

Clinical Practice Updates

Canadian Cardiovascular Society and National Advisory Committee on Blood and Blood Products Joint Statement on Blood Utilization and Transfusion for Patients With Acute Coronary Syndromes

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ABSTRACT

Although the evidence base broadly recommends a restrictive red blood cell (RBC) transfusion strategy for anemic patients, its appropriateness for patients with anemia and acute coronary syndromes is not definitive. The publication of the MINT trial has challenged the value of a restrictive transfusion strategy; our panel sought to provide an overview of the evidence and a data-informed expert opinion on the best practices for these patients. Four primary trials, including REALITY and MINT, individually showed no significant differences in their primary outcomes. However, published meta-analyses suggest liberal transfusion strategies might benefit patients. Our expert opinion in the joint statement is to consider patient clinical characteristics and systems factors when choosing an RBC transfusion threshold for patients with acute coronary syndromes and anemia. It is reasonable to consider a liberal RBC transfusion strategy, acknowledging uncertainty across patients, where a target hemoglobin of > 90 g/L might be

RÉSUMÉ

Si les données probantes recommandent largement une stratégie de transfusion de globules rouges restrictive chez les patients anémiques, sa pertinence chez les patients qui présentent une anémie et un syndrome coronarien aigu (SCA) n'est pas établie de façon définitive. La publication des résultats de l'essai MINT a remis en question la valeur de la stratégie de transfusion restrictive. Notre groupe d'experts a cherché à fournir un aperçu des données probantes et à formuler des opinions fondées sur les données quant aux meilleures pratiques chez ces patients. Quatre essais principaux, dont les essais REALITY et MINT, pris séparément, n'ont pas observé de différences significatives en ce qui a trait aux principaux paramètres d'évaluation. Toutefois, selon les données publiées de méta-analyses, les stratégies de transfusion libérales pourraient être avantageuses pour les patients. L'opinion que nous émettons en tant qu'experts dans cette déclaration commune est de prendre en considération à la fois les caractéristiques

Keywords: acute coronary syndrome; myocardial infarction; red blood cell; transfusion; restrictive transfusion strategy; liberal transfusion strategy

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources.

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Multiple randomized controlled trials (RCTs) in various patient populations have shown that a restrictive blood transfusion strategy results in similar or improved outcomes compared with a liberal transfusion strategy, which has led to clinical practice guidelines recommending a restrictive transfusion strategy for most clinical scenarios.¹ However, the optimal transfusion threshold for acute coronary syndromes (ACS) has not been well defined in the literature. Cardiac oxygen delivery is unique, and it has been postulated that a higher transfusion threshold might be physiologically more important in the setting of myocardial ischemia. The recent publication of the Myocardial Ischemia and Transfusion (MINT) trial, which challenged the value of a restrictive transfusion strategy in patients with ACS has resulted in clinical equipoise among practitioners who care for cardiac patients and those responsible for ensuring the availability of

considered appropriate. Our expert opinion is that it is not possible to suggest a differential transfusion strategy on the basis of patients with type 1 or 2 myocardial infarction alone, although patient and system factors should be strongly considered for type 2 myocardial infarction before considering a liberal transfusion strategy. Transfusion-associated circulatory overload is more common using a liberal transfusion target; mitigation strategies should be used if risk factors are present. Minimizing iatrogenic anemia and treating iron deficiency reduces the need for blood transfusion and could improve patient outcomes. In this joint statement we aim to provide practical guidance in the absence of definitive evidence.

blood products. This Canadian Cardiovascular Society (CCS) joint statement, co-developed with the Canadian National Advisory Committee on Blood and Blood Products (NAC) provides an overview of the current evidence, and a data-informed expert opinion on the best practices of blood transfusion in the setting of ACS.

Methods and Scope

This document was developed similarly to a Clinical Practice Update in accordance with the published CCS framework.² The writing group members identified a set of transfusion thresholds in ACS questions and performed comprehensive literature searches limited to RCTs or pre-specified secondary analyses of RCTs. Observational studies and other guidelines were not included in the expert opinions in relation to transfusion thresholds in patients with ACS but follow-up studies of the original RCTs (including meta-analyses) were reviewed and considered. All of the authors performed independent literature searches. Initially, CCS and NAC members independently drafted the sections most relevant to their area of expertise. The committee then revised the initial drafts to prepare the final document. All expert opinions are ungraded and derived by consensus.

Transfusion Thresholds in Patients With ACS: A Summary of the Evidence and Expert Opinions

Four primary published RCTs have addressed this clinical scenario, including 2 pilot trials, which are summarized in Table 1.³⁻⁶ Of note, some examples of previous trials other than the 4 aforementioned studies assessed those with risk factors for cardiac ischemia including the Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair published in 2011 and the Transfusion Requirements in Cardiac Surgery (TRICS) trials with TRICS 3 published in 2017.^{7,8} Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair and TRICS 3 suggested, in

cliniques des patients et les facteurs systémiques au moment de déterminer un seuil de transfusion de globules rouges chez les patients qui présentent un SCA et une anémie. Le fait d'envisager une stratégie de transfusion de globules rouges libérale est raisonnable, compte tenu des incertitudes liées aux différences entre les patients, et où un taux d'hémoglobine cible > 90 g/l pourrait être considéré approprié. Notre opinion en tant qu'experts est qu'il n'est pas possible de suggérer une stratégie différentielle de transfusion fondée uniquement sur le type d'infarctus du myocarde (type 1 ou 2), bien qu'en cas d'infarctus du myocarde de type 2, il convient d'examiner attentivement les facteurs liés au patient et les facteurs systémiques avant d'envisager une stratégie de transfusion libérale. La surcharge circulatoire associée à la transfusion est plus fréquente en cas d'utilisation d'une stratégie de transfusion libérale. Des stratégies d'atténuation devraient être mises en place si des facteurs de risque sont présents. Le fait de diminuer au maximum l'anémie iatrogène et de traiter la déficience en fer réduit le nombre de transfusions et pourrait permettre d'améliorer les résultats thérapeutiques des patients. Cette déclaration conjointe vise à fournir des orientations pratiques en l'absence de données probantes définitives.

patients with a history or risk factors for cardiovascular disease and cardiac surgery on cardiopulmonary bypass respectively, no meaningful differences in outcomes with a restrictive transfusion strategy.

The largest and most recent trials to examine anemia and ACS were the **Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction (REALITY)** and **MINT**. In REALITY 668 patients were randomized to a restrictive (targeting a hemoglobin [Hb] level of 70-80 g/L) vs liberal (targeting a Hb level of 100 g/L) transfusion strategy with myocardial ischemic symptoms and elevation of biomarkers maintained from admission to 30 days after randomization.⁶ Inclusion criteria were that ischemic symptoms had to occur within 48 hours of admission. Patients had an average age of 77 years, and ST-elevation myocardial infarction (MI) comprised approximately two-thirds of patients. Major adverse cardiovascular events (MACE) at 30 days were the primary outcome. The overall trial showed no significant difference in the composite primary outcome of MACE with a relative risk (RR) of 0.79 (95% confidence interval [CI], 0-1.19) for restrictive transfusion vs liberal transfusion. The authors acknowledged the trial was of moderate size and not powered for evaluating superiority.

The MINT trial enrolled 3504 patients with an elevated troponin level and anemia (Hb < 100 g/L) and randomized them to a restrictive (< 70 g/L if asymptomatic, < 80 g/L if angina present) or liberal (< 100 g/L) transfusion strategy.⁴ Patients had an average age of 72 years, non-ST elevation MI comprised 81.3% of patients, and 55.8% were classified as type 2 MI. The primary outcome was MI or death from any cause up to 30 days after randomization and occurred more frequently in the restrictive arm (16.9%) than the liberal arm (14.5%); RR, 1.15 (95% CI, 0.99-1.34; *P* = 0.07).

With a statistically neutral result for the primary outcome of the trial, clinicians have been confused as to how to interpret the findings of MINT. Further evaluation of the trial using a reverse fragility index showed that if 2 additional patients among the 1749 in the restrictive-strategy group had

Table 1. Summary of 4 primary randomized transfusion trigger trials in patients with anemia and acute coronary syndrome

Trial	CRIT pilot	MINT pilot	REALITY	MINT
Number of patients enrolled	45	100	668	3504
Inclusion criteria	Adult patients with AMI (ischemic symptoms ≥ 30 minutes) with increased CK-MB or troponin) and Hct $\leq 30\%$ within 72 hours of symptom onset	Adult patients with either STEMI, NSTEMI, unstable angina, or cardiac catheterization and Hb < 100 g/L	Adult acute MI patients (with symptoms 48 hours before admission and biomarker elevation) and Hb 70-100 g/L	Adult MI patients on the basis of the third universal definition ⁴⁷ and Hb < 100 g/L
Definition of restrictive transfusion trigger	Transfusion at Hct $< 24\%$ to target 24%-27%	Permitted at Hb < 80 g/L or symptoms	Transfusion at Hb < 80 g/L, with a target to 80-100 g/L	Permitted at Hb < 80 g/L, strongly recommended at Hb < 70 g/L or with symptoms
Definition of liberal transfusion trigger	Transfusion at Hct $< 30\%$ to target 30%-33%	Transfusion at Hb < 100 g/L	Transfusion at Hb < 100 g/L, with a target of > 110 g/L	Transfusion at Hb < 100 g/L
Primary outcome chosen	In-hospital death, recurrent MI, or worsening CHF at 30 days	Composite of all-cause mortality, MI, or unscheduled coronary revascularization at 30 days	Major adverse cardiovascular events: all-cause death, nonfatal stroke, nonfatal recurrent MI, or emergency revascularization prompted by ischemia at 30 days	Composite of all-cause mortality or MI at 30 days
Primary outcome results (restrictive vs liberal)	13% vs 38% ($P = 0.046$)	25.5% vs 10.9% ($P = 0.054$)	11.0% vs 14.0% (RR, 0.79; 1-sided 97.5% CI, 0.00-1.19)	16.9% vs 14.5% ($P = 0.07$)
Notable utilization outcomes	Average Hct higher and proportion of patients transfused higher in liberal arm (30.6% vs 27.9%; 100% vs 54%) Average number of units of RBCs transfused trended higher in liberal arm (2.5 ± 1.3 vs 1.6 ± 2.0 ; $P = 0.07$)	Mean Hb concentration and number of units transfused higher in liberal arm (13-18 g/L higher in liberal; 87 vs 27 units transfused)	Average Hb at discharge and proportion of patients transfused higher in liberal arm (11.1 vs 9.7 g/L; 99.7% vs 35.7%) Patients who received at least 1 unit of RBCs higher in liberal arm (99.7% vs 35.7%)	Mean number of units higher in liberal arm (2.5 ± 2.3 vs 0.7 ± 1.6) Discontinuation of the protocol higher in liberal arm (13.7% vs 2.6%); clinical reasons were provided for 89 of these patients and included adverse effects, fluid overload, dialysis, and transfusion reactions
Notable secondary patient outcomes	In-hospital new or worsening heart failure higher in liberal arm (39% vs 8%; $P = 0.03$) No difference in death, recurrent MI, recurrent ischemia, and hospital length of stay	Composite of death, MI, and unscheduled revascularization or pneumonia higher in restrictive arm (29.6% vs 20.2%; $P = 0.015$) Death higher in restrictive arm (13.0% vs 1.8%; $P = 0.032$) No difference in MI, unscheduled coronary revascularization, unscheduled hospital admission, stroke, congestive heart failure, and other individual outcomes	No difference in all-cause mortality, nonfatal recurrent MI, emergency revascularization, stroke	Higher risk of cardiac death in restrictive arm (RR, 1.74; 95% CI, 1.26-2.40) No difference in death and MI individually, heart failure, stroke, or any other individual outcomes. No difference in composite outcomes including death, MI, revascularization, rehospitalization, or unstable angina Higher risk of primary outcome in patients with type 1 MI (RR, 1.32; 95% CI, 1.04-1.67); NSTEMI (RR, 1.19; 95% CI, 1.00-1.41); CHF, acute heart failure, or low left ventricular ejection fraction (RR, 1.25; 95% CI, 1.02-1.52); and estimated glomerular filtration rate < 30 mL/min (RR, 1.36; 95% CI, 1.02-1.83) No difference in risk of primary outcome in different Hb categories, acute vs chronic anemia, sex, or age groups

Continued

Table 1. Continued.

Trial	CRIT pilot	MINT pilot	REALITY	MINT
Notable significant safety outcomes	No transfusion reactions occurred	Transfusion reactions and adverse events not reported	No statistical testing done; acute lung injury or acute respiratory distress syndrome (adjudicated according to investigator judgement) and infection numerically higher in liberal arm (2.2% vs 0.3%; 1.5% vs 0%)	Transfusion-associated cardiac overload and febrile nonhemolytic transfusion reaction significantly lower in restrictive arm (RR, 0.35; 95% CI, 0.16-0.78; RR, 0.07; 95% CI, 0.01-0.54) Acute hemolytic transfusion reaction numerically higher in liberal arm (4 cases vs 0)
AMI, acute myocardial infarction; CHF, congestive heart failure; CI, confidence interval; CRIT, Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction trial; Hb, hemoglobin; Hct, hematocrit; MI, myocardial infarction; MINT, Myocardial Ischemia and Transfusion trial; NSTEMI, non-ST-elevation myocardial infarction; RBC, red blood cell; REALITY, Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction trial; RR, relative risk; STEMI, ST-elevation myocardial infarction.				

had a primary outcome event—or 2 additional patients among the 1755 in the liberal strategy group had not had a primary outcome event—the results would have been significant in favour of the liberal transfusion strategy.⁹

Currently published meta-analyses have various findings but indicate signals to support liberal transfusion strategies in patients with ACS. Although a meta-analysis of Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction (CRIT), MINT pilot, REALITY, and MINT trials does not indicate differences between transfusion strategies for 30-day outcomes,¹⁰ the addition of a cohort with acute MI and anemia from the TRICS 3 study suggests that a restrictive transfusion was associated with a trend toward an increased risk of MACE (while not demonstrating benefit) and suggests that a liberal transfusion strategy might decrease the risk of long-term MACE and MI.¹¹ An additional Bayesian analysis including data from CRIT, MINT pilot, REALITY, and MINT trials showed that liberal transfusion might decrease the risk of early mortality or MI and their frequentist analysis showed a significant increase in the risk of death or MI with a restrictive strategy.¹² Another meta-analysis including other randomized transfusion trigger trials that coincidentally enrolled subjects with preexisting cardiovascular disease (but did not specifically have it as inclusion criteria) favoured liberal transfusion strategies for MI and death as outcomes.¹³

A patient-level meta-analysis incorporating individual patient data from CRIT, MINT pilot, REALITY, and MINT trials included a total of 4311 patients and the primary outcome was death or MI at 30 days.¹⁴ The primary outcome occurred in 334 patients (15.4%) in the restrictive and 296 patients (13.8%) in the liberal strategy (RR, 1.13; 95% CI, 0.97-1.30). Death at 30 days occurred in 9.3% in the restrictive and 8.1% in the liberal strategy group (RR, 1.15; 95% CI, 0.95-1.39). Cardiac death at 30 days occurred in 5.5% in the restrictive and 3.7% in the liberal strategy group (RR, 1.47; 95% CI, 1.11-1.94). Heart failure (RR, 0.89; 95% CI, 0.70-1.13) was similar in the 2 transfusion strategy groups. All-cause death at 6 months was increased in the restrictive (20.5%) compared with the liberal (19.1%) strategy group (hazard ratio [HR], 1.08; 95% CI, 1.05-1.11).

Finally, REALITY and MINT had prespecified analyses of longer-term outcomes at 1 year and 6 months, respectively. At 1 year, REALITY showed that the primary outcome of MACE did not achieve noninferiority when the restrictive vs liberal transfusion strategy were compared, with a higher MACE-free survival in the liberal arm (HR, 1.16; 95% CI, 0.88-1.53).¹⁵ At 6 months, MINT did not show significant differences between strategies for all-cause death, cardiac and non-cardiac causes of death, and unknown causes of death.¹⁶ Both trials were not powered for longer-term outcomes. The panel's expert opinion is that these findings do not offer significant justification to alter practice.

Our panel favoured assessing the primary outcomes of the 4 principal trials and could not make a definitive statement on the basis of those results, placing less weight on subgroup analyses and meta-analyses. Thus, our panel believes that in patients with ACS and anemia, clinicians might consider individual patient characteristics and systems factors, that could tip the balance in favour of a liberal or restrictive transfusion strategy (Fig. 1). We acknowledge that a liberal transfusion

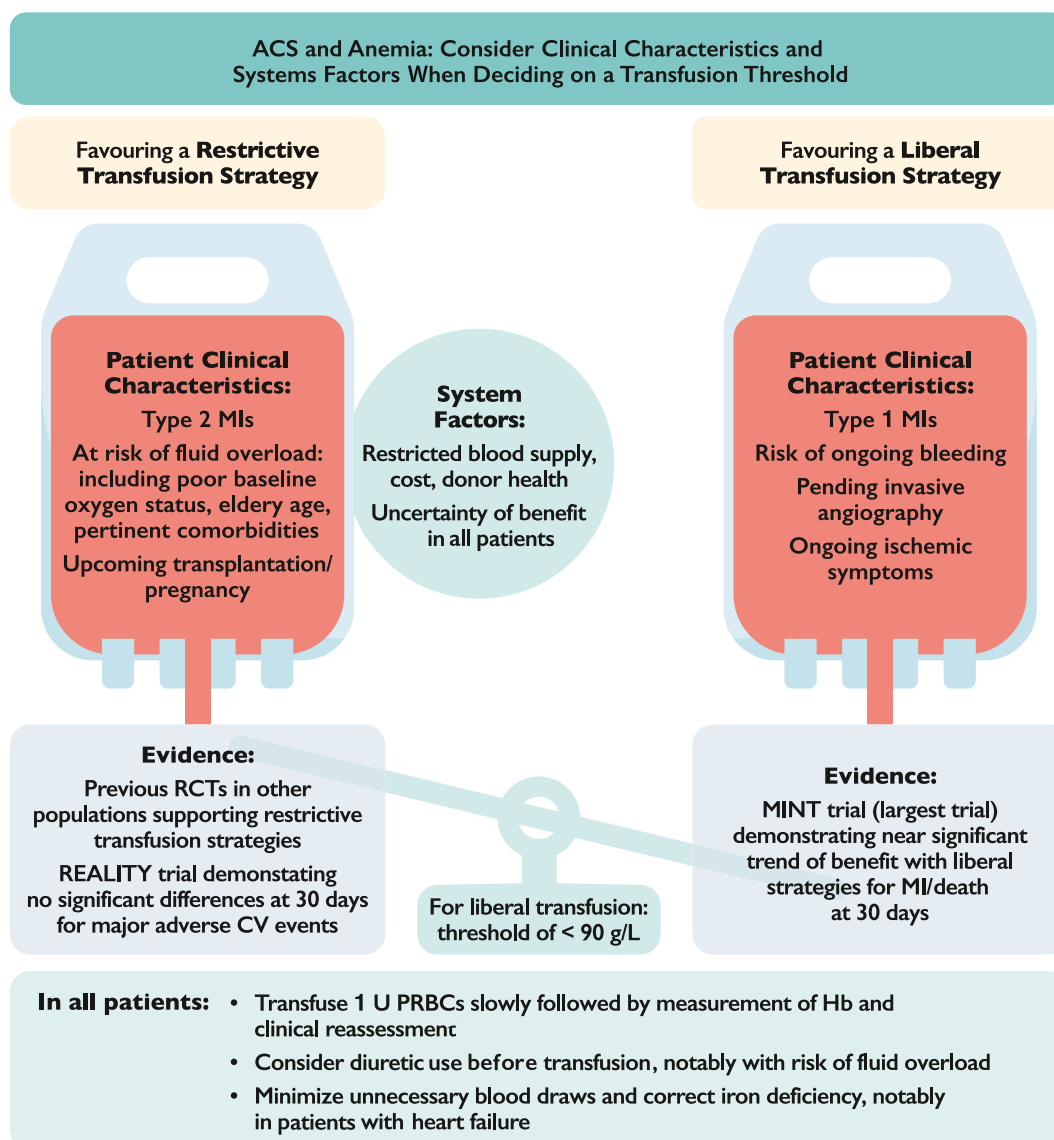


Figure 1. Considerations for transfusion strategies in patients with anemia and acute coronary syndrome (ACS). CV, cardiovascular; Hb, hemoglobin; MI, myocardial infarction; MINT, Myocardial Ischemia and Transfusion trial; PRBC, packed red blood cell; RCT, randomized controlled trial; REALITY, Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction.

strategy might not benefit all patients, hence, our suggestion toward a nuanced patient-specific approach.

It is unlikely that additional RCT data will be forthcoming in the immediate future to alter the strength of the current evidence. A Canadian population-based cohort study of 7922 patients with ACS and anemia (nadir Hb level of 60-89 g/L), of whom 3498 received a transfusion, was recently published. The cumulative incidence rate for the primary outcome of all-cause death and hospitalization for MI at 30 days after discharge, after application of propensity score adjustment, was 28.6% in the transfusion group and 33.3% in the no-transfusion group (HR 0.83; 95% CI, 0.75-0.91), which persisted at 1 year after hospital discharge and across sensitivity analyses. Although this study shows an association of harm when withholding transfusion in severely anemic patients, it should be highlighted that these are observational

data and the proportion of patients with Hb levels closer to 60 g/L was not delineated, and transfusion using extremely low Hb thresholds have less equipoise.¹⁷

A prespecified secondary analysis of the MINT trial to evaluate the effects of 4 different transfusion strategies has been published.¹⁸ The authors emulated a hypothetical target trial using the data from MINT to evaluate the effects of Hb thresholds for transfusion of < 100 g/L, < 90 g/L, < 80 g/L, and < 70 g/L on the primary outcome of death or recurrent MI at 30 days. The adjusted estimated 30-day risk for death and/or MI ranged from 14.8% (95% CI, 11.8%-18.4%) in the < 100 g/L strategy to 18.3% (95% CI, 14.6%-22.0%) in the < 70 g/L strategy. Relative to the < 100 g/L strategy the absolute risk differences and risk ratios increased as the Hb thresholds decreased, although there was minimal difference between the < 100 g/L and < 90 g/L strategies. However, the

Table 2. Factors differentiating type 1 and type 2 MI^{19,20,48}

Type 1 MI (plaque rupture)	Type 2 MI (supply-demand mismatch)
Presentation with MI symptoms	Primary diagnosis other than MI
Acute	More comorbidities (eg, renal failure, bleeding)
Known coronary artery disease	More chronic anemia
ST elevation on electrocardiogram	More arrhythmias (especially atrial fibrillation)
Higher dynamic increase in troponin level	Lower dynamic increase in troponin level
Younger	Older (although not seen in MINT)
	Severe hypertension or hypotension and/or shock
	Female sex
	(although not seen in MINT)

MI, myocardial infarction; MINT, Myocardial Ischemia and Transfusion trial.

authors note that the 95% CIs included the null values. Although the appropriate specific threshold for Hb for a liberal transfusion strategy remains unknown, our panel considers a threshold of < 90 g/L is reasonable on the basis of current evidence placing an emphasis on preserving blood supply.

Expert opinion

In patients with ACS and anemia, an approach that considers patient clinical characteristics and systems factors is appropriate when choosing a transfusion threshold (Fig. 1). It is reasonable to consider a red blood cell (RBC) transfusion in accordance with a liberal transfusion strategy, acknowledging the uncertainty of benefit in all patients. RBC units may be transfused 1 at a time, followed by measurement of the Hb level and clinical assessment of improvement.

Practical tips

1. A transfusion threshold of < 90 g/L may be considered as an appropriate balance between therapeutic efficacy and preserving blood component availability, when choosing to transfuse in accordance with a liberal strategy, but a specific threshold may be altered according to individual patient clinical factors.

Type 1 vs Type 2 MI: Is There a Difference?

An important subgroup of patients to consider are the patients with type 1 vs type 2 MI (Table 2). Type 1 MI is due to thrombotic occlusion of a coronary vessel at the site of a disrupted atherosclerotic plaque. Type 2 MI results from a mismatch in myocardial oxygen supply and demand most commonly occurring in the setting of increased physiological stress with underlying fixed coronary artery disease.¹⁹ Blood transfusion might be helpful (increased oxygen delivery) or harmful (volume overload, nitric oxide sequestration, platelet activation, increased blood viscosity) in both clinical scenarios. It was hypothesized that patients with type 2 MI would derive a greater benefit from a liberal transfusion strategy because of their underlying comorbidities and mechanism of injury.²⁰ Although patients enrolled in the REALITY trial were required to have ischemic symptoms

48 hours before admission (more suggestive of a type 1 MI), when type 1 vs 2 MI were compared, this specific distinction was only made in the MINT trial.

A prespecified subgroup analysis of the MINT trial in which type 1 and type 2 MI were compared has been published, overall suggesting a benefit of liberal transfusion strategies in patients with type 1 MI.²⁰ In the MINT trial 3504 patients were enrolled of whom 1460 (42%) were identified as having a type 1 and 1955 (56%) were identified as having a type 2 index MI. Compared with patients with a type 1 MI, those with a type 2 MI were similar in age and sex, had a similar or higher baseline prevalence of cardiovascular risk factors (except current smoking), and more chronic illnesses, including a history of anemia, but a lower rate of a previous diagnosis of coronary artery disease. Patients with type 1 MI randomized to a restrictive transfusion strategy had a higher rate of the primary outcome of death or MI (18.2% vs 13.8%; RR, 1.32; 95% CI, 1.04-1.67). There was no difference in the primary outcome, or any of the secondary outcomes among patients with type 2 MI randomized to a restrictive vs liberal transfusion strategy. However, the risk of cardiac death was higher at 30 days in the restrictive strategy (4.6% vs 2.3%; RR, 1.95; 95% CI, 1.19-3.21) and at 6 months (7.8% vs 5.5%; RR, 1.42; 95% CI, 1.01-1.99). The authors concluded that considering the greater likelihood of negative outcomes with a restrictive transfusion strategy and lower likelihood of harm with a liberal transfusion strategy, these data are supportive of a liberal transfusion strategy in patients with type 1 MI and anemia.

There are, however, significant limitations to using type 1 or 2 MI as a primary criterion for choosing a transfusion strategy. Classifying an MI as type 1 or type 2 can be very subjective and there was significant variation in the proportions of patients with type 1 and type 2 MIs in different countries.²⁰ Careful interpretation must be made when comparing subgroup data from a single trial (MINT), which was not powered to detect a difference in this outcome. Some considerations assessed in the Instrument for Assessing the Credibility of Effect Modification Analyses (ICEMAN) also suggest limitations.²¹ The direction of the effect modification was not anticipated (type 2 MI patients were hypothesized to derive more benefit from transfusion), the benefit to type 1 MI patients was not supported by previous evidence, the number of subgroup analyses, or effect modifiers was relatively large (> 3), and perhaps most importantly the test of interaction for a differential effect of transfusion according to MI type was not statistically significant in this analysis.

Patients with type 2 MI represent a heterogeneous population with a variety of clinical circumstances and comorbidities. Although the evidence favouring a particular transfusion strategy between type 1 and type 2 MI is equivocal, we suggest that it is particularly important to consider individual clinical patient characteristics when deciding upon a transfusion strategy for patients with type 2 MI, especially in the absence of additional features to suggest coronary ischemia.

Expert opinion

Currently, the data do not support a differential transfusion strategy in type 1 vs type 2 MI patients. Individual patient characteristics, comorbidities, and systems factors

should be considered for patients with type 2 MI before considering a liberal transfusion strategy.

Potential Risks of Transfusion

Adverse reactions attributable to transfusions are well known. Transfusion-related acute lung injury was previously identified as the most significant risk for mortality, though it is less common now with donor mitigation strategies (approximately 1 in 10,000).^{22,23} Transfusion-associated circulatory overload (TACO) is now the most common transfusion event associated with mortality on the basis of US and United Kingdom data,^{24,25} and is seen in up to 11% of critically ill patients who have received transfusion.²⁶ Notable risk factors include history of congestive heart failure (CHF), renal failure, elderly age, cardiac dysfunction, and preexisting fluid overload. TACO can be mitigated through the use of pretransfusion diuretics, decreasing the administration rate (to a maximum of 1 unit of RBCs over 4 hours), and importantly, preventing inappropriate transfusions.²⁷

Overall, the findings regarding patients who had heart failure in RCTs that assessed transfusion strategies in patients with ACS are difficult to interpret. A subgroup analysis of heart failure patients in REALITY showed a higher rate of death at 30 days in the liberal arm (RR, 0.40; 95% CI, 0.19-0.84), but the MINT trial showed a lower rate of MI or death at 30 days in a subgroup of patients with heart failure in the liberal arm (RR, 1.25; 95% CI, 1.02-1.52).^{4,28} However, there were fewer episodes of TACO in the restrictive transfusion group in MINT (0.5% vs 1.3% with the liberal transfusion strategy; RR, 0.35), along with a high discontinuation rate of the liberal protocol (13.7% vs 2.6% with the restrictive transfusion strategy) with fluid overload being one of the provided reasons.

Nevertheless, when considering the REALITY and MINT trials, on a population level we can be reassured that cardiovascular outcomes and death are not increased with a liberal transfusion strategy. Thus, the liberal transfusion strategy can be safe for patients, but pretransfusion risk factors must be considered and mitigated.

Other serious and potentially fatal reactions include anaphylactic reactions, in transfusing ABO-incompatible units, and transfusion-transmitted infections. The latter is now uncommon, with bacterial contamination now the most common serious transfusion-transmitted infection.²² Many jurisdictions including Canada, have implemented donor screening, testing of donations, and pathogen-inactivating technologies to drastically mitigate this risk. However, currently in Canada pathogen-inactivating technologies do not apply to RBCs, so septic transfusion reactions should be highly suspected when the patient has symptoms of infection and a temperature above 39°C with an absolute rise of > 1°C.²⁹

There are indirect risks of transfusion that are emerging as well. The biological interactions between the donor product and recipient are not well known, which have been implicated in transfusion-related immunomodulation.³⁰ This might, in part, explain why many patient populations counterintuitively do not have better outcomes by correcting anemia with transfusion.¹ Another emerging risk that has been observed is a higher risk of thrombosis in liberal transfusion strategies vs

restrictive transfusion strategies.³¹ Unknown transfusion-transmitted diseases might also exist, as suggested by association of intracerebral hemorrhage in patients who received blood from donors who decades later had multiple intracerebral hemorrhages, which is hypothesized to be due to cerebral amyloid angiopathy.³²

Finally, one should be cognizant of alloimmunization in persons of childbearing potential (usually female sex and aged younger than 45 years in Canadian jurisdictions) as well as persons who might require future organ transplantation. Crossmatched transfusions typically match for ABO and Rh, along with any antigens for which the patient has an RBC alloantibody. Thus, patients might still form RBC alloantibodies to antigens on the transfused RBC, making it more challenging to find compatible blood. In pregnancy, the alloantibodies crossing the placenta in pregnancy can cause hemolytic disease of the fetus and newborn. Alloantibodies to HLA antigens can also occur from residual white blood cells in the transfused blood component, which might negatively affect the ability of the recipient to receive either solid organ or bone marrow transplantation.

Expert opinion

Although there are adverse effects of RBC transfusions in patients with ACS, the body of evidence suggests the overall risk of cardiovascular outcomes and death is not worse with a liberal transfusion strategy.

Practical tips

1. For patients with and/or at risk of heart failure, patient outcomes as described are also similar. However, transfusion-associated circulatory overload is more common using a liberal transfusion target. Pretreatment with diuretics and slow transfusion can mitigate this issue.

State of Transfusion Health: Impacts and Implications of a Liberal Transfusion Strategy

Canada relies on voluntary donors for producing RBCs and other blood components. The blood supply in Canada remains adequate while maintaining high safety standards. However, like many jurisdictions internationally, Canada also has had episodes of blood supply challenges, which have prompted transient changes in hospital policy and practice to conserve blood for the patients at highest risk without transfusion. This occurs through activation of the National Shortages Plan for Labile Blood Components (excluding Quebec where that province and their blood supplier, Hema-Quebec, have an analogous plan), which is a plan created and activated by the National Emergency Blood Management Committee in concert with membership from the NAC, Canadian Blood Services, and Provincial and/or Territorial Ministries of Health.³³

Activation of this plan has occurred more frequently in the past years, in part due to changing donor demographic characteristics and behaviour. The transient changes agreed upon in policy and practice for RBCs are usually to hold back blood supply to hospitals where necessary and to screen transfusions to adhere to restrictive transfusion policies where possible. Fortunately, when implemented, these changes have

not produced evidence of patient harm, which is consistent with RCT evidence that supports restrictive transfusion strategies.

The effect of using liberal transfusion strategies on the blood supply in Canada is broadly unknown and no data specific to Canada have been published at the time of writing. Although administrative data are available to determine the number of admissions for acute MI, the proportion that would be eligible for liberal transfusion strategies remains unclear. Salisbury et al. suggest approximately 5% of patients with acute MIs develop severe hospital-acquired anemia as defined by Hb < 90 g/L.³⁴ These patients, if managed with a liberal transfusion strategy, would receive at least 1 unit conservatively and likely closer to 2 units during hospital admission.

Further pressure on the blood supply is warranted if patients benefit. A liberal transfusion strategy might benefit some patients with ACS and should be informed by the patient's clinical characteristics as described previously herein. This balances improving patient outcomes while also concurrently considering donor health, because iron deficiency can be precipitated in repeat donors.³⁵

Minimizing iatrogenic anemia and correcting reversible causes of anemia should be considered as part of a comprehensive patient blood management strategy. Daily bloodwork for approximately 3-5 days, or approximately 100 mL of blood drawn, can decrease the Hb by 8 g/L.³⁶ Evidence shows that small-volume (soft draw) tubes can improve iatrogenic anemia without affecting care in many settings.³⁷ Iron deficiency is common in patients with MI and/or heart failure, affecting nearly 50% of patients, so iron replacement should strongly be considered in patients with and without anemia.^{38,39} Interpretation of iron studies in patients with MI and CHF is complicated by inflammation; whereas ferritin levels < 30 µg/L indicate iron deficiency, inflammation will spuriously raise ferritin levels, and obscure its interpretation. Instead, transferrin saturations < 20% and/or isolated serum iron < 13 µmol/L in MI and CHF patients are indicative of iron deficiency and are prognostic for increased risk of mortality in both populations.^{40,41} Intravenous iron should be considered in patients with heart failure and iron deficiency to improve exercise tolerance, quality of life, and reduce number of hospitalizations.^{42,43} Although intravenous iron has not been adequately studied in the setting of acute MI, it does decrease the incidence of MI in patients receiving hemodialysis,⁴⁴ and is an important area for future studies.

Expert opinion

Unnecessary blood sampling should be minimized. Managing iron and other nutritional deficiencies that contribute to anemia can also reduce the need for blood transfusions and should be particularly considered in heart failure patients.

Current Knowledge Gaps and Future Directions

Practitioners had awaited the results of the MINT trial to help clarify transfusion strategies in ACS patients. Unfortunately, the results are not definitive, and subgroup analyses and secondary outcomes should only be hypothesis-generating, making interpretation of the findings difficult. This is the largest and most pragmatic trial in this domain,

which was reliant on peer-reviewed government funding for completion. Our panel believes that there is need for further definitive research, either through additional RCTs into the subgroups identified or well performed observational (and ideally prospective) studies. Because of the monumental effort required to complete a trial such as MINT, additional multicentre RCT data are unlikely to be available soon. Therefore, guidelines and consensus statements are important to guide and harmonize ongoing practice.

Evidence supports the use of intravenous iron therapy in patients with heart failure. Because of the high prevalence of iron deficiency in patients admitted with ACS, it would be interesting to generate evidence on iron supplementation in the subset of these patients who are iron deficient regardless of Hb level.^{38,39}

Implementation strategies to minimize iatrogenic blood loss are ongoing. These include initiatives on the basis of the use of small-volume blood tubes, which have been reported to reduce number of transfusions in the intensive care unit setting and minimize unnecessary daily bloodwork; the latter including the **Don't Misuse My Blood** (DMMB) project in Alberta, the **Choosing Wisely Canada** Pause the Draws toolkit, and the **Re-Purposing the Ordering of Routine** laboratory Tests trial.^{37,45,46} We believe these strategies represent best practice, which will be further supported by findings of these implementation strategies when available, and will be applicable to cardiac patients in the cardiac care unit and/or cardiac intensive care unit environment.

Conclusions

In this joint statement we have reviewed the current state of evidence pertaining to the treatment of patients with anemia and ACS. There is ongoing debate about the interpretation of the MINT trial results, but we have endeavored to provide additional clarity by contextualizing the results within the body of evidence and in the Canadian context. This joint statement aims to provide clinicians with practical guidance regarding the management of anemia in patients with ACS.

Ethics Statement

Research ethics approval was not required for this article as this is an assessment only of published data.

Patient Consent

The authors confirm that patient consent is not applicable to this article, because this is an assessment only of published data.

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