# Clinical practice guideline: evidence, recommendations and algorithm for the preoperative optimization of anemia, hyperglycemia and smoking

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Preoperative optimization has not been explored comprehensively in the surgical literature, as this responsibility has often been divided among surgery, anesthesia and medicine. We developed an evidence-based clinical practice guideline to summarize existing evidence and present diagnostic and treatment algorithms for use by surgeons caring for patients scheduled to undergo major elective surgery. We focus on 3 common comorbid conditions seen across surgical specialties — anemia, hyperglycemia and smoking — as these conditions increase complication rates in patients undergoing major surgery and can be optimized successfully as soon as 6–8 weeks before surgery. With the ability to address these conditions earlier in the patient journey, surgeons can positively affect patient outcomes. The aim of this guideline is to bring optimization in the preoperative period under the existing umbrella of evidence-based surgical care.

L'optimisation préopératoire n'a pas été explorée de manière exhaustive dans la littérature chirurgicale, car cette responsabilité a souvent été divisée entre la chirurgie, l'anesthésie et la médecine. Cette ligne directrice de pratique clinique fondée sur des données probantes a été conçue pour résumer les données existantes et présenter des algorithmes diagnostics et thérapeutiques relatifs à des comorbidités fréquentes chez les patients vus dans toutes les spécialités chirurgicales. L'accent a été placé sur l'optimisation préopératoire de l'anémie, de l'hyperglycémie et du tabagisme, étant donné que ces problèmes de santé accroissent le risque de complications chez les patients qui doivent subir une chirurgie majeure et qu'il est possible de les corriger en bonne partie dans les 6–8 semaines précédant la chirurgie. Or, si les chirurgiens arrivent à corriger ces problèmes de santé plus tôt dans le parcours des patients, ils pourraient améliorer leurs résultats. Le but de cette ligne directrice est que l'optimisation préopératoire soit intégrée à l'ensemble actuel des soins chirurgicaux fondés sur des données probantes.

For most of the 20th century, the focus of research in surgery was improvements in intraoperative technique, which led to major technical paradigm shifts exemplified by the evolution of transurethral resection of the prostate,[1] laparoscopic cholecystectomy,[2] endovascular aneurysm repair[3] and total mesorectal excision for rectal cancer,[4] among many others. The late 1990s and early 2000s marked a shift in surgical research toward the evidence-based management of patients in the perioperative period, beginning with the Enhanced Recovery After Surgery Group's systematic review of patients undergoing colorectal surgery.[5] That publication introduced a new paradigm focused on the impact that standardized perioperative care could have on patient outcomes such as length of stay, postoperative pain and overall complication rates.[6,7]

Although a large body of literature now exists to help guide the intraoperative and perioperative management of surgical patients, our working group believes that the preoperative period, which we define as the 8 weeks

preceding elective surgical procedures, is an area of inquiry that remains underexplored in surgical literature. This "orphan" period in the care of a surgical patient exists for many reasons. The preoperative period has not traditionally been the responsibility of any single clinical specialty, with care often divided among surgeons, anesthetists and internists. As a result, there is little in the way of a standardized, evidence-based approach to the identification and treatment of comorbid conditions that could be effectively optimized in the preoperative period to improve patient outcomes.

In this evidence-based clinical practice guideline, we summarize existing evidence and present diagnostic and treatment algorithms for use by surgeons caring for patients undergoing major elective surgery. We focus on 3 common comorbid conditions seen across surgical specialties — anemia, hyperglycemia and smoking — and present evidence of improved patient outcomes with optimization strategies started as soon as 6–8 weeks before surgery.

The evidence presented here points to a new paradigm shift in the way multidisciplinary teams care for patients undergoing elective surgery, bringing the preoperative period under the existing umbrella of evidence-based surgical care.

## Literature search

Our search strategy for anemia is presented in Appendix 1 (available at canjsurg.ca). A similar search strategy was used for hyperglycemia and for smoking, with lines 1 and 3 changed to reflect the different components. We determined the strength of recommendations and the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[8] Recommendations were developed by 2 reviewers for each subject area (anemia and diabetes: J.A.G. and T.M.Z., smoking: J.S. and J.A.G.). Disagreements were resolved by a third reviewer (H.M.).

## Anemia

The prevalence of preoperative anemia is high. In 2 large studies of patients undergoing noncardiac surgery ($n$ = 319 703), preoperative anemia was identified in 28%–30% of patients across multiple specialties.[9,10] In certain surgical specialties, the prevalence approaches half of all patients, as seen in colorectal surgery (40.4%–47.4%),[11,12] orthopedic surgery (25%–44%)[13–15] and urology (8%–45%).[16] According to the World Health Organization (WHO), a prevalence of anemia greater than 40% in a population has severe health consequences, and, therefore, anemia should be an essential consideration in most surgical patients.[17]

The WHO defines anemia as a hemoglobin level less than 120 g/L in women and less than 130 g/L in men.[18,19] These definitions have been validated by large population studies examining mean hemoglobin values by age, race and sex.[20] A second definition of anemia is a hematocrit value less than 0.39 for both sexes, which has also been validated in large database studies.[9,11] The WHO estimates a prevalence of anemia of 29.4% among all women of reproductive age,[18] which makes anemia an underrecognized condition warranting consideration even in young, healthy populations.

Anemia may be caused by chronic inflammatory conditions, kidney disease, malnutrition, ongoing small-volume blood loss and iron deficiency. Iron-deficiency anemia (IDA) is widely accepted to be the most common cause, and, in a recent study of 3342 patients undergoing gynecologic, urologic, colorectal, cardiac or orthopedic surgery, almost two-thirds (62%) of patients with preoperative anemia had some component of IDA.[21] In patients with cancer, chronic bleeding from gastrointestinal tumours can also contribute to preoperative anemia.[22–24] Given the increased incidence of most surgical conditions with increasing age, the mean age of surgical patients is older than that of other cohorts and is associated with an increased prevalence of anemia.[20,22] Unlike in the general population, the cause of anemia in older patients is multifactorial in almost two-thirds of cases.[25]

Several centres have reported improved postsurgical outcomes through preoperative diagnosis of anemia and treatment plans. These outcomes include shorter length of hospital stay,[15,26] decreased rates of postoperative nosocomial infections,[26] decreased 90-day readmission rates[15] and lower rates of blood transfusion.[15,26–28] The following clinical practice guideline summarizes the current evidence informing the recommendations within the proposed diagnostic and treatment algorithm for preoperative anemia (Figure 1).

### *Recommendations*

**1. Preoperative anemia is associated with adverse surgical outcomes, and all patients undergoing major surgery should be screened for anemia at their first surgical clinic visit and investigated further, as appropriate (Table 1).**

Preoperative anemia was shown to be an independent risk factor associated with increased 1-year and overall mortality in 319 703 patients undergoing noncardiac surgery (adjusted hazard ratio [HR] 2.86, 95% confidence interval [CI] 2.56–3.20, and odds ratio [OR] 1.42, 95% CI 1.31–1.54, respectively).[9,10] In a propensity-matched cohort of 7759 patients undergoing noncardiac surgery, an independent association between preoperative anemia and increased 90-day mortality was shown (OR 2.29, 95% CI 1.45–3.63).[29] A National Surgical Quality Improvement Program (NSQIP) study of 5081 patients undergoing vascular surgery showed increased mortality for both moderate (OR 2.6, 95% CI 1.2–5.5) and severe (OR 2.8, 95% CI 1.3–6.3) anemia.[30]

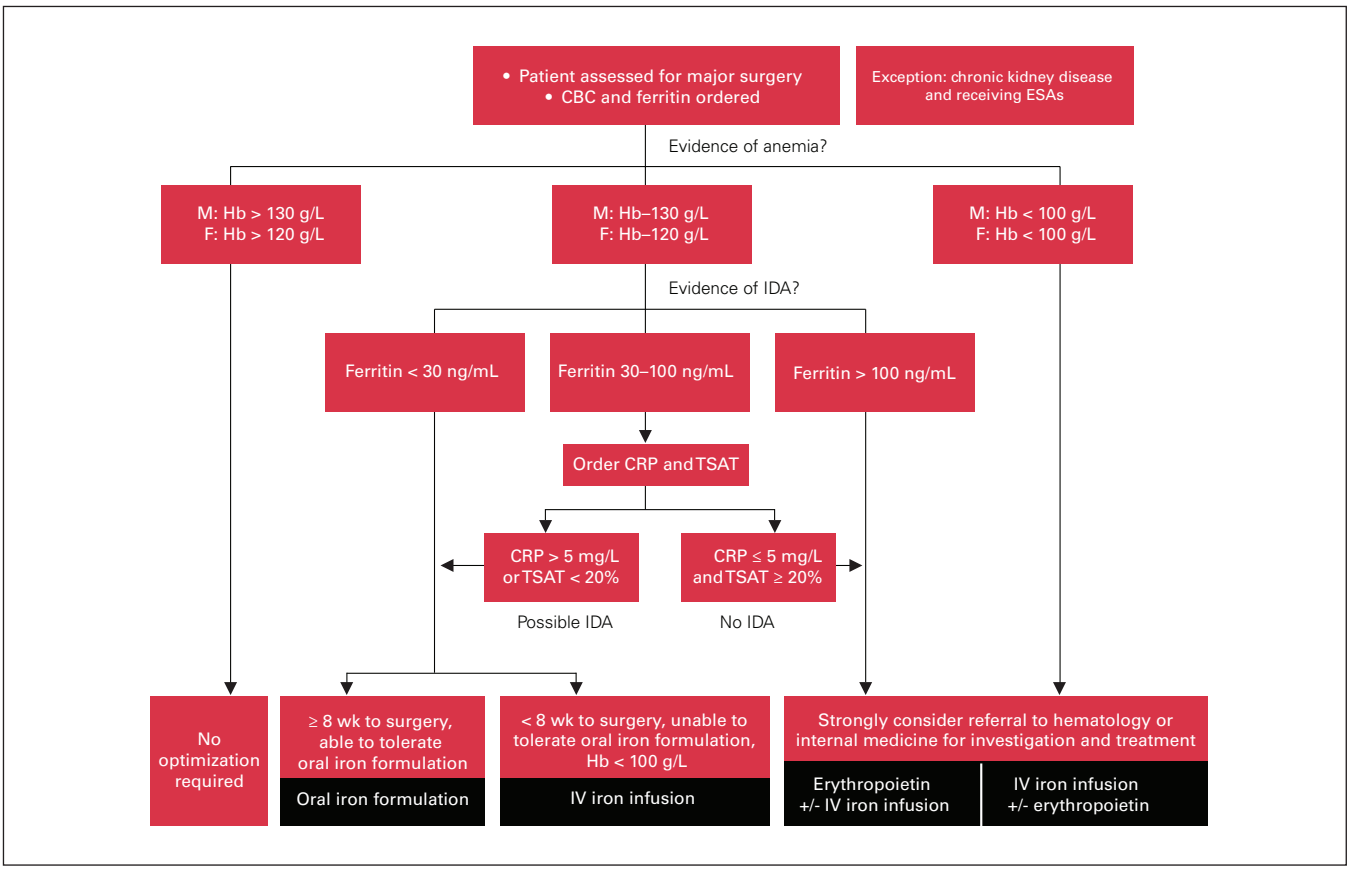


**Fig. 1.** Algorithm for diagnosis and treatment of preoperative anemia in patients undergoing major elective surgery. CBC = complete blood count; CRP = C-reactive protein; ESA = erythropoietin-stimulating agent; F = female; Hb = hemoglobin; IDA = iron-deficiency anemia; IV = intravenous; M = male; TSAT = transferrin saturation index.

Preoperative anemia is independently associated with early postoperative complications such as increased overall 30-day postoperative morbidity in patients undergoing noncardiac surgery (OR 1.35, 95% CI 1.30–1.40),[9] increased rates of major cardiac events (5.1%–6.8% v. 2.6%; $p$ = 0.001) and acute kidney injury (52.0%–63.2% v. 31.0%; $p$ = 0.01) in patients undergoing vascular surgery,[30,31] and increased infectious complication rates in patients undergoing orthopedic surgery (57.1% v. 6.3%; $p$ = 0.006)[32] and those with gastric cancer (OR 3.70, 95% CI 1.43–9.58).[33] In a large NSQIP database study, preoperative anemia in patients undergoing colorectal surgery was independently associated with a significantly increased frequency of composite outcome events (myocardial infarction, acute renal injury, stroke and death) that was proportional to anemia severity (mild: OR 1.49, 95% CI 1.20–1.86; moderate: OR 2.19, 95% CI 1.63–2.94; severe: OR 1.83, 95% CI 1.05–3.19).[11]

Preoperative anemia was independently associated with significant increases in length of postoperative hospital stay in a systematic review of orthopedic literature,[13] a retrospective analysis of 2394 patients who underwent total knee arthroplasty (OR 1.71–2.29; $p$ < 0.001)[14] and an NSQIP study of 23 348 patients who underwent colorectal surgery (0.5–2.2 d longer; $p$ < 0.01).[11]

Unsurprisingly, preoperative anemia is independently associated with significantly increased rates of postoperative blood transfusion. This association has been shown after urologic (OR 6.28, 95% CI 3.43–11.51),[34] colorectal (24% v. 3%)[35] and orthopedic (OR 4.13–9.13; $p$ < 0.001)[14] procedures. Compared to anemic values, a normal preoperative hemoglobin value was shown to significantly reduce the likelihood of transfusion after laparoscopic colorectal resection (HR 0.547, 95% CI 0.468–0.637).[36]

Finally, preoperative anemia is independently associated with worse oncologic outcomes in patients with urologic, gastric, colorectal or mesenchymal cancer, with decreased disease-free survival,[37,38] cancer-specific survival[39,40] and overall survival,[39,41–43] and increased rates of cancer recurrence.[40,44]

### 2. Complete blood count and ferritin are the most appropriate screening blood tests.

Hemoglobin levels, as determined by a complete blood count, represent the gold standard diagnostic test for anemia. This was established through a series of reports published by the WHO between 1968 and 2015 in which

**Table 1. Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis of clinical practice guideline evidence for the preoperative optimization of anemia, hyperglycemia and smoking**

| Recommendation no. | Recommendation | Strength of recommendation* | Quality of evidence† |
|---|---|---|---|
| **Anemia** | | | |
| 1 | Preoperative anemia is associated with adverse surgical outcomes, and all patients undergoing major surgery should be screened for anemia at their first surgical clinic visit and investigated further, as appropriate. | Strong | High |
| 2 | Complete blood count and ferritin are the most appropriate screening blood tests. | Strong | Moderate |
| 3 | Patients without evidence of anemia should not be treated with iron supplementation. | Weak | Low |
| 4 | For patients with anemia and a serum ferritin level of 30–100 ng/mL, transferrin saturation index and C-reactive protein tests should be ordered to better determine the presence of iron deficiency. | Strong | Low |
| 5 | Oral iron supplementation is the preferred treatment for patients with iron-deficiency anemia (IDA) and no contraindications (i.e., ≥ 8 wk until surgery, able to tolerate/absorb oral iron formulation, hemoglobin level ≥ 100 g/L). | Strong | High |
| 6 | 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). | Strong | High |
| 7 | For patients with anemia who have no evidence of IDA or IDA refractory to iron supplementation, referral to a hematologist should be considered for treatment with erythropoietin and intravenous iron infusions. | Strong | High |
| **Hyperglycemia** | | | |
| 1 | Perioperative hyperglycemia increases the risk of postoperative complications, and all patients undergoing major surgery should be screened for diabetes. | Strong | Moderate |
| 2 | Measurement of the glycated hemoglobin ($HbA_{1c}$) level is the most appropriate screening test for hyperglycemia. | Weak | Low |
| 3 | A preoperative $HbA_{1c}$ less than 6.0% does not require any further action or preoperative optimization. | Strong | High |
| 4 | A preoperative $HbA_{1c}$ level of 6.0%–6.9% in a patient with no history of diabetes does not require preoperative optimization. However, it may represent prediabetes or a new diagnosis of diabetes, and the patient should be referred to a family physician, internist or endocrinologist for follow-up and confirmation. | Strong | Low |
| 5 | A preoperative $HbA_{1c}$ level of 7.0%–8.4% requires preoperative optimization, and these patients should be referred to their family physician, an internist or an endocrinologist for optimization to a target blood glucose level of 5–10 mmol/L. | Strong | High |
| 6 | A preoperative $HbA_{1c}$ level of 8.5% or greater indicates poor glycemic control and requires preoperative optimization, and these patients should be referred to an internist or endocrinologist for preoperative optimization. | Strong | High |
| 7 | Patients with known diabetes with a preoperative $HbA_{1c}$ level less than 7.0% do not require preoperative optimization. | Strong | Low |
| 8 | All patients (both with and without diabetes) with a preoperative $HbA_{1c}$ level greater than 6.0% should undergo intra- and postoperative blood glucose monitoring, with a target blood glucose level of 6–10 mmol/L, to reduce the risk of postoperative complications. | Strong | Moderate |
| **Smoking** | | | |
| 1 | Tobacco smoking is associated with increased adverse postoperative outcomes, and all patients undergoing major surgery should have their smoking status identified and documented at every preoperative clinic visit. | Strong | High |
| 2 | All surgical patients who smoke should be advised to quit smoking preoperatively and have their willingness to quit assessed to guide next steps. Because of the high risk of relapse, those who have quit within the previous 6 months should be treated as active smokers. | Strong | Moderate |
| 3 | A quit date should be set more than 8 weeks preoperatively to achieve the most substantial improvements in postoperative outcomes; however, outcome benefits may still be seen with cessation as late as the day of surgery. | Strong | Moderate |
| 4 | In patients who are unwilling to quit smoking, motivational interviewing techniques can be used to increase motivation to quit, thereby increasing quit rates. | Strong | Moderate |
| 5 | In patients who are unwilling to quit smoking but willing to reduce, clinicians should offer full cessation treatment to support reduction goals. | Strong | Moderate |
| 6 | All surgical patients who smoke should be offered the combination of counselling and pharmacotherapy preoperatively. When this is not possible, they should still be offered either intervention individually. | Strong | High |
| 7 | All surgical patients who smoke should be offered combination nicotine replacement therapy (NRT) preoperatively. Prescribers capable of follow-up may consider varenicline as a first-line agent. Second-line options include single-agent NRT and bupropion. | Strong | High |
| 8 | All surgical patients who smoke should be given brief counselling on the consequences of smoking and the benefits of smoking cessation preoperatively. When possible, counselling should be face to face, frequent and of sufficient duration, all of which increase cessation rates. | Strong | High |
| 9 | All surgical patients who smoke should be offered clinical follow-up. | Strong | Moderate |

*Represents a combination of quality of supporting evidence, balance between desired and undesired effects, how wise the proposed use of resources is, and variability of individual preferences and values. Can be "strong" or "weak."
†Based on how likely further research is to change confidence in the estimate of effect. Classified in 1 of 4 levels: "high," "moderate," "low" or "very low."

the normal hemoglobin ranges for adult and pediatric populations (by sex) were determined and the definitions of anemia refined.[17–19,45–48] Large population-based studies examining mean hemoglobin values by age, race and sex further validated the accepted normal ranges and the use of hemoglobin level to diagnose anemia.[20] The hematocrit, as determined by a complete blood count, has also been validated as an indicator of anemia in more recent large database studies, such as those using NSQIP data.[9,11,49]

Iron-deficiency anemia is the most common cause of anemia in surgical patients and should be assessed as part of the initial investigation.[21,50–52] In a meta-analysis of 55 studies, Guyatt and colleagues[53] compared several blood tests to the gold standard for the diagnosis of IDA (absence of stainable iron in a bone marrow aspirate). They found the serum ferritin radioimmunoassay to be the most reliable test for the diagnosis of IDA, with an area under the ROC curve of 0.95. Although the radioimmunoassay is no longer commonplace, equivalence has been shown between this assay and the enzyme-linked immunoassays that are more common today, with an intraclass correlation coefficient of at least 0.98, which implies that the tests are interchangeable.[54] A serum ferritin level less than 30 μg/L has been shown to be both sensitive (92%) and specific (98%) for the diagnosis of IDA.[55–57] The diagnostic utility of serum ferritin level as an effective first-line test for IDA was reaffirmed in more recent reviews on the topic.[47,55,58]

**3. Patients without evidence of anemia should not be treated with iron supplementation.**

Pratt and Khan[59] advocated consideration of iron supplementation for patients with nonanemic iron deficiency. However, currently there is insufficient evidence of clinical benefit to recommend treatment for patients with a preoperative hemoglobin level greater than 130 g/L for men or greater than 120 g/L for women. Although the rate of serious toxic effects related to oral iron supplementation is low, gastrointestinal adverse effects are common.[60] Therefore, given the low potential for benefit and high probability of adverse effects, this therapy should not be recommended for patients without evidence of anemia.

**4. For patients with anemia and a serum ferritin level of 30–100 ng/mL, transferrin saturation index and C-reactive protein tests should be ordered to better determine the presence of iron deficiency.**

In cases in which anemia is diagnosed but the serum ferritin level is nondiagnostic (30–100 ng/mL), 2 tests should be added to confirm IDA: measurement of the transferrin saturation index and the C-reactive protein level.[56,58] In the context of anemia with a serum ferritin level of 30–100 ng/mL, a transferrin saturation index less than 20% implies inadequate iron for normal erythropoiesis and is therefore strongly suggestive of IDA.[51,56,58]

Serum ferritin is known to be an acute-phase reactant,[61,62] and the level can rise with increasing age.[20,62] Therefore, in the context of anemia with a serum ferritin level of 30–100 ng/mL, a C-reactive protein level greater than 5 mg/L is consistent with an inflammatory state and falsely elevated serum ferritin levels, and is therefore strongly suggestive of IDA.[51,56,58]

**5. Oral iron supplementation is the preferred treatment for patients with IDA and no contraindications (i.e., ≥ 8 wk until surgery, able to tolerate/absorb oral iron formulation, hemoglobin level ≥ 100 g/L).**

A randomized controlled trial (RCT) involving 90 older inpatients with IDA showed significant increases in mean hemoglobin level after 60 days of treatment with low-, medium- or high-dose oral iron supplementation (increases of 13 g/L, 14 g/L and 14 g/L, respectively; $p < 0.001$ for all dosages).[63] In a multicentre RCT involving 46 patients with inflammatory bowel disease and IDA, an oral iron regimen administered for 6 weeks resulted in a mean increase in hemoglobin level of 21 g/L, which was not significantly different from that in patients receiving intravenous iron infusions.[64] In an RCT involving 45 patients awaiting resection for colon or rectal cancer, 2 weeks of oral iron treatment resulted in significantly higher hemoglobin levels at the time of surgery (mean 131 g/L v. 118 g/L; $p = 0.04$),[65] and a second prospective study in 58 similar patients showed a significant increase in preoperative hemoglobin level (+17.3 g/L; $p < 0.001$) after an average of 39 days of oral iron treatment.[66]

Owing to the demonstrated effectiveness of oral iron therapy, and the lower cost and ease of administration for both the patient and the health care system, most blood management strategies recommend oral iron supplementation as first-line treatment for patients with IDA with no contraindications.[15,51,53,67] Although many dosages have been found to be effective, there is evidence to suggest that lower dosages (e.g., elemental iron equivalent of 40–60 mg orally daily or 80–100 mg orally every 2 d) are associated with fewer adverse effects such as abdominal discomfort, nausea, vomiting and changes in bowel habits.[51,63,68]

A recent summary of evidence regarding the safety of oral iron supplementation did not identify any major safety concerns, although adverse effects such as nausea, heartburn, pain, and constipation or diarrhea are more common with oral formulations than with intravenous iron infusions.[69]

**6. 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).**

In an RCT involving 76 patients with menorrhagia and severe IDA comparing 3 weeks of intravenous versus oral iron supplementation, intravenous iron supplementation

was associated with a larger increase in posttreatment hemoglobin levels (mean +30 g/L v. +8 g/L; $p < 0.001$) and ferritin levels (mean +170.1 μg/L v. +4.1 μg/L; $p < 0.001$), and a higher frequency of reaching a target hemoglobin level of 100 g/L or greater (76.7% v. 11.5%; $p < 0.001$).[70] A prospective trial involving 266 patients with colon cancer receiving intravenous versus oral iron supplementation showed that intravenous iron supplementation was associated with a significantly shorter mean length of stay (8.4 d [standard deviation (SD) 6.8 d] v. 10.9 d [SD 12.4 d]; $p < 0.001$), lower frequency of transfusion (9.9% v. 38.7%, $p < 0.001$]), and larger increases in preoperative (+15 g/L v. +5 g/L; $p < 0.001$) and 30-day postoperative (+31 g/L v. +15 g/L; $p < 0.001$) hemoglobin levels.[71] In addition, patients receiving iron intravenously had a higher rate of normalized hemoglobin 30 days postoperatively (40% v. 26.7%; $p < 0.05$). In a multicentre RCT involving 116 patients undergoing elective surgery for colorectal cancer, the mean increase in total hemoglobin level was significantly greater with intravenous than oral iron therapy (+15.5 g/L v. +5.0 g/L; $p < 0.001$), and a smaller proportion of patients in the intravenous iron group were anemic at the time of surgery (75% v. 90%; $p = 0.048$).[72] These findings are consistent with those of a systematic review of 8 low-bias RCTs showing that patients with IDA preoperatively may have earlier and more robust recovery of the hemoglobin level with intravenous iron therapy than with oral supplementation.[73] In a prospective RCT, 72 patients with IDA were randomly allocated to receive intravenous iron supplementation versus usual care within 3 weeks before elective abdominal surgery.[74] Increases in hemoglobin level were significantly higher in the intravenous iron group preoperatively and 4 weeks after discharge (+8 g/L v. +1 g/L, $p = 0.01$; and 19 g/L v. 9 g/L, $p = 0.01$, respectively), with a significant associated reduction in postoperative allogenic blood transfusion (12.5% v. 53%; $p < 0.001$). Finally, a retrospective review of 318 patients with colorectal cancer and anemia who received intravenous iron treatment less than 6 weeks before surgery showed a significantly greater increase in hemoglobin level compared to no treatment (+10.5 g/L v. +1.6 g/L; $p < 0.001$).[75]

Two studies have shown the utility of intravenous iron infusion for patients with anemia with minimal time until surgery. An RCT in 108 patients undergoing bilateral total knee replacement showed that, compared to no infusions, intraoperative intravenous infusions of iron and erythropoietin resulted in significantly higher hemoglobin levels in the first, second and sixth weeks postoperatively, and a significantly lower rate of blood transfusion (20.4% v. 53.7%; $p = 0.01$).[76] In a retrospective analysis of 2547 patients at risk for severe postoperative anemia who underwent major orthopedic surgery, compared to standard treatment, intravenous iron treatment at any time from 5 days preoperatively to 3 days postoperatively was associated with a significantly lower rate of postoperative nosocomial infections (10.7% v. 26.9%; $p = 0.001$) and shorter length of stay (11.9 d v. 13.4 d; $p = 0.001$), independent of transfusion status; the proportion who received transfusions was also lower (32.4% v. 48.8%; $p = 0.001$).[26]

The safety of intravenous iron therapy is comparable to that of oral iron therapy, as shown in a systematic review of 8 low-bias RCTs and a prospective study of 266 patients that showed no deaths, hypersensitivity reactions or other serious drug reactions.[71,73] In addition to being safe, intravenous iron treatment is rarely associated with the adverse gastrointestinal effects seen with oral iron supplementation, which results in increased compliance with intravenous treatment.[28,70]

**7. For patients with anemia who have no evidence of IDA or IDA refractory to iron supplementation, referral to a hematologist should be considered for treatment with erythropoietin and intravenous iron infusions.**

In a systematic review of 8 low-bias RCTs, Lin and colleagues[73] concluded that a short preoperative course of erythropoietin or a single dose of erythropoietin plus intravenous iron infusion pre- or intraoperatively may reduce transfusion requirements significantly, with a number needed to treat to avoid allogenic blood transfusion of 3–6. In an RCT involving 201 patients with undifferentiated anemia scheduled to undergo hip arthroplasty, participants were randomly allocated to receive 4 weeks of high-dose erythropoietin with oral iron therapy, low-dose erythropoietin with oral iron therapy, or placebo; there was a significant dose-proportional reduction in the blood transfusion rate (11.4%, 22.8% and 44.9%, respectively; $p < 0.003$) and increase in the preoperative hemoglobin level (+19.5 g/L, +17.2 g/L and +1.2 g/L, respectively; $p < 0.001$).[77] In an RCT in which 74 patients with anemia undergoing valvular heart surgery were randomly allocated to receive erythropoietin and intravenous iron infusion or placebo 1 day before surgery, the intervention was associated with was a significant reduction in the rate of blood transfusion (59% v. 86%; $p = 0.009$), with a number needed to treat to avoid allogenic blood transfusion of 4, as well as a reduction in the mean number of units of packed red blood cells transfused per patient (3.3 [SD 2.2] v. 1.0 [SD 1.1]; $p = 0.001$).[78] In an RCT involving 108 iron-deficient patients undergoing bilateral total knee replacement, compared to standard care, administration of erythropoietin and intravenous iron infusion intraoperatively resulted in a significantly lower perioperative transfusion rate (20.4% v. 53.7%; $p = 0.01$), significantly fewer units of packed red blood cells transfused per patient (mean 0.2 [SD 0.5] v. 0.8 [SD 0.8]; $p = 0.005$), and significantly higher hemoglobin levels 1, 2 and 3 days, and 2 and 6 weeks postoperatively.[76] Finally, in a retrospective study involving 412 patients with IDA who underwent elective orthopedic surgery, Basora and colleagues[79]

compared those who received intravenous iron treatment alone to those who received intravenous iron treatment and erythropoietin preoperatively and found a significantly greater increase in the preoperative hemoglobin level with the latter treatment (+15 g/L v. +8 g/L; $p < 0.01$).

A safety/noninferiority RCT involving 680 patients undergoing spinal surgery showed a significantly increased risk of deep vein thrombosis (DVT) in those who received erythropoietin compared with standard care (4.7% v. 2.1%, 97.5% CI exceeding the boundary for noninferiority); however, only mechanical (no pharmacologic) venous thromboembolism prophylaxis was used.[80] Importantly, neither the DVT rate, confirmed on Doppler imaging (4.1% v. 2.1%), nor the rate of all adverse events (76.5% v. 73.2%) was statistically significant.

The safety of treatment with erythropoietin-stimulating agents (ESAs) in patients undergoing active treatment for malignant disorders has been questioned owing to concerns regarding tumour progression.[81] Thus, the use of ESAs in this patient population should be considered with caution.

### *Special considerations*

#### Inflammatory bowel disease

In a 2015 systematic review on the management of IDA in patients with inflammatory bowel disease that included 13 studies (2906 patients), Nielsen and colleagues[82] recommended oral iron therapy for patients with quiescent disease or mild anemia, and intravenous iron infusions for patients with moderate to severe anemia, active inflammatory bowel disease flare-ups or intolerance to oral supplementation.

#### Severely impaired renal function

Owing to decreased or absent production of erythropoietin, anemia is a nearly universal complication in patients with severely impaired renal function. The mainstay of treatment for anemia in these patients is ESAs, often with the adjunct use of iron supplementation. The Canadian Society of Nephrology does not recommend targeting a hemoglobin level within the standard normal range for these patients but, rather, maintaining a level around 100 g/L.[83] Thus, patients with renal impairment who are already taking an ESA or who may have anemia requiring ESA therapy may not be candidates for treatment according to the algorithm (Figure 1). For this reason, management of perioperative anemia in patients with renal disease should be undertaken in collaboration with the patient's nephrologist.

### *Conclusion*

Preoperative anemia is a risk factor independently associated with a variety of postoperative complications. There is sufficient evidence from high-quality trials to inform recommendations for the diagnosis and management of preoperative anemia. Routine screening, investigation and treatment for preoperative anemia in keeping with the evidence presented in this guideline is a cost-effective, high-yield approach to optimizing anemia in any patient being assessed for major surgery. Coordinated preoperative assessment and treatment programs have proven effective in reducing rates of preoperative anemia and its associated complications, but they require collaboration among perioperative specialties including surgeons, anesthetists, internists, hematologists and perioperative nurses.[15,26–28,84] Given the potential for substantial benefit to patient outcomes, as well as the efficiencies to be gained by health care systems, development of such preoperative optimization programs is recommended for all centres with moderate- to high-volume surgical services, whether academic or community-based. To ensure the effectiveness of these programs, continuous quality-assurance projects should be carried out.

## HYPERGLYCEMIA

Diabetes has been defined as a fasting blood glucose level of 7.0 mmol/L or greater, a glycated hemoglobin ($HbA_{1c}$) value of 6.5% or greater, a 2-hour plasma glucose level in a 75-g oral glucose tolerance test of 11.1 mmol/L or greater, or a random plasma glucose level of 11.1 mmol/L or greater.[85,86] Prediabetes (fasting plasma glucose level of 6.1–6.9 mmol/L, a 2-hour plasma glucose level in an oral glucose tolerance test of 7.8–11.0 mmol/L, and an $HbA_{1c}$ level of 6.0%–6.4%) places patients at very high risk for diabetes. The American Diabetes Association (ADA) expands the $HbA_{1c}$ range for prediabetes to 5.7%–6.4%.[86] Screening guidelines for the general population vary by organization.[85,87,88]

The prevalence of diabetes continues to rise, with the disease affecting an estimated 371 million people worldwide in 2012; this number is expected to increase to 552 million by 2030.[85] In the United States, the prevalence was 9.4% in 2015, and in Canada, the estimated prevalence was 6.8% in 2009.[85,89] Diabetes is even more common in surgical patients than in the general population: patients with diabetes account for an estimated 10%–20% of all surgical patients; a further 23%–60% of surgical patients have undiagnosed diabetes.[90–93]

Major surgical procedures produce a catabolic state and lead to transient hyperglycemia in patients without diabetes. This physiologic response is more pronounced in patients who have insulin resistance or no insulin production.[93] Diabetes-related complications include those from macrovascular and microvascular disease, such as myocardial infarction, stroke, retinopathy, nephropathy and neuropathy.[94]

The appropriate management of hyperglycemia intra- and postoperatively has been shown to improve outcomes.[95] The preoperative management of hyperglycemia is an area that can be improved. The following clinical practice

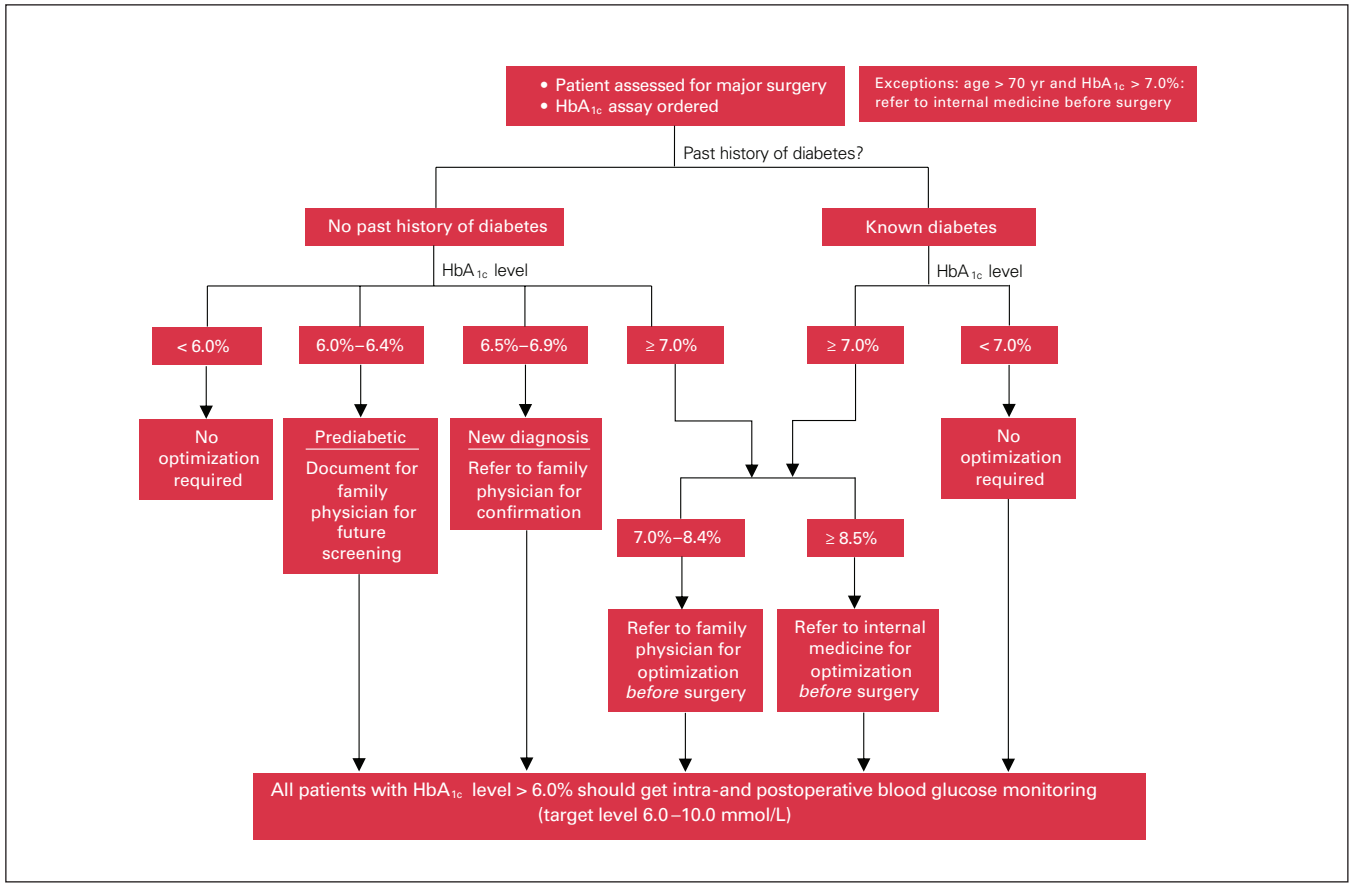


**Fig. 2.** Algorithm for diagnosis and treatment of preoperative hyperglycemia in patients with and without diabetes. $HbA_{1c}$ = glycated hemoglobin.

guidelines summarize the evidence that we used to develop the recommendations in the proposed diagnostic and treatment algorithm for preoperative hyperglycemia (Figure 2).

### *Recommendations*

**1. Perioperative hyperglycemia increases the risk of postoperative complications, and all patients undergoing major surgery should be screened for diabetes.**

In its clinical practice guidelines, Diabetes Canada recommends admission screening with a random blood glucose test for all hospitalized patients owing to a high prevalence of undiagnosed and poorly controlled diabetes.[85] Diabetes Canada and the ADA also recommend measuring the $HbA_{1c}$ level in all patients with diabetes or hyperglycemia if this has not been done in the previous 3 months.[96] In addition, an increased risk of postoperative complications has been well documented in the literature for patients with preoperative hyperglycemia in many different surgical specialties.[97–104]

An elevated $HbA_{1c}$ level (≥ 6.5%) and perioperative hyperglycemia were associated with an increased risk of major complications (Clavien–Dindo grade III–V) in a prospective cohort of 478 patients undergoing abdominal surgery (OR 1.95, 95% CI 1.17–3.24).[97] Analysis of prospectively collected colorectal cancer data showed that diabetes was a risk factor for increased postoperative surgical complications such as surgical site infection (SSI), wound dehiscence, anastomotic leak, enterocutaneous fistula, ileus, hemorrhage, obstruction, urinary retention and ureteric injury (OR 1.44, 95% CI 1.02–2.04) but not mortality.[98] Patients with diabetes who had diabetic complications also had increased 30-day mortality (OR 13.7, 95% CI 3.4–54.7) and length of stay (3.8 d, 95% CI 0.7–7.1) compared to patients without complications. A systematic review showed that patients with diabetes who underwent carotid artery revascularization were at higher risk for perioperative stroke (OR 1.38, 95% CI 1.02–1.88), death (OR 1.94, 95% CI 1.36–2.75) and long-term mortality (OR 1.57, 95% CI 1.22–2.03).[99] In a large retrospective study, elevated $HbA_{1c}$ levels in patients with peripheral vascular disease were associated with an increased risk of amputation and other complications.[100] Amputation was increasingly likely with $HbA_{1c}$ levels of 6.1%–7.0% (HR 1.26, 95% CI 1.15–1.39), 7.1%–8.0% (HR 1.53, 95% CI 1.37–1.7) and greater than 8% (HR 2.05, 95% CI 1.87–2.26). The study also highlighted the increased risk of preoperative hyperglycemia in patients without diabetes compared to patients with diabetes with good control ($HbA_{1c}$ level < 7.0%).

Preoperative hyperglycemia has also been shown to increase the rate of postoperative complications in patients undergoing cardiac surgery. A large retrospective study showed an increased risk of death or major cardiac event with an $HbA_{1c}$ level of 8.1% or higher (8.1%–9.0%: HR 1.17, 95% CI 1.04–1.33; 9.1%–10.0%: HR 1.44, 95% CI 1.22–1.70; > 10.0%: HR 1.50, 95% CI 1.22–1.84).[101] Subramaniam and colleagues[102] conducted a prospective cohort study of patients undergoing coronary artery bypass grafting and found an increase in major adverse events including in-hospital death, myocardial infarction, tamponade, reoperation, SSI, renal failure, pneumonia and stroke in those with an $HbA_{1c}$ level of 6.5% or higher (OR 1.6, 95% CI 1.1–2.3).

There is conflicting evidence in the orthopedic literature with regard to preoperative diabetes and $HbA_{1c}$ levels. In a large NSQIP study, diabetes was found to be an independent predictor of postoperative complications (OR 1.67, 95% CI 2.217–1.253) and longer length of stay (OR 1.878, 95% CI 2.262–1.559).[103] Miller and colleagues[104] reported that an $HbA_{1c}$ level greater than 6.4% was an independent risk factor for reoperation (HR 1.13, 95% CI 1.02–1.29) among patients who underwent spinal operations. However, 2 previous studies showed no difference in rates of postoperative joint infection, revision or DVT in patients with elevated $HbA_{1c}$ levels.[105,106]

Patients with previously undiagnosed diabetes (elevated $HbA_{1c}$ level without a documented history of diabetes) have been shown to be at higher risk for postoperative complications than patients with known diabetes or patients with normal preoperative blood glucose levels.[92,107–109] A recent systematic review showed that patients with undiagnosed diabetes have an increased risk for overall postoperative complications after bariatric (OR 1.16, 95% CI 1.00–1.33), cardiac (OR 1.148, 95% CI 1.003–1.313), colorectal (OR 2.9, 95% CI 1.1–7.9) and vascular (risk ratio [RR] 7.0, 95% CI 2.8–17.2) surgery.[92] Patients with undiagnosed diabetes undergoing cardiac surgery also have an increased risk for 30-day mortality (OR 1.53, 95% CI 1.24–1.91).[110] Using NSQIP data for patients without known diabetes, Wang and colleagues[108] found that those with elevated preoperative random blood glucose levels (5.5–8 mmol/L and 8–10 mmol/L) had significantly higher postoperative infection rates than those with normal random blood glucose levels (9.33% and 10.16% v. 5.62%; $p < 0.001$).

A robust association exists between postoperative hyperglycemia and postoperative morbidity and mortality in general surgery patients, which makes preoperative identification of patients at risk essential for effective perioperative planning. Kwon and colleagues[114] used data from the Surgical Care and Outcomes Assessment Program to assess the outcomes of 11 633 patients who underwent colon, rectal or bariatric surgery and had their blood glucose level monitored postoperatively. Those with hyperglycemia were found to have an increased risk of infection (OR 2.0, 95% CI 1.63–2.44), reoperation (OR 1.8, 95% CI 1.41–2.30) and death (OR 2.71, 95% CI 1.72–4.28). Patients with hyperglycemia who received insulin did not have an increased risk of infection (OR 1.01, 95% CI 0.72–1.42), reoperation (OR 1.29, 95% CI 0.89–1.89) or death (OR 1.21, 95% CI 0.61–2.42) compared to patients with blood glucose levels within the normal range.

A systematic review of papers published from 2001 to 2013 assessing preoperative testing identified a benefit in screening patients undergoing orthopedic and vascular procedures but not other procedures.[115] However, none of the studies in the review reported on changes in clinical management based on preoperative screening. Also, patients with diabetes and patients with undiagnosed diabetes were considered together. This review, therefore, has limited utility but is helpful in identifying some benefit of screening.

Although there is insufficient evidence to show that patients with hyperglycemia (both those with known diabetes and those with previously undiagnosed diabetes) benefit from preoperative treatment, screening identifies patients who would benefit from intra- and postoperative treatment of hyperglycemia, which has been proven to reduce postoperative morbidity and mortality.[95] With routine screening, the effect of treatment can also be studied properly.

**2. Measurement of the $HbA_{1c}$ level is the most appropriate screening test for hyperglycemia.**

Although there is debate regarding the ideal test to diagnose diabetes, an $HbA_{1c}$ test is easier and more convenient for patients than a fasting blood glucose or oral glucose tolerance test, and the result is less affected by day-to-day variability.[85,86] An $HbA_{1c}$ test will also show the level of control over the previous 2–3 months.[87] Care must be taken to ensure that an $HbA_{1c}$ assay that has been standardized by the National Glycohemoglobin Standardization Program to the Diabetes Control and Complications Trial reference is used, as considerable variation may exist between different $HbA_{1c}$ assays.[85,86]

Existing guidelines vary in their recommendations for screening. The Strong for Surgery program (American College of Surgeons) recommends screening all patients without a previous diagnosis of diabetes by means of a fasting blood glucose test on the morning of surgery if their body mass index is greater than 30 or they are older than 45 years. Patients with diabetes who have an $HbA_{1c}$ level greater than 7.0% should be referred for optimization. The National Institute for Health and Care Excellence recommends obtaining an $HbA_{1c}$ level for patients with diabetes but not screening patients with no prior history of diabetes.[116] In their guidelines for primary care physicians evaluating patients preoperatively, Feely and colleagues[117] state that, in patients with known diabetes,

the preoperative $HbA_{1c}$ value is more likely to be useful if results would change perioperative management. Preoperative random glucose measurement could be considered in patients at very high risk for undiagnosed diabetes and in those with signs or symptoms of undiagnosed diabetes.[117]

**3. A preoperative $HbA_{1c}$ level less than 6.0% does not require any further action or preoperative optimization.**

As per Diabetes Canada guidelines, an $HbA_{1c}$ level less than 6.0% is generally considered to be normal and therefore does not require preoperative optimization.[85]

**4. A preoperative $HbA_{1c}$ level of 6.0%–6.9% in a patient with no history of diabetes does not require preoperative optimization. However, it may represent prediabetes or a new diagnosis of diabetes, and the patient should be referred to a family physician, internist or endocrinologist for follow-up and confirmation.**

Patients with a preoperative $HbA_{1c}$ level of 6.0%–6.4% are at increased risk for diabetes (prediabetic). These patients are also at higher risk for postoperative complications and should have their blood glucose monitored while in hospital[100] (see recommendation 8).

Patients with confirmed or suspected diabetes ($HbA_{1c}$ level ≥ 6.5%) are at increased risk for postoperative complications, even if their $HbA_{1c}$ level is within the target range.[97,102,118] After identification of a preoperative $HbA_{1c}$ level of 6.5% or higher, a second confirmation test is required to diagnose diabetes unless clear symptoms are present.[85,86] These patients should be referred to their family physician, an internist or an endocrinologist for confirmation.[85] In addition, they should be referred to a community diabetes education program for ongoing support. They should receive glycemic monitoring intra- and postoperatively, and should be treated as indicated (see recommendation 8).

**5. A preoperative $HbA_{1c}$ level of 7.0%–8.4% requires preoperative optimization, and these patients should be referred to their family physician, an internist or an endocrinologist for optimization to a target blood glucose level of 5–10 mmol/L.**

Patients with suboptimal glycemic control are at increased risk for postoperative complications. The ADA and Diabetes Canada recommend an $HbA_{1c}$ target of less than 7% (blood glucose level < 8.5 mmol/L) for most nonpregnant patients with diabetes.[85,118] Diabetes Canada also recommends a postprandial glycemic target of 5–10 mmol/L for patients with diabetes. It has also been shown that an $HbA_{1c}$ level higher than 8% increases hospital length of stay from 5.2 to 6.7 days ($p = 0.02$),[119] and a recent systematic review and meta-analysis showed a decrease in SSI rates (OR 0.43, 95% CI 0.29–0.64) with an intensive protocol aimed at strict intra- and postoperative blood glucose control (< 8.3 mmol/L), with no increase in rates of death or stroke related to hypoglycemia.[95] Patients with suboptimal glycemic control should receive optimization of their glycemic control regardless of whether or not they are having surgery. They should receive glycemic monitoring intra- and postoperatively, and should be treated as indicated (see recommendation 8).

**6. A preoperative $HbA_{1c}$ level of 8.5% or greater indicates poor glycemic control and requires preoperative optimization, and these patients should be referred to an internist or endocrinologist for preoperative optimization.**

An $HbA_{1c}$ level of 8.5% or greater is substantially above target. Postoperative complication rates have been shown to increase with increasing $HbA_{1c}$ levels.[100,101] Optimization may be expedited and enhanced by the involvement of an internist or endocrinologist, and preoperative involvement may be helpful for postoperative management. These patients should receive glycemic monitoring intra- and postoperatively, and should be treated as indicated (see recommendation 8).

**7. Patients with known diabetes with a preoperative $HbA_{1c}$ level less than 7.0% do not require preoperative optimization.**

Diabetes Canada and the ADA recommend a target $HbA_{1c}$ level of less than 7.0% for most nonpregnant patients with diabetes in order to reduce the risk of microvascular complications.[85,118] Below 7.0%, it is a balance among smaller incremental benefits, polypharmacy and harm from hypoglycemia. These patients should receive glycemic monitoring intra- and postoperatively, and should be treated as indicated (see recommendation 8).

**8. All patients (both with and without diabetes) with a preoperative $HbA_{1c}$ level greater than 6.0% should undergo intra- and postoperative blood glucose monitoring, with a target blood glucose level of 6–10 mmol/L, to reduce the risk of postoperative complications.**

Hyperglycemia increases the risk of postoperative complications. A large NSQIP study of 55 408 patients with diabetes undergoing noncardiac surgery showed an increased risk of postoperative infections (incidence rate ratio 1.22, 95% CI 1.04–1.43).[120] Data from the Surgical Care and Outcomes Assessment Program also confirmed an increased risk of morbidity and mortality for patients with hyperglycemia.[114] There is conflicting evidence regarding intensive versus conventional glucose control postoperatively. A recent systematic review and meta-analysis showed a reduction in SSI rates (OR 0.43, 95% CI 0.29–0.64) with an intensive protocol aimed at stricter intra- and

postoperative blood glucose control (< 8.3 mmol/L), with no increase in mortality or strokes related to hypoglycemia.[95] However, a previous Cochrane review did not show any difference in infectious complications or mortality, but did show an increase in hypoglycemic episodes.[121] Diabetes Canada recommends a target blood glucose level of 6–10 mmol/L for critically ill patients and those undergoing major surgery.[85] To meet this target, it is recommended that a basal bolus insulin regimen be used rather than a correctional sliding scale.[85,96]

### *Preoperative management of diabetic medications*

All patients with diabetes should be assessed in a preadmission clinic to help with the preoperative management of their medications. The ADA suggests holding all oral hypoglycemic agents the morning of surgery and giving 50% of the dosage of NPH insulin, or 60%–80% of the dosage of long-acting analogues or basal pump insulin.[96] Hypoglycemia is a serious preventable condition that patients may experience while they are fasting and are receiving insulin or other diabetic medications, such as sulphonylureas; these patients should be monitored for hypoglycemia and treated if it develops.[96] Sodium–glucose cotransporter-2 inhibitors should be avoided during fasting owing to an association with diabetic ketoacidosis.[96,122]

### *Special considerations*

Diabetes Canada and the ADA recommend personalized $HbA_{1c}$ targets, which may translate to less stringent $HbA_{1c}$ targets for older or frail patients.[85,123] It is important to consider this when such patients are presenting for surgery, as they may have higher $HbA_{1c}$ levels than expected. Regardless, it is still important to assess and treat them for hyperglycemia perioperatively to decrease the risk of associated complications.

### *Conclusion*

Surgical patients with preoperative hyperglycemia are at increased risk for postoperative complications regardless of surgical specialty. There is a lack of evidence regarding screening for hyperglycemia and optimization of preoperative hyperglycemia. In the absence of high-quality prospective studies assessing the benefits of preoperative management of hyperglycemia, it would be appropriate to treat patients undergoing major surgical procedures according to guidelines that address the management of diabetes in the general population. Given the high rate of undiagnosed diabetes and prediabetes in surgical patients, patients undergoing major surgery should be screened so that treatment may be initiated, as there is a clear benefit of proper intra- and postoperative control of hyperglycemia.

## SMOKING

Tobacco smoking remains highly prevalent in North America, and, despite decreased rates in recent decades, it remains the leading cause of preventable disease and death in Canada.[124] In 2016, 16.9% of Canadians aged 13 years or older (roughly 5.2 million people) were reported to be smokers.[125] The prevalence of smoking in clinical populations is even higher (> 20%).[126]

Clinicians may not appreciate the adverse effect of smoking on postsurgical outcomes.[127] For example, a retrospective cohort study of more than 600 000 patients who underwent noncardiac surgery showed that preoperative smoking was associated with a 40% increase in 30-day mortality (OR 1.38, 95% CI 1.11–1.72) and a 70% increase in major morbidity (OR 1.72, 95% CI 1.67–1.78).[128]

Several systematic reviews and meta-analyses have shown that interventions that help patients quit smoking before surgery lead to reductions in adverse surgical outcomes, including wound, pulmonary and overall complications.[129,130] The following clinical practice guideline summarizes the current evidence informing the recommendations within the proposed diagnostic and treatment algorithm for preoperative smoking (Figure 3).

### *Recommendations*

**1. Tobacco smoking is associated with increased adverse postoperative outcomes, and all patients undergoing major surgery should have their smoking status identified and documented at every preoperative clinic visit.**

A retrospective review of 400 000 patients who underwent noncardiac surgery showed that, compared to nonsmokers, smokers had a 29% increase in 30-day mortality (OR 1.29, 95% CI 1.20–1.39) and a 55% increase in 1-year mortality (OR 1.55, 95% CI 1.50–1.61).[131] One-year postoperative mortality decreased significantly for prior smokers who had not smoked in the previous year (OR 1.14, 95% 1.10–1.19).[131]

A meta-analysis of 107 studies published since 2000 showed preoperative smoking to be significantly associated with general morbidity (RR 1.52, 95% CI 1.33–1.74), wound complications (RR 2.15, 95% CI 1.87–2.49), pulmonary complications (RR 1.73, 95% CI 1.35–2.23), neurologic complications (RR 1.38, 95% CI 1.01–1.88) and intensive care unit admission (RR 1.60, 95% CI 1.14–2.25).[130] Smoking is a demonstrated risk factor in most surgical procedures, increasing rates of incisional hernia after laparotomy (OR 3.93, 95% CI 1.82–8.49),[132] spinal fusion nonunion (OR 2.01; $p < 0.02$),[133] disease recurrence (HR 1.25; $p = 0.02$) and metastasis (HR 2.64; $p = 0.03$) after radical prostatectomy,[134] anastamotic leakage after anterior resection for rectal cancer (OR 1.88, 95% CI 1.02–3.46)[135] and fracture after shoulder arthroplasty (HR 3.63; $p = 0.02$).[136] Smoking also leads to increased wound

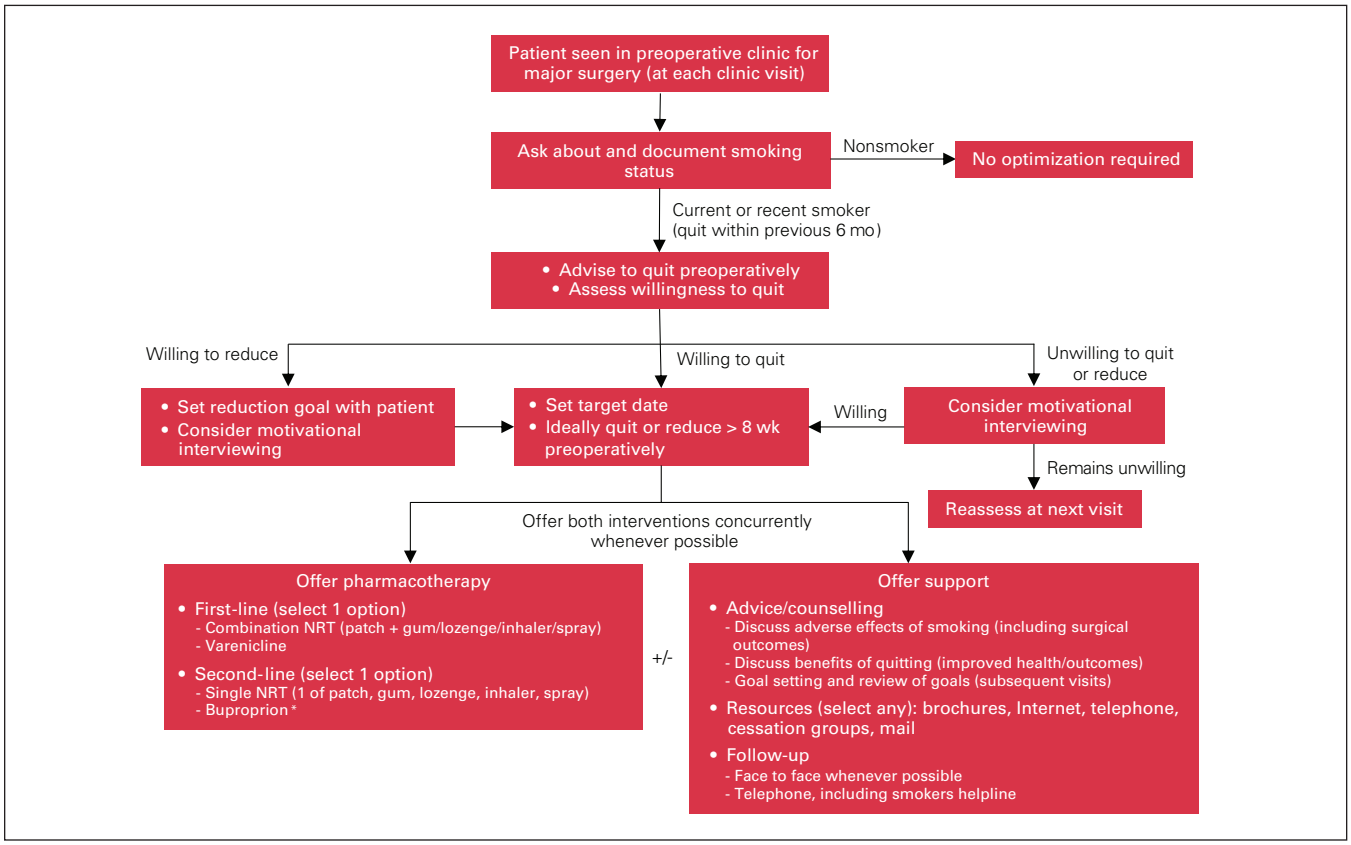


**Fig. 3.** Algorithm for diagnosis and treatment of smoking in patients undergoing major elective surgery. *Use with caution in patients older than 65 years of age. NRT = nicotine replacement therapy.

complication rates after both laparoscopic (OR 1.20; $p$ = 0.02) and open (OR 1.28; $p$ = 0.01) cholecystectomy, and results in a longer average postoperative length of stay, by 2–4 days ($p < 0.001$).[137]

Although roughly 25% of surgical patients are smokers,[128] more than half of patients undergoing elective outpatient procedures report not having been informed about the adverse effects of smoking before surgery.[138] Of 116 consecutive patients surveyed after a surgical clinic appointment at a Canadian tertiary care centre, less than 10% had been asked about smoking status, and none had been asked about quitting or offered any form of intervention.[139] Smoking status should be documented systematically in all patients undergoing surgery. Combining clinician training with a charting system has been shown to increase the rates of assessing tobacco use, setting a quit date, providing materials and arranging for follow-up.[140]

**2. All surgical patients who smoke should be advised to quit smoking preoperatively and have their willingness to quit assessed to guide next steps. Because of the high risk of relapse, those who have quit within the previous 6 months should be treated as active smokers.**

More than 70% of all tobacco smokers report wanting to quit.[140] Half of Canadian smokers try to quit each year,[141] but patient-driven smoking cessation is ineffective: 80%–90% of self-quitters relapse within 3 months of cessation, and less than 5% achieve long-term success.[141] However, patients often view surgery as a "wake-up call" regarding their health and are more likely to be receptive to advice offered by health care professionals, particularly regarding the perioperative risks of smoking, at this time.[142–144] A recent systematic review and meta-analysis suggested that cessation rates almost doubled (from 24.5% to 46.2%; effect size g = 0.56, 95% CI 0.32–0.80) before surgery with proactive, clinician-driven behavioural interventions.[145] The preoperative period is therefore an ideal time to intervene.

All patients who smoke should be advised to quit preoperatively in a clear, strong and personalized way, and have their willingness to quit assessed.[140] It is important to stratify patients by willingness to quit to determine the best management approach (see recommendations 3–5). Those who are willing to quit should set a quit date, and can choose between abrupt cessation or gradual reduction leading up to their quit date, which were shown to be equally effective in a meta-analysis of quit approaches (RR 0.94, 95% CI 0.79–1.13).[146] Among those who are unwilling to quit but willing to reduce the amount smoked per day, the use of pharmacotherapy should be encouraged to assist with smoking reduction.[147] Increased cessation rates have been reported after motivational

interviewing (a patient-centred approach focusing on the "5 Rs" strategy: relevance, risks, rewards, roadblocks and repetition at every visit[140]) among patients who were initially unwilling to quit.[140]

Smoking relapse most frequently occurs early after quitting but can occur as late as months to years later.[148] A Cochrane review of 63 RCTs showed that multiple behavioural techniques used by patients to prevent relapse failed to show any benefit but that success rates may be improved with pharmacotherapy.[149] Given the high relapse rate, we recommend treating patients who have quit within the previous 6 months as active smokers. This provides them with the best available evidence-based cessation treatments to promote sustained abstinence.

**3. A quit date should be set more than 8 weeks preoperatively to achieve the most substantial improvements in postoperative outcomes; however, outcome benefits may still be seen with cessation as late as the day of surgery.**

In a meta-analysis of 25 RCTs and cohort studies (combined $n > 21\,000$), smoking cessation more than 8 weeks before surgery significantly reduced rates of postoperative pulmonary complications compared to active smoking (RR 0.53, 95% CI 0.37–0.76), with rates approaching those among nonsmokers (RR 1.16, 95% CI 0.76–1.77).[150] Cessation 4 weeks preoperatively had a smaller but significant effect on pulmonary complication rates (RR 0.77, 95% CI 0.61–0.96), but the risk remained higher than that among nonsmokers (RR 1.39, 95% CI 1.18–1.65). There was no significant pulmonary benefit to cessation 2–4 weeks or less than 2 weeks preoperatively (RR 1.14, $p = 0.3$; and RR 1.20, $p = 0.1$, respectively).[150]

The same meta-analysis also showed that smoking cessation more than 3–4 weeks preoperatively reduced wound complication rates (RR 0.69, 95% CI 0.56–0.84), with rates approaching those among nonsmokers (RR 1.44, 95% CI 0.97–2.15).[150] A retrospective cohort study of 188 patients with head or neck cancer with flaps showed a similar reduction in wound failure rates among smokers who quit 3–6 weeks (RR 0.17, 95% CI 0.04–0.75) or more than 6 weeks (RR 0.17, 95% CI 0.05–0.60) before surgery.[151]

Two landmark RCTs involving behavioural interventions and nicotine replacement therapy (NRT) showed improved postsurgical outcomes with smoking cessation programs 4 weeks or less before surgery.[152,153] Møller and colleagues[152] found that a program with a target quit date of 4 weeks before surgery led to significant reductions in rates of overall (18% v. 52%; $p < 0.001$) and wound-related (5% v. 31%; $p = 0.001$) complications. Lindström and colleagues[153] reported that a program with a target quit date of 3 weeks before surgery was associated with a significant reduction in any postoperative complication (21% v. 41%; RR 0.51; $p = 0.03$).

A recent observational nested matched case–control study showed benefit to quitting as late as the day of surgery, showing a significant decrease in SSI rates (OR 1.96, 95% CI 1.23–3.13).[154] However, 2 prior studies showed no significant reduction in wound complication rates with cessation less than 3 weeks before surgery.[150,151]

**4. In patients who are unwilling to quit smoking, motivational interviewing techniques can be used to increase motivation to quit, thereby increasing quit rates.**

An RCT involving 616 patients who were unmotivated to quit smoking showed that motivational interviewing based on the US Public Health Service 2008 smoking cessation guideline[140] led to a quit rate of 23% at 6 months and an average reduction of 30% in the amount smoked per day.[155] Motivational interviewing is a specialized skill, and interested clinicians can learn more[140] or consider referral to a specialist. Even patients unwilling to quit should be encouraged to abstain from smoking at least 24 hours before surgery, as this may reduce the occurrence of SSI.[154]

**5. In patients who are unwilling to quit smoking but willing to reduce, clinicians should offer full cessation treatment to support reduction goals.**

In a meta-analysis of RCTs involving smokers who did not intend to quit, smoking-reduction support with pharmacotherapy versus no intervention was found to be beneficial in achieving complete cessation (RR 1.93, 95% CI 1.41–2.64).[147] Of note, the authors used only long-term follow-up (> 6 mo) data, and, to our knowledge, no similar shorter-term data exist. Although the data are limited, pharmacotherapy is likely a major contributor to the success of smoking-reduction plans. Reduction counselling and support alone versus no intervention did not significantly increase abstinence (RR 1.49, 95% CI 0.56–3.93). Both reduction counselling and support with varenicline therapy (RR 2.66, 95% CI 2.10–3.36) and reduction counselling and support with NRT (RR 1.94, 95% CI 1.26–3.00) were far superior to reduction support with placebo.

Although there is currently no good evidence that preoperative smoking reduction without cessation improves surgical outcomes,[152] supporting surgical patients who are interested in smoking reduction preoperatively has no adverse consequences, improves long-term quit rates and may lead to preoperative cessation.[147]

**6. All surgical patients who smoke should be offered the combination of counselling and pharmacotherapy preoperatively. When this is not possible, they should still be offered either intervention individually.**

Both pharmacotherapy and cessation counselling are effective alone[145,156,157] and should be provided even if a patient is not interested in combined therapy. Whenever

possible, patients who are willing to quit should be provided both interventions: a meta-analysis showed that combining therapies has increased efficacy compared to pharmacotherapy (OR 1.4, 95% CI 1.2–1.6) or behavioural therapy (OR 1.7, 95% CI 1.3–2.1) alone.[140]

**7. All surgical patients who smoke should be offered combination nicotine replacement therapy (NRT) preoperatively. Prescribers capable of follow-up may consider varenicline as a first-line agent. Second-line options include single-agent NRT and bupropion.**

Three therapies approved in Canada have been shown to increase smoking cessation rates in the general population: varenicline, NRT and bupropion.[158] Combination NRT (combining daily use of a nicotine patch with a short-acting adjunct [gum, lozenge, inhaler or spray, according to patient preference]) is more effective than NRT patch (OR 1.43, 95% CI 1.08–1.91), NRT gum (OR 1.63, 95% CI 1.21–2.20), or NRT lozenge/inhaler/spray (OR 1.34, 95% CI 1.00–1.80) alone. Varenicline is superior to any single-agent NRT (OR 1.57, 95% CI 1.29–1.91) and to bupropion (OR 1.56, 95% CI 1.26–1.93). Bupropion is less effective than combination NRT (OR 0.68, 95% CI 0.50–0.91).[156] Nicotine replacement therapy options are sold over the counter, whereas both varenicline and bupropion require a prescription.[156]

We recommend combination NRT and varenicline as first-line treatments, as they are the most effective smoking-cessation interventions (Appendix 1), with no significant difference between them in direct comparison (OR 1.06, 95% CI 0.75–1.48).[156] Combination NRT has no absolute contraindications[156] or required follow-up, and was associated with reduced postoperative complication rates in 2 RCTs.[152,153] It can easily be prescribed by surgeons, who can place patient concerns about the cost of patches ($20/wk) and adjuncts ($15–$40/wk) in the context of savings from cigarette purchases[159] and overall health benefits.

Varenicline is the most effective monotherapy for smoking cessation (OR 2.89, 95% CI 2.40–3.48)[156] but has not been as well studied in the perioperative setting as NRT. Wong and colleagues[160] reported that 12 weeks of varenicline therapy initiated 1 week preoperatively significantly increased cessation rates 1 year after surgery (RR 1.45; $p = 0.04$). Given its efficacy, we consider varenicline a first-line treatment.

Bupropion is an atypical antidepressant that has been shown to improve smoking cessation rates versus placebo (OR 1.85, 95% CI 1.63–2.10).[156] It is contraindicated in patients with increased seizure risk. As it has not been well studied in the perioperative setting and is less effective than both combination NRT and varenicline, we consider it a second-line option.

Randomized controlled trials across 140 centres in 16 countries have shown no evidence that any of these 3 therapies are associated with an increased risk of adverse cardiovascular[161] or neuropsychiatric[162] events. A 2012 systematic review showed no clinical evidence of a detrimental effect of NRT on postoperative wound or tissue healing.[163]

**8. All surgical patients who smoke should be given brief counselling on the consequences of smoking and the benefits of smoking cessation preoperatively. When possible, counselling should be face to face, frequent and of sufficient duration, all of which increase cessation rates.**

Physician counselling to quit smoking has been shown to increase the likelihood of short-term abstinence by 30% (OR 1.3, 95% CI 1.1–1.6), and even interventions as brief as 3 minutes can increase cessation rates significantly (OR 1.3, 95% CI 1.01–1.60).[140]

A meta-analysis of 22 studies in patients scheduled to undergo elective surgery showed 6 behaviour-change techniques leading to higher rates of smoking abstinence: provision of information on the consequences of smoking and smoking cessation; facilitation of goal setting; prompt review of cessation goals; regular monitoring by others (e.g., friends or family members); options for additional and later support; and provision of information on withdrawal symptoms.[145] Of these, providing information on the consequences of smoking and smoking cessation was the most significant predictor of quitting ($\beta = 0.69$, $p = 0.01$). Counselling interventions may be delivered (in order of most to least effective) face to face, by telephone, over the Internet[164] or in print. Higher cessation rates have been shown with increased duration ($\beta = 0.01$, $p = 0.02$) and frequency ($\beta = 0.22$, $p = 0.002$) of intervention sessions,[145] which is reflected in the US and Canadian guidelines.[140,165]

Several other techniques have been attempted in perioperative RCTs, without evidence of increased preoperative cessation rates. These include a decision aid with laminated graphics to facilitate discussion,[166] a behavioral tapering regimen (scheduled reduced smoking) via handheld computer[167] and planned checks of carbon monoxide levels on the day of surgery.[168]

**9. All surgical patients who smoke should be offered clinical follow-up.**

Offering follow-up provides cessation support after the initial intervention, and follow-up interventions with increased frequency are more effective.[140] Lindström and colleagues[153] reported that a weekly face-to-face or telephone intervention of smoking cessation therapy with individual counselling and NRT delivered by a trained nurse starting 4 weeks preoperatively led to both increased perioperative cessation rates (39.6% v. 1.9%) and decreased postoperative complication rates (21% v. 41%, $p = 0.03$) compared to standard care.

A meta-analysis of RCTs or quasi-randomised controlled trials in which telephone counselling was offered to smokers or recent quitters to assist smoking cessation

showed an increase in smoking cessation rates when used as the primary intervention (RR 1.34, 95% CI 1.22–1.46), when following a face-to-face intervention (RR 1.41, 95% CI 1.20–1.66) and when used as an adjunct to NRT or varenicline (RR 1.14, 95% CI 1.03–1.27).[169] Having 3 or more follow-up telephone calls showed additional benefit (RR 1.32, 95% CI 1.23–1.42). In busy surgical clinics, repeat preoperative visits and follow-up with specialized nurses may not always be feasible or cost-effective. Lee and colleagues[170] conducted an RCT in which patients seen at least 3 weeks preoperatively received either no specific smoking-cessation intervention, or an intervention consisting of brief counselling by the preadmission nurse, brochures on smoking cessation, referral to a smokers helpline (available at no cost in all Canadian provinces) and a free 6-week supply of NRT. Significantly reduced smoking rates were observed in the intervention group at the time of surgery (14.3% v. 3.6%; $p = 0.03$).

### *Conclusion*

Smoking is the most important risk factor for postoperative complications and should be routinely identified, documented and treated preoperatively according to the patient's willingness to quit. By targeting a quit date of at least 8 weeks before surgery and offering a combination of brief counselling with pharmacotherapy and follow-up, clinicians can reduce perioperative smoking rates and postoperative complication rates. Given the minimal time and resources required, along with the substantial benefits of cessation, a preoperative smoking-cessation program should be offered in all surgical clinics.

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## References

1. Stern M. Resection of obstructions at the vesical orifice. *JAMA* 1926; 87:1726.
2. Mühe E. Laparoscopic cholecystectomy — late results [article in German]. *Langenbecks Arch Chir Suppl Kongressbd* 1991;416-23.
3. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg* 1991;5: 491-9.
4. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;1:1479-82.
5. Fearon KCH, Ljungqvist O, Von Meyenfeldt M, et al. Enhanced Recovery After Surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr* 2005;24:466-77.
6. Yang R, Tao W, Chen YY, et al. Enhanced Recovery After Surgery programs versus traditional perioperative care in laparoscopic hepatectomy: a meta-analysis. *Int J Surg* 2016;36:274-82.
7. Ni X, Jia D, Chen Y, et al. Is the Enhanced Recovery After Surgery (ERAS) program effective and safe in laparoscopic colorectal cancer Surgery? A meta-analysis of randomized controlled trials. *J Gastrointest Surg* 2019;23:1502-12.
8. Guyatt GH, Oxman AD, Vist GE, et al.; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6.
9. Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet* 2011;378:1396-407.
10. Sim YE, Wee HE, Ang AL, et al. Prevalence of preoperative anemia, abnormal mean corpuscular volume and red cell distribution width among surgical patients in Singapore, and their influence on one year mortality. *PLoS One* 2017;12:e0182543.
11. Leichtle SW, Mouawad NJ, Lampman R, et al. Does preoperative anemia adversely affect colon and rectal surgery outcomes? *J Am Coll Surg* 2011;212:187-94.
12. Aydinli HH, Benlice C, Ozuner G, et al. Risk factors associated with postoperative morbidity in over 500 colovesical fistula patients undergoing colorectal surgery: a retrospective cohort study from ACS-NSQIP database. *Int J Colorectal Dis* 2017;32: 469-74.
13. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. *Anesthesiology* 2010;113: 482-95.
14. Abdullah HR, Sim YE, Hao Y, et al. Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty in Singapore: a single-centre retrospective study. *BMJ Open* 2017;7:e016403.
15. Frew N, Alexander D, Hood J, et al. Impact of a blood management protocol on transfusion rates and outcomes following total hip and knee arthroplasty. *Ann R Coll Surg Engl* 2016;98:380-6.
16. Cui HW, Turney BW, Griffiths J. The preoperative assessment and optimization of patients undergoing major urological surgery. *Curr Urol Rep* 2017;18:54.
17. Haemoglobin concentrations for the diagnosis of anemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization; 2011.
18. *The global prevalence of anaemia in 2011*. Geneva: World Health Organization; 2015.
19. *Worldwide prevalence of anaemia 1993–2005: WHO Global Database on Anaemia*. Geneva: World Health Organization; 2008.
20. Hollowell JG, van Assendelft OW, Gunter EW, et al. Hematological and iron-related analytes — reference data for persons aged 1 year and over: United States, 1988–94. *Vital Health Stat 11* 2005;(247):1-156.

21. Muñoz M, Laso-Morales MJ, Gómez-Ramírez S, et al. Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. *Anaesthesia* 2017;72: 826-34.
22. Edna TH, Karlsen V, Jullumstrø E, et al. Prevalence of anaemia at diagnosis of colorectal cancer: assessment of associated risk factors. *Hepatogastroenterology* 2012;59:713-6.
23. Park SH, Lee J, Lee SH, et al. Anemia is the strongest prognostic factor for outcomes of 5-fluorouracil-based first-line chemotherapy in patients with advanced gastric cancer. *Cancer Chemother Pharmacol* 2006;57:91-6.
24. Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. *Am J Hematol* 2014;89:203-12.
25. Andrès E, Serraj K, Federici L, et al. Anemia in elderly patients: new insight into an old disorder. *Geriatr Gerontol Int* 2013;13:519-27.
26. Muñoz M, Gómez-Ramírez S, Cuenca J, et al. Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: a pooled analysis of observational data from 2547 patients. *Transfusion* 2014;54:289-99.
27. Heschl M, Gombotz H, Haslinger-Eisterer B, et al. The efficacy of pre-operative preparation with intravenous iron and/or erythropoietin in anaemic patients undergoing orthopaedic surgery. *Eur J Anaesthesiol* 2018;35:289-97.
28. Theusinger OM, Kind SL, Seifert B, et al. Patient blood management in orthopaedic surgery: a four-year follow-up of transfusion requirements and blood loss from 2008 to 2011 at the Balgrist University Hospital in Zurich, Switzerland. *Blood Transfus* 2014;12:195-203.
29. Beattie WS, Karkouti K, Wijeysundera DN, et al. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. *Anesthesiology* 2009;110:574-81.
30. Bodewes TCF, Pothof AB, Darling JD, et al. Preoperative anemia associated with adverse outcomes after infrainguinal bypass surgery in patients with chronic limb-threatening ischemia. *J Vasc Surg* 2017; 66:1775-1785.e2.
31. Gorla R, Tsagakis K, Horacek M, et al. Impact of preoperative anemia and postoperative hemoglobin drop on the incidence of acute kidney injury and in-hospital mortality in patients with type B acute aortic syndromes undergoing thoracic endovascular aortic repair. *Vasc Endovascular Surg* 2017;51:131-8.
32. Dix B, Grant-McDonald L, Catanzariti A, et al. Preoperative anemia in hindfoot and ankle arthrodesis. *Foot Ankle Spec* 2017;10:109-15.
33. Chang CC, Sun JT, Chen JY, et al. Impact of peri-operative anemia and blood transfusions in patients with gastric cancer receiving gastrectomy. *Asian Pac J Cancer Prev* 2016;17:1427-31.
34. Soria F, de Martino M, Leitner CV, et al. Perioperative allogenic blood transfusion in renal cell carcinoma: risk factors and effect on long-term outcomes. *Clin Genitourin Cancer* 2017;15:e421-7.
35. Benoist S, Panis Y, Pannegeon V, et al. Predictive factors for perioperative blood transfusions in rectal resection for cancer: a multivariate analysis of a group of 212 patients. *Surgery* 2001;129:433-9.
36. Abu-Ghanem Y, Mahajna H, Ghinea R, et al. Predictive factors for perioperative blood transfusions in laparoscopic colorectal surgery. *Int J Colorectal Dis* 2014;29:723-8.
37. Chen C, Hu L, Li X, et al. Preoperative anemia as a simple prognostic factor in patients with urinary bladder cancer. *Med Sci Monit* 2017; 23:3528-35.
38. Berardi R, Braconi C, Mantello G, et al. Anemia may influence the outcome of patients undergoing neo-adjuvant treatment of rectal cancer. *Ann Oncol* 2006;17:1661-4.
39. Szkandera J, Gerger A, Liegl-Atzwanger B, et al. Pre-treatment anemia is a poor prognostic factor in soft tissue sarcoma patients. *PLoS One* 2014;9:e107297.
40. Rink M, Sharifi N, Fritsche HM, et al. Impact of preoperative anemia on oncologic outcomes of upper tract urothelial carcinoma treated with radical nephroureterectomy. *J Urol* 2014;191: 316-22.
41. Shen JG, Cheong JH, Hyung WJ, et al. Pretreatment anemia is associated with poorer survival in patients with stage I and II gastric cancer. *J Surg Oncol* 2005;91:126-30.
42. Kulik U, Schrem H, Bektas H, et al. Prognostic relevance of hematological profile before resection for colorectal liver metastases. *J Surg Res* 2016;206:498-506.
43. Celik O, Akand M, Keskin MZ, et al. Predictive effect of preoperative anemia on long-term survival outcomes with non-muscle invasive bladder cancer. *Asian Pac J Cancer Prev* 2016;17:1755-8.
44. Talukder Y, Stillwell AP, Siu SK, et al. Comparing survival and recurrence in curative stage I to III colorectal cancer in transfused and nontransfused patients. *Int Surg* 2014;99:8-16.
45. *Nutritional anaemias: report of a WHO scientific group*. World Health Organization Technical Report series no. 405. Geneva: World Health Organization; 1968.
46. DeMaeyer E. *Preventing and controlling iron deficiency anaemia through primary health care: a guide for health administrators and programme managers*. Geneva: World Health Organization; 1989.
47. *Assessing the iron status of populations*. Geneva: World Health Organization; 2004.
48. Wong CJ, Vandervoort MK, Vandervoort SL, et al. A cluster-randomized controlled trial of a blood conservation algorithm in patients undergoing total hip joint arthroplasty. *Transfusion* 2007;47:832-41.
49. Wu WC, Schifftner TL, Henderson WG, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA* 2007;297:2481-8.
50. Ng O, Keeler BD, Mishra A, et al. Iron therapy for pre-operative anaemia. *Cochrane Database Syst Rev* 2019;(12):CD011588.
51. Muñoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia* 2017;72:233-47.
52. Bisbe E, Basora M, Colomina MJ, et al. Peri-operative treatment of anaemia in major orthopaedic surgery: a practical approach from Spain. *Blood Transfus* 2017;15:296-306.
53. Guyatt GH, Oxman AD, Ali M, et al. Laboratory diagnosis of iron-deficiency anemia: an overview. *J Gen Intern Med* 1992;7:145-53.
54. Stacy DL, Han P. Serum ferritin measurement and the degree of agreement using four techniques. *Am J Clin Pathol* 1992;98:511-5.
55. Muñoz M, García-Erce JA, Remacha ÁF. Disorders of iron metabolism. Part II: iron deficiency and iron overload. *J Clin Pathol* 2011;64:287-96.
56. Camaschella C. Iron-deficiency anemia. *N Engl J Med* 2015;372: 1832-43.
57. Mast AE, Blinder MA, Gronowski AM, et al. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem* 1998;44:45-51.
58. Cook JD. Diagnosis and management of iron-deficiency anaemia. *Best Pract Res Clin Haematol* 2005;18:319-32.
59. Pratt JJ, Khan KS. Non-anaemic iron deficiency — a disease looking for recognition of diagnosis: a systematic review. *Eur J Haematol* 2016;96:618-28.
60. Tolkien Z, Stecher L, Mander AP, et al. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS One* 2015;10:e0117383.
61. Coenen JL, van Dieijen-Visser MP, van Pelt J, et al. Measurements of serum ferritin used to predict concentrations of iron in bone marrow in anemia of chronic disease. *Clin Chem* 1991;37:560-3.
62. Joosten E. Iron deficiency anemia in older adults: a review. *Geriatr Gerontol Int* 2018;18:373-9.
63. Rimon E, Kagansky N, Kagansky M, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med* 2005;118:1142-7.
64. Schröder O, Mickisch O, Seidler U, et al. Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease — a randomized, controlled, open-label, multicenter study. *Am J Gastroenterol* 2005; 100:2503-9.

65. Lidder PG, Sanders G, Whitehead E, et al. Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery — a prospective, randomised, controlled trial. *Ann R Coll Surg Engl* 2007; 89:418-21.
66. Quinn M, Drummond RJ, Ross F, et al. Short course pre-operative ferrous sulphate supplementation — Is it worthwhile in patients with colorectal cancer? *Ann R Coll Surg Engl* 2010;92:569-72.
67. Meybohm P, Froessler B, Goodnough LT, et al. "Simplified International Recommendations for the Implementation of Patient Blood Management" (SIR4PBM). *Perioper Med (Lond)* 2017;6:5.
68. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood* 2015;126:1981-9.
69. Muñoz M, Gómez-Ramírez S, Bhandari S. The safety of available treatment options for iron-deficiency anemia. *Expert Opin Drug Saf* 2018;17:149-59.
70. Kim YH, Chung HH, Kang SB, et al. Safety and usefulness of intravenous iron sucrose in the management of preoperative anemia in patients with menorrhagia: a phase IV, open-label, prospective, randomized study. *Acta Haematol* 2009;121:37-41.
71. Calleja JL, Delgado S, del Val A, et al. Ferric carboxymaltose reduces transfusions and hospital stay in patients with colon cancer and anemia. *Int J Colorectal Dis* 2016;31:543-51.
72. Keeler BD, Simpson JA, Ng O, et al. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. *Br J Surg* 2017;104:214-21.
73. Lin DM, Lin ES, Tran MH. Efficacy and safety of erythropoietin and intravenous iron in perioperative blood management: a systematic review. *Transfus Med Rev* 2013;27:221-34.
74. Froessler B, Palm P, Weber I, et al. The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: a randomized controlled trial. *Ann Surg* 2016;264:41-6.
75. Wilson MJ, Dekker JW, Bruns E, et al. Short-term effect of preoperative intravenous iron therapy in colorectal cancer patients with anemia: results of a cohort study. *Transfusion* 2018;58:795-803.
76. Na HS, Shin SY, Hwang JY, et al. Effects of intravenous iron combined with low-dose recombinant human erythropoietin on transfusion requirements in iron-deficient patients undergoing bilateral total knee replacement arthroplasty. *Transfusion* 2011;51: 118-24.
77. Feagan BG, Wong CJ, Kirkley A, et al. Erythropoietin with iron supplementation to prevent allogeneic blood transfusion in total hip joint arthroplasty. A randomized, controlled trial. *Ann Intern Med* 2000;133:845-54.
78. Yoo YC, Shim JK, Kim JC, et al. Effect of single recombinant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. *Anesthesiology* 2011;115:929-37.
79. Basora M, Colomina MJ, Tio M, et al. Optimizing preoperative haemoglobin in major orthopaedic surgery using intravenous iron with or without erythropoietin. An epidemiologic study. *Rev Esp Anestesiol Reanim* 2015;62:313-21.
80. Stowell CP, Jones SC, Enny C, et al. An open-label, randomized, parallel-group study of perioperative epoetin alfa versus standard of care for blood conservation in major elective spinal surgery: safety analysis. *Spine* 2009;34:2479-85.
81. Mikhael J, Melosky B, Cripps C, et al. Canadian supportive care recommendations for the management of anemia in patients with cancer. *Curr Oncol* 2007;14:209-17.
82. Nielsen OH, Ainsworth M, Coskun M, et al. Management of iron-deficiency anemia in inflammatory bowel disease: a systematic review. *Medicine (Baltimore)* 2015;94:e963.
83. Harwood L, Wazny L, Wilson JA. Recent changes in anemia management: the Kidney Disease Improving Global Outcomes (KDIGO) Anemia Guideline versus the Canadian Society of Nephrology (CSN). *CANNT J* 2014;24:12-9.
84. Frank SM, Thakkar RN, Podlasek SJ, et al. Implementing a health system-wide patient blood management program with a clinical community approach. *Anesthesiology* 2017;127:754-64.
85. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2018;42 (Suppl 1):S1-325.
86. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes — 2018*. *Diabetes Care* 2018;41(Suppl 1):S13-27.
87. Pottie K, Jaramillo A, Lewin G, et al. Recommendations on screening for type 2 diabetes in adults. *CMAJ* 2012;184:1687-96.
88. Siu AL; U.S. Preventive Services Task Force. Screening for abnormal blood glucose and type 2 diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2015; 163;861-8.
89. National Diabetes Statistics Report, 2017: estimates of diabetes and its burden in the United States. Atlanta: Centers for Disease Control and Prevention; 2017.
90. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care* 2010;33:1783-8.
91. Membership of the Working Party; Barker P, Creasey PE, Dhatariya K, et al. Peri-operative management of the surgical patient with diabetes 2015: Association of Anaesthetists of Great Britain and Ireland. *Anaesthesia* 2015;70:1427-40.
92. Karimian N, Niculiseanu P, Amar-Zifkin A, et al. Association of elevated pre-operative hemoglobin $A_{1c}$ and post-operative complications in non-diabetic patients: a systematic review. *World J Surg* 2018;42:61-72.
93. Dhatariya K, Levy N, Kilvert A, et al.; Joint British Diabetes Societies. NHS Diabetes guideline for the perioperative management of the adult patient with diabetes. *Diabet Med* 2012;29:420-33.
94. Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev* 2013;93:137-88.
95. de Vries FEE, Gans SL, Solomkin JS, et al. Meta-analysis of lower perioperative blood glucose target levels for reduction of surgical-site infection. *Br J Surg* 2017;104:e95-105.
96. American Diabetes Association. 14. Diabetes care in the hospital: *Standards of Medical Care in Diabetes — 2018*. *Diabetes Care* 2018;41 (Suppl 1):S144-51.
97. Goodenough CJ, Liang MK, Nguyen MT, et al. Preoperative glycosylated hemoglobin and postoperative glucose together predict major complications after abdominal surgery. *J Am Coll Surg* 2015;221:854-61.e1.
98. Yap R, Wilkins S, Staples M, et al. The effect of diabetes on the perioperative outcomes of colorectal cancer surgery patients. *PLoS One* 2016;11:e0167271.
99. Hussain MA, Bin-Ayeed SA, Saeed OQ, et al. Impact of diabetes on carotid artery revascularization. *J Vasc Surg* 2016;63:1099-107.e4.
100. Arya S, Binney ZO, Khakharia A, et al. High hemoglobin $A_{1c}$ associated with increased adverse limb events in peripheral arterial disease patients undergoing revascularization. *J Vasc Surg* 2018;67:217-28.e1.
101. Kuhl J, Sartipy U, Eliasson B, et al. Relationship between preoperative hemoglobin $A_{1c}$ levels and long-term mortality after coronary artery bypass grafting in patients with type 2 diabetes mellitus. *Int J Cardiol* 2016;202:291-6.
102. Subramaniam B, Lerner A, Novack V, et al. Increased glycemic variability in patients with elevated preoperative $HbA_{1c}$ predicts adverse outcomes following coronary artery bypass grafting surgery. *Anesth Analg* 2014;118:277-87.
103. Worley N, Buza J, Jalai CM, et al. Diabetes as an independent predictor for extended length of hospital stay and increased adverse post-operative events in patients treated surgically for cervical spondylotic myelopathy. *Int J Spine Surg* 2017;11:10.
104. Miller JA, Webb MR, Benzel EC, et al. Association between hemoglobin $A_{1c}$ and reoperation following spine surgery. *Neurosurgery* 2016;63(Suppl 1):193.

105. Maradit Kremers H, Lewallen LW, Mabry TM, et al. Diabetes mellitus, hyperglycemia, hemoglobin $A_{1c}$ and the risk of prosthetic joint infections in total hip and knee arthroplasty. *J Arthroplasty* 2015;30: 439-43.
106. Adams AL, Paxton EW, Wang JQ, et al. Surgical outcomes of total knee replacement according to diabetes status and glycemic control, 2001 to 2009. *J Bone Joint Surg* 2013;95:481-7.
107. Kotagal M, Symons RG, Hirsch IB, et al. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. *Ann Surg* 2015;261:97-103.
108. Wang R, Panizales MT, Hudson MS, et al. Preoperative glucose as a screening tool in patients without diabetes. *J Surg Res* 2014;186: 371-8.
109. Abdelmalak BB, Knittel J, Abdelmalak JB, et al. Preoperative blood glucose concentrations and postoperative outcomes after elective noncardiac surgery: an observational study. *Br J Anaesth* 2014;112:79-88.
110. Hudson CCC, Welsby IJ, Phillips-Bute B, et al. Glycosylated hemoglobin levels and outcome in non-diabetic cardiac surgery patients. *Can J Anaesth* 2010;57:565-72.
111. Stenberg E, Szabo E, Näslund I; Scandinavian Obesity Surgery Registry Study Group. Is glycosylated hemoglobin $A_{1c}$ associated with increased risk for severe early postoperative complications in nondiabetics after laparoscopic gastric bypass? *Surg Obes Relat Dis* 2014;10:801-5.
112. Gustafsson UO, Thorell A, Soop M, et al. Haemoglobin $A_{1c}$ as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery. *Br J Surg* 2009;96:1358-64.
113. O'Sullivan CJ, Hynes N, Mahendran B, et al. Haemoglobin $A_{1c}$ ($HbA_{1c}$) in non-diabetic and diabetic vascular patients. Is $HbA_{1c}$ an independent risk factor and predictor of adverse outcome? *Eur J Vasc Endovasc Surg* 2006;32:188-97.
114. Kwon S, Thompson R, Dellinger P, et al. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. *Ann Surg* 2013;257:8-14.
115. Bock M, Johansson T, Fritsch G, et al. The impact of preoperative testing for blood glucose concentration and haemoglobin $A_{1c}$ on mortality, changes in management and complications in noncardiac elective surgery. *Eur J Anaesthesiol* 2015;32:152-9.
116. Glycated haemoglobin ($HbA_{1c}$) test. London (UK): National Guideline Centre; 2016.
117. Feely MA, Collins CS, Daniels PR, et al. Preoperative testing before noncardiac surgery: guidelines and recommendations. *Am Fam Physician* 2013;87:414-8.
118. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes — 2018*. *Diabetes Care* 2018;41:S55-64.
119. Underwood P, Askari R, Hurwitz S, et al. Preoperative $A_{1c}$ and clinical outcomes in patients with diabetes undergoing major noncardiac surgical procedures. *Diabetes Care* 2014;37:611-6.
120. King JT, Goulet JL, Perkal MF, et al. Glycemic control and infections in patients with diabetes undergoing noncardiac surgery. *Ann Surg* 2011;253:158-65.
121. Buchleitner AM, Martínez-Alonso M, Hernández M, et al. Perioperative glycaemic control for diabetic patients undergoing surgery. *Cochrane Database Syst Rev* 2012;(9)CD007315.
122. Umpierrez G, Korytkowski M. Diabetic emergencies — ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nat Rev Endocrinol* 2016;12:222-32.
123. American Diabetes Association. 11. Older adults: *Standards of Medical Care in Diabetes — 2018*. *Diabetes Care* 2018;41(Suppl 1):S119-25.
124. Janz T. Current smoking trends. Canada. Cat no 82-624-X. Available: https://www150.statcan.gc.ca/n1/pub/82-624-x/2012001/article/11676-eng.htm (accessed 2019 July 10).
125. Smoking, 2017. *Health Fact Sheets* ser. Statistics Canada; 2018. Cat no 82-625-X. Available: https://www150.statcan.gc.ca/n1/en/pub/82-625-x/2018001/article/54974-eng.pdf?st=oBSbLpyN (accessed 2019 July 10).
126. Pipe AL, Eisenberg MJ, Gupta A, et al. Smoking cessation and the cardiovascular specialist: Canadian Cardiovascular Society position paper. *Can J Cardiol* 2011;27:132-7.
127. Owen D, Bicknell C, Hilton C, et al. Preoperative smoking cessation: a questionnaire study. *Int J Clin Pract* 2007;61:2002-4.
128. Turan A, Mascha EJ, Roberman D, et al. Smoking and perioperative outcomes. *Anesthesiology* 2011;114:837-46.
129. Thomsen T, Villebro N, Møller AM. Interventions for preoperative smoking cessation. *Cochrane Database Syst Rev* 2014;2014:(3) CD002294.
130. Grønkjær M, Eliasen M, Skov-Ettrup LS, et al. Preoperative smoking status and postoperative complications: a systematic review and meta-analysis. *Ann Surg* 2014;259:52-71.
131. Hawn MT, Houston TK, Campagna EJ, et al. The attributable risk of smoking on surgical complications. *Ann Surg* 2011;254:914-20.
132. Sørensen LT, Hemmingsen UB, Kirkeby LT, et al. Smoking is a risk factor for incisional hernia. *Arch Surg* 2005;140:119-23.
133. Andersen T, Christensen FB, Laursen M, et al. Smoking as a predictor of negative outcome in lumbar spinal fusion. *Spine* 2001;26: 2623-8.
134. Moreira DM, Aronson WJ, Terris MK, et al. Cigarette smoking is associated with an increased risk of biochemical disease recurrence, metastasis, castration-resistant prostate cancer, and mortality after radical prostatectomy: results from the SEARCH database. *Cancer* 2014;120:197-204.
135. Bertelsen CA, Andreasen AH, Jørgensen T, et al. Anastomotic leakage after anterior resection for rectal cancer: risk factors. *Colorectal Dis* 2010;12:37-43.
136. Hatta T, Werthel JD, Wagner ER, et al. Effect of smoking on complications following primary shoulder arthroplasty. *J Shoulder Elbow Surg* 2017;26:1-6.
137. Selvarajah S, Ahmed AA, Schneider EB, et al. Cholecystectomy and wound complications: smoking worsens risk. *J Surg Res* 2014;192:41-9.
138. Shannon-Cain J, Webster SF, Cain BS. Prevalence of and reasons for preoperative tobacco use. *AANA J* 2002;70:33-40.
139. Sadek J, Moloo H, Belanger P, et al. Implementation of a systematic tobacco treatment protocol in a surgical outpatient setting: a feasibility study. *Can J Surg* 2021;64:E51-8.
140. Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med* 2008;35:158-76.
141. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 2004;99:29-38.
142. Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. *Anesthesiology* 2010;112:102-7.
143. Bottorff JL, Seaton CL, Lamont S. Patients' awareness of the surgical risks of smoking: implications for supporting smoking cessation. *Can Fam Physician* 2015;61:e562-9.
144. Webb AR, Robertson N, Sparrow M. Smokers know little of their increased surgical risks and may quit on surgical advice. *ANZ J Surg* 2013;83:753-7.
145. Prestwich A, Moore S, Kotze A, et al. How can smoking cessation be induced before surgery? A systematic review and meta-analysis of behavior change techniques and other intervention characteristics. *Front Psychol* 2017;8:915.
146. Lindson N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. *Cochrane Database Syst Rev* 2010;(3) CD008033.
147. Wu L, Sun S, He Y, et al. Effect of smoking reduction therapy on smoking cessation for smokers without an intention to quit: an updated systematic review and meta-analysis of randomized controlled trials. *Int J Environ Res Public Health* 2015;12:10235-53.
148. Herd N, Borland R. The natural history of quitting smoking: findings from the International Tobacco Control (ITC) four country survey. *Addiction* 2009;104:2075-87.

149. Hajek P, Stead LF, West R, et al. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev* 2009;(1): CD003999.
150. Wong J, Lam DP, Abrishami A, et al. Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. *Can J Anaesth* 2012;59:268-79.
151. Kuri M, Nakagawa M, Tanaka H, et al. Determination of the duration of preoperative smoking cessation to improve wound healing after head and neck surgery. *Anesthesiology* 2005;102:892-6.
152. Møller AM, Villebro N, Pedersen T, et al. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet* 2002;359:114-7.
153. Lindström D, Sadr Azodi O, Wladis A, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: a randomized trial. *Ann Surg* 2008;248:739-45.
154. Nolan MB, Martin DP, Thompson R, et al. Association between smoking status, preoperative exhaled carbon monoxide levels, and postoperative surgical site infection in patients undergoing elective surgery. *JAMA Surg* 2017;152:476-83.
155. Carpenter MJ, Hughes JR, Solomon LJ, et al. Both smoking reduction with nicotine replacement therapy and motivational advice increase future cessation among smokers unmotivated to quit. *J Consult Clin Psychol* 2004;72:371-81.
156. Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* 2013;(5):CD009329.
157. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012;(11):CD000146.
158. Reid RD, Pritchard G, Walker K, et al. Managing smoking cessation. *CMAJ* 2016;188:E484-92.
159. Mullen KA, Coyle D, Manuel D, et al. Econonic evaluation of a hospital-initiated intervention for smokers with chronic disease, in Ontario, Canada. *Tob Control* 2015;24:489-96.
160. Wong J, Abrishami A, Yang Y, et al. A perioperative smoking cessation intervention with varenicline: a double-blind, randomized, placebo-controlled trial. *Anesthesiology* 2012;117:755-64.
161. Benowitz NL, Pipe A, West R, et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. *JAMA Intern Med* 2018;178:622-31.
162. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;387:2507-20.
163. Sørensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann Surg* 2012;255:1069-79.
164. Taylor GM, Dalili M, Semwal M, et al. Internet-based interventions for smoking cessation. *Cochrane Database Syst Rev* 2017;(9):CD007078.
165. *Canadian smoking cessation clinical practice guideline*. Toronto: Canadian Action Network for the Advancement, Dissemination, and Adoption of Practice-informed Tobacco Treatment (CAN-ADAPTT), Centre for Addiction and Mental Health; 2011.
166. Warner DO, LeBlanc A, Kadimpati S, et al. Decision aid for cigarette smokers scheduled for elective surgery. *Anesthesiology* 2015;123: 18-28.
167. Ostroff JS, Burkhalter JE, Cinciripini PM, et al. Randomized trial of a presurgical scheduled reduced smoking intervention for patients newly diagnosed with cancer. *Health Psychol* 2014;33:737-47.
168. Shi Y, Ehlers S, Hinds R, et al. Monitoring of exhaled carbon monoxide to promote preoperative smoking abstinence. *Health Psychol* 2013;32:714-7.
169. Stead LF, Hartmann-Boyce J, Perera R, et al. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev* 2013;(8):CD002850.
170. Lee SM, Landry J, Jones PM, et al. The effectiveness of a perioperative smoking cessation program: a randomized clinical trial. *Anesth Analg* 2013;117:605-13.