 2	Intravenous iron Adverse perioperative events not stated	Placebo		?	-	-
Keeler, 2017, UK	RCT M: < 120 g/l F: < 110 g/l	I = 55 (mean Hb 102 g/l, 95% CI 4g/l) C = 61 (mean Hb 104g/l, CI 3 g/l) n.s.	I = 2 C = 4	Intravenous iron "No difference in complication severity (p=0.995) and rate (p=0.305)	Oral iron		+	-	-
Keeler 2019, UK	RCT M: < 120 g/l F: < 110 g/l	I=55 (Mean Hb 96; SD 13 g/l) C=61 (Mean Hb 99; SD 11 g/l) n.s.	116-92=24	Intravenous iron Infective complications Day 7: 28%; p=0.112 Day 28:.39.6% p=0.091	Oral iron Infective complications Day 7: 15.8% Day 28: 24.6%		+	-	?

Project: HTA-Iron infusion
Appendix 4:5
Outcome variable: Peri- and postoperative complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Hb-level	Number of patients Initial Hb	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Calleja, 2016, Spain	Cohort (historic controls) M: < 130 g/l F: < 120 g/l	I = 111 (mean Hb 96 ;SD 14 g/l) C = 155 (mean Hb 100; SD 12 g/l) p<0.005	Not stated	Intravenous iron Number of complications: 22.5/111=20% NS Surgical interventions: 6.7% NS Hospital readmissions: 4.0% NS	No intravenous iron 25.5/155=16% Surgical interventions: 6.7% Hospital readmissions: 3.9%		-	-	-

Project: HTA-Iron infusion
Appendix 4:5
Outcome variable: Peri- and postoperative complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Hb-level	Number of patients Initial Hb	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Laso-Morales, 2017, Spain	Cohort (retrospective) M+F: 130g/l	I = 232 (mean Hb 108; SD 15 g/d C = 90 (mean Hb 120; SD 9 g/l)	Not stated	Intravenous iron Infections complications: 42/232 (18%) p=0.018 Hemorrhagic complications: 26/223 (11%) p=0.256 Paralytic ileus: 21/232 (9%) NS Thromboembolic complications: 0/232 p=0.280	No intravenous iron Infections complications: 26/90 (29%) Hemorrhagic complications: 13/90 (14%) Paralytic ileus: 7/90 (8%) Thromboembolic complications: 1/90		+	?	-
Wilson, 2018a, Netherlands	Cohort (retrospective) M: 129g/l F: 120g/l	I = 52 (mean Hb 63; SD 8 g/l) C = 153 (mean Hb 69; SD 7 g/l)	Not stated	Intravenous iron OR for complications w. i.v iron= 0.91(0.50-1.68) p=0.77	No intravenous iron		+	-	-

Project: HTA-Iron infusion
Appendix 4:6
Outcome variable: Health-related quality of life

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients Initial Hb	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Keeler, 2019, UK	RCT M: < 120 g/l F: < 110 g/l	I = 55 (Mean Hb 96; SD 13 g/l) C = 61 (Mean Hb 99; SD 11 g/l) n.s.	I = 13 C = 11	Functional Assessment of Cancer Therapy – Anaemia subscale (median, IQR, range) I.v. iron 90 (80–90 [50–100]), p = 0.001). Functional Assessment of Cancer Therapy – Anaemia trial outcome index i.v. iron 71 (66–77 [46–80]); p = 0.002) I.v. iron Improvement of role limitation due to pain, general health, vitality (?), social functioning	Oral iron 70, (60–85 [20–95]) Oral iron 66 (55–72 [23–80]); Oral iron Most parameters remain stable before and after surgery		+	-	-

Project: HTA-Iron infusion
Appendix 4:7
Outcome variable: Length of hospital stay

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients Initial Hb	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Edwards, 2009, UK	RCT M: < 135 g/l F: < 125 g/l	I = 9 (mean Hb 118; CI 2g/l) C = 9 (mean Hb 124; CI 2 g/l)		Intravenous iron 10 days (median) No data given! p=0.273	Placebo 8 days (median)		?	-	-
Laso-Morales, 2017, Spain	Cohort (retrospective) M+F: <130g/l	I = 232 (mean Hb 108; SD 15 g/d) C = 90 (mean Hb 120; SD 9 g/l)	Not stated	Intravenous iron 9±6 days p=0.889	No intravenous iron 9±5 days		+	-	-

Project: HTA-Iron infusion
Appendix 5
Clinical trials

NCT Number	NCT03565354	NCT04653181	NCT02243735	NCT00199277	NCT01701310	NCT03295851	NCT02057471
Title	Efficacy of Preoperative Intravenous Iron in Anaemic Colorectal Cancer Surgical Patients	Preoperative i.v. Iron Substitution in Patients With Colon Cancer	Trial Comparing Ferric(III)Carboxymaltose Infusion With Oral Iron Suppletion as Treatment of Anaemia	Iron Therapy in Colo-Rectal Neoplasm and Iron Deficiency Anemia: Intravenous Iron Sucrose Versus Oral Ferrous Sulphate.	IVICA: Intravenous Iron in Colorectal Cancer Associated Anaemia	Preoperative Intravenous Iron Infusion to Reduce Post-surgical Complications: a Pilot Randomised Control Trial	Intravenous Iron: Measuring Response in Anemic Surgical Patients
Status	Completed	Recruiting	Unknown status	Unknown status	Completed	Unknown status	Completed
Study Results	No Results Available	No Results Available	No Results Available	No Results Available	No Results Available	No Results Available	No Results Available
Conditions	Anemia, Iron-Deficiency|Colorectal Cancer	Colon Cancer	Anemia|Colorectal Carcinoma|Surgery	Colorectal Neoplasm|Iron Deficiency Anemia	Anemia|Colorectal Neoplasm	Anemia|Major Abdominal Surgery|Pre-operative	Colorectal Neoplasm|Anemia
Interventions	Drug: iron isomaltoside(Monofer®)	Drug: Ferric carboxymaltose	Drug: Ferrous fumarate|Drug: ferric(III)carboxymaltose	Drug: i.v. iron sucrose|Drug: Oral iron	Drug: Ferric carboxymaltose|Drug: Ferrous Sulphate	Drug: Ferric carboxymaltose|Drug: Ferrous Fumarate	Drug: Intravenous ferric carboxymaltose
Outcome Measures	Hb, need for transfusions, QoL	postoperative complications|Need for red blood cell transfusion	Normalization of Hb-level.|Difference in Morbidity score	Hb, needs for transfusion, reintervention, complications, death, LoS	Need for transfusion, Hb, postioerative outcomes	Mortality, peri- and poperative morbidities, health related quality of life.	Transfusions
Study Type	Interventional	Interventional	Interventional	Interventional	Interventional	Interventional	Interventional
Study Designs	RCT	RCT	RCT	RCT	RCT	Allocation: RCT	Open observational?
Completion Date	June 30, 2020	December 31, 2024	dec-19		dec-14	March 2019	March 2012
Locations	Prince of Wales Hospital, Shatin, Hong Kong	Jorvi Hospital, Espoo, HUS, Finland	Multicenter Netherlands	Multicenter Europé	Multicenter UK	Singapore General Hospital, Singapore, Singapore	Nottingham University Hospitals NHS Trust, Nottingham, Nottinghamshire, United Kingdom
URL	https://ClinicalTrials.gov/show/NCT03565354	https://ClinicalTrials.gov/show/NCT04653181	https://ClinicalTrials.gov/show/NCT02243735	https://ClinicalTrials.gov/show/NCT00199277	https://ClinicalTrials.gov/show/NCT01701310	https://ClinicalTrials.gov/show/NCT03295851	https://ClinicalTrials.gov/show/NCT02057471

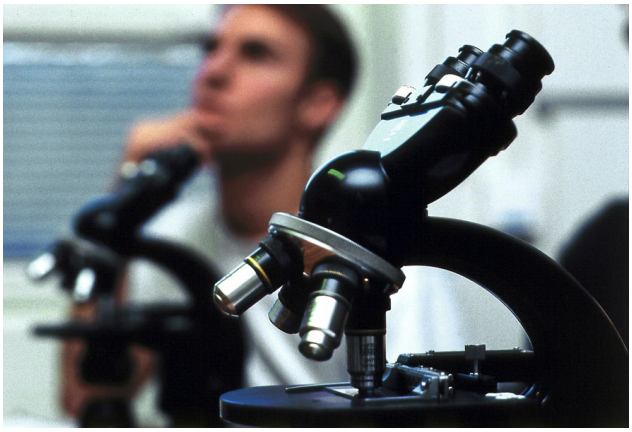
Innehållsdeklaration

Denna HTA-rapport är baserad på följande moment:

- [x] Metodbeskrivning
- [x] PICO
- [x] Uttömmande litteratursökning
- [x] Flödesschema
- [x] Urval relevans
- [x] Kvalitetsgranskning
- [x] Tabelldata
- [x] Sammanvägning av resultat
- [ ] Metaanalys
- [x] Evidensgradering enligt GRADE
- [x] Sammanfattning
- [x] Ekonomi
- [x] Organisation
- [x] Etik
- [x] Pågående studier
- [x] Exkluderade artiklar
- [x] Expertgrupp deltar
- [x] Extern granskning
- [x] Kunskapsluckor identifierade
- [x] Jävsdeklaration inhämtad från projektdeltagarna

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

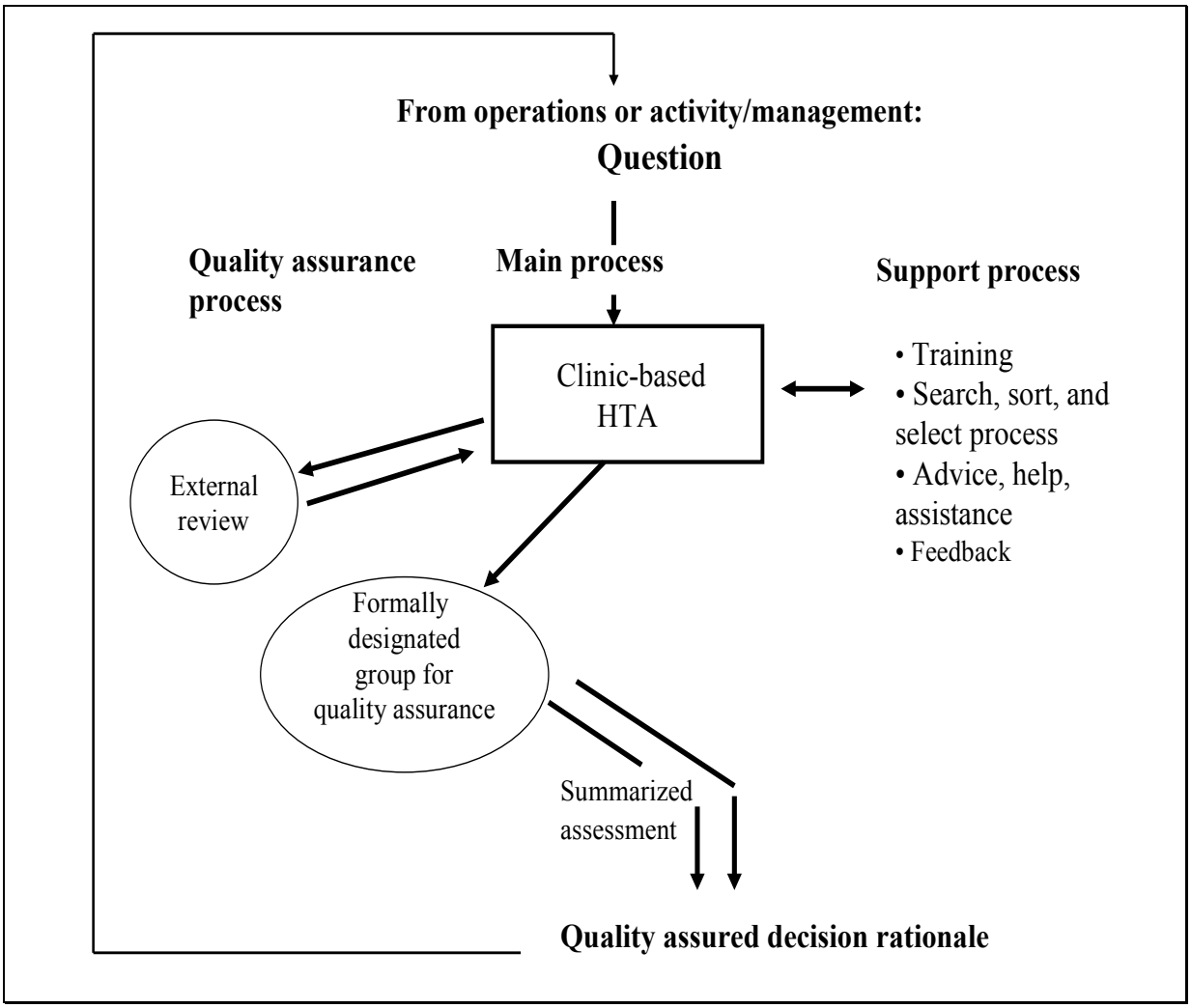
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh
Professor, MD
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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