In reply

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would be an important step toward personalized blood transfusion. The meta-analysis by Hovaguimian and Myles.[5] has made important progress toward this goal.

Competing Interests

The authors declare no competing interests.

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In Reply:

We would like to thank Drs. Warner, Qiu, and colleagues for their valuable inputs regarding our systematic review.[1]

Dr. Warner rightly points out that CIs crossing the equality line correspond to nonsignificant results and suggests that the wording of our findings may have failed to reflect this lack of statistical significance. Although we agree that "borderline" results (*i.e.*, where one end of the CI just overlaps the null value) should be interpreted with caution, it is worth to note that the Cochrane Collaboration discourages formulations such as "nonsignificant" or "not statistically significant," since these terms are commonly misinterpreted as an indication that "the intervention has no effect."[2] Although some authors would describe such findings as a "tendency" or a "trend" toward an effect, we opted for a more moderate wording (*i.e.*, using formulations such as "seemed to" or "possible increase"), as suggested elsewhere.[3] As for the interpretation of borderline findings, it might help to remember that the true effect is more likely to lie around the point estimate (*i.e.*, around the risk ratio) than at the margins of the CI.[3] The traditionally significant $P < 0.05$ may well be suitable for testing efficacy, but CIs rather than hypothesis testing are preferred when testing safety, equivalence, or noninferiority.[4]

A second concern of Dr. Warner's is that our analysis did not include transfusion-related pulmonary complications, which may have resulted in an underestimation of potential harmful effects associated with liberal transfusion strategies. The rationale behind the exclusion of pulmonary complications was mainly related to the quality of the reported data in the original trials: in most studies, there was no distinction between transfusion-related events (such as acute lung injury or pulmonary edema due to circulatory overload) and events secondary to inadequate oxygen supply, such as left-sided heart failure due to myocardial infarction. Including outcomes with opposite etiologies could have resulted in a dilution of the intervention effects.

Qui *et al.* highlight a potential issue encountered in trials addressing transfusion strategies, *i.e.*, the fact that heterogeneity in hemoglobin levels within individual treatment groups may potentially dilute treatment effects. Their concern is based on the assumption that patients assigned to a restrictive strategy who received blood transfusions would eventually have the same (posttransfusion) hemoglobin levels as those from the liberal group. A similar issue may occur if some patients assigned to a restrictive strategy never developed anemia (*i.e.*, perioperative hemoglobin levels maintained in the range of the liberal group). This could indeed lead to an underestimation of adverse events, since only a small fraction of patients assigned to a restrictive strategy would truly be at risk of developing anemia-related complications. To address this potential source of heterogeneity, Qui *et al.* propose to stratify the analysis according to hemoglobin levels (see table 1, which provides a detailed description of hemoglobin levels across studies). Although the idea is very elegant, such exploratory analyses should be carried out with caution, since the quality of the reported data remains limited (data not extractable, heterogeneity in the frequency or duration of hemoglobin measurements, or use of inadequate statistics [*e.g.*, Student's *t* test for data correlated over time]). It is also worth noting that the randomized design used in the original studies tends to protect from bias and residual confounding. We certainly agree that large, well-designed randomized controlled trials are still needed to fully explore the effects of transfusion strategies and eagerly await the results of the ongoing Transfusion Requirements in Cardiac Surgery-III trial (NCT 02042898).

Competing Interests

The authors declare no competing interests.

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Table 1. Hemoglobin Levels across Studies

Study Characteristics		Intervention Characteristics							
		Hemoglobin Threshold (g/l)		Mean Hemoglobin Levels (g/l)		Corresponding Hematocrit (%)		Mean Hemoglobin/ Hematocrit Levels: Number of Measurements and Time Frame	Hemoglobin Levels Differed Significantly Over Time?
Study ID	Setting or Reason for Admission	Restrictive	Liberal	Restrictive	Liberal	Restrictive	Liberal		
Group 1: cardiovascular disease, cardiac/vascular surgery, or interventional catheterization									
Bracey 1999[47]	Elective cardiac (CABG)	80	90	NE	NE	NE	NE	—	No
Bush 1997[48]	Elective vascular (aortic + infrainguinal)	90	100	98	110	*29.4*	*33*	6 measurements during 48 h	Yes
Carson 2013[6]	Interventional catheterization	S (80)	100	91	106	*28.4*	*31.8*	Mean hemoglobin levels at day 3 POP	Yes
Cooper 2011[51]	Interventional catheterization or cardiac surgery	*80*	*100*	*93*	*102*	27.9	30.6	Daily measurements during 14 d	Yes
Hajjar 2010[55]	Elective cardiac (CABG, valve)	*80*	*100*	91	105	28.4	31.8	6 measurements during 7 d	Yes
Murphy 2015[60]	Elective cardiac (CABG, valve, aortic)	75	90	NE	NE	NE	NE	—	Yes
Shehata 2012[66]	Elective cardiac (CABG, valve)	70 IOP 75 POP	95 IOP 100 POP	91	107	*27.3*	*32.1*	Daily measurements during 6 d	Yes
Slight 2008[67]	Elective cardiac (CABG, valve)	RCV schema	80–90	102	102	*30.6*	*30.6*	Mean hemoglobin levels at day 6 POP	No
Group 2: elderly and orthopedic surgery									
Carson 1998[49]	Hip fracture	S (80)	100	97	107	*29.1*	*32.1*	Mean hemoglobin levels at discharge	Yes
Carson 2011[50]	Hip fracture	S (80)	100	NE	NE	NE	NE	—	Yes
Fan 2014[52]	Elective lower limb joint replacement (hip)	80	100	87	104	*26.1*	*31.2*	Mean hemoglobin levels at day 3 POP	Yes
Foss 2009[8]	Hip fracture	80	100	NE	NE	NE	NE	—	No
Gregersen 2015[9]	Hip fracture	97	113	113	122	*33.9*	*36.6*	5 measurements during 30 d	Yes
Grover 2006[54]	Elective lower limb joint replacement	80	100	99	111	*29.7*	*33.3*	4 measurements during 5 d	Yes
Nielsen 2014[62]	Elective hip revision	73	89	102	99	*30.6*	*29.7*	Unclear	No
Parker 2013[63]	Hip fracture	S	100	112	115	*33.6*	*34.5*	Mean hemoglobin levels at 6 wk	NR
So-Osman 2010[68]	Elective lower limb joint replacement	Standardized schema	Non standardized	114	114	*34.2*	*34.2*	Mean hemoglobin levels at discharge	No

(*Continued*)

Table 1. (Continued)

Study Characteristics		Intervention Characteristics							
		Hemoglobin Threshold (g/l)		Mean Hemoglobin Levels (g/l)		Corresponding Hematocrit (%)		Mean Hemoglobin/ Hematocrit Levels: Number of Measurements and Time Frame	Hemoglobin Levels Differed Significantly Over Time?
Study ID	Setting or Reason for Admission	Restrictive	Liberal	Restrictive	Liberal	Restrictive	Liberal		
Group 3: mixed medical/surgical cases and acute care									
de Almeida 2015[7]	Surveillance post major abdominal surgery	70	90	NE	NE	NE	NE	—	Yes
Fortune 1987[53]	Trauma or surgical bleeding	100*	133*	101	127	*30.3*	*38.1*	NR	Yes
Hebert 1995[57]	Various diagnoses	70–75	100–105	90	109	*27*	*32.7*	Daily measurements during ICU stay	Yes
Hebert 1999[56]	Various diagnoses	70	100	85	107	*25.5*	*32.1*	Daily measurements during ICU stay	Yes
Holst 2014[58]	Septic shock	70	90	NE	NE	NE	NE	—	Yes
Jairath 2015[34]	Upper gastrointestinal bleeding	80	100	115	115	*34.5*	*34.5*	Mean hemoglobin levels during the entire study period	No
Markatou 2012[59]	Surveillance post major abdominal surgery	77	99	NE	NE	NE	NE	—	Yes
Topley 1956[69]	Trauma	70–80% of RCV	Normal RCV	113	156	*3.9*	*46.8*	NR	Yes
Villanueva 2013[70]	Upper gastrointestinal bleeding	70	90	92	101	*27.6*	*30.3*	Daily measurements during hospital stay	Yes
Walsh 2013[35]	Various diagnoses	70	90	82	96	*24.6*	*28.8*	Daily measurements during ICU stay (maximum 14 d)	Yes
				83	98	*24.9*	*29.4*	Daily measurements during hospital stay	
Group 4: younger, fitter, and brain injury/intracranial bleeding									
Naidech 2010[61]	Neuro-ICU	100	115	NE	NE	NE	NE	—	Yes
Robertson 2014[65]	Neuro-ICU	70	100	96	112	*28.8*	*33.6*	Mean hemoglobin levels at day 16 post injury	Yes
Group 5: other patients and settings									
Prick 2014[64]	Postpartum hemorrhage	S	89	74	90	*22.2*	*27*	Mean hemoglobin levels at discharge	Yes
Webert 2008[71]	Hematologic cancer	80	120	93	106	*27.9*	*31.8*	12 measurements during 30 d	Yes

Variables in italic correspond to converted values using the following formula: hemoglobin [g/l] = hematocrit [%]/0.3.

CABG = coronary artery bypass graft; ICU = intensive care unit; IOP = intraoperative; NE = not extractable (graphs only, no numerical data); NR = not reported; POP = postoperative; RCV = red cell volume; S = symptoms of anemia.

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