Canadian Journal of Cardiology 40 (2024) 1705–1714

Clinical Research

Restrictive vs Liberal Blood Transfusions for Patients With Acute Myocardial Infarction and Anemia by Heart Failure Status: An RCT Subgroup Analysis

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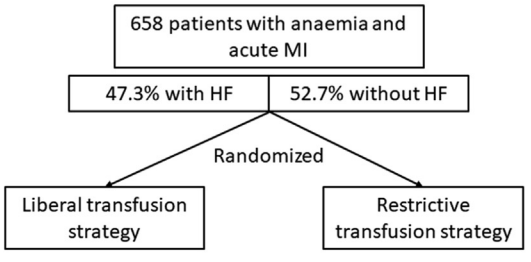
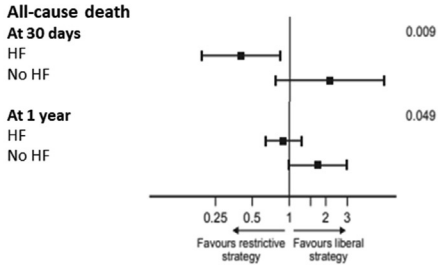
See editorial by Yao and Fordice, pages 1715-1717 of this issue.

Restrictive vs Liberal Blood Transfusions for Patients with Acute Myocardial Infarction and Anaemia by Heart Failure Status: A Subgroup Analysis





https://doi.org/10.1016/j.cjca.2024.02.013

ABSTRACT

Background: Red blood cell transfusion can cause fluid overload. We evaluated the interaction between heart failure (HF) at baseline and transfusion strategy on outcomes in acute myocardial infarction (AMI).

Methods: We used data from the randomized REALITY trial. HF was defined as history of HF or Killip class $>$ 1 at randomization. Primary outcome was major adverse cardiovascular events (MACE): composite of all-cause death, nonrecurrent AMI, stroke, or emergency revascularization prompted by ischemia at 30 days.

Results: Among 658 randomized patients, 311 (47.3%) had HF. Patients with HF had higher rates of MACE at 30 days and 1 year and higher rates of nonfatal new-onset HF. There was no interaction between HF and effect of randomized assignment on the primary outcome or nonfatal new-onset HF. A liberal transfusion strategy was associated with increased all-cause death at 30 days and at 1 year in patients with HF ($P_{interaction} = 0.009$ and $P = 0.049$, respectively). The main numerical difference in cause of death between restrictive and liberal strategies was death by HF at 30 days (4 vs 11).

Conclusions: HF is frequent in patients with AMI and anemia and is associated with higher risk of MACE (including all-cause death) and nonfatal new-onset HF. Although there was no interaction of HF with effect of transfusion strategy on MACE, a liberal transfusion strategy was associated with higher all-cause death that appears driven by a higher risk of early death caused by HF.

Clinical Trial Registration: NCT02648113.

RÉSUMÉ

Contexte : La transfusion de globules rouges peut entraîner une surcharge hydrosodée. Nous avons évalué l'interaction entre l'insuffisance cardiaque (IC) initiale et la stratégie de transfusion sur le pronostic d'infarctus aigu du myocarde (IAM).

Méthodes : Nous avons utilisé les données de l'essai randomisé REALITY. L'IC était définie par des antécédents d'IC ou une classe de Killip $>$ 1 au moment de la randomisation. Le critère principal d'évaluation était les événements cardiovasculaires indésirables majeurs (ECIM) : un composite regroupant les décès toutes causes confondues, l'IAM non récidivant, l'accident vasculaire cérébral ou la revascularisation d'urgence motivée par une ischémie à 30 jours.

Résultats : Parmi les 658 patients randomisés, 311 (47,3 %) souffraient d'IC. Les patients atteints d'IC présentaient des taux plus élevés d'ECIM à 30 jours et à 1 an, ainsi que des taux plus élevés de nouvelle IC non fatale. Il n'a pas été observé d'interaction entre l'IC et l'effet de la randomisation sur le critère principal d'évaluation ou les épisodes d'IC non mortels. Une stratégie de transfusion libérale a été associée à une augmentation des décès toutes causes confondues à 30 jours et à 1 an chez les patients atteints d'IC ($P_{interaction} = 0{,}009$ et $P = 0{,}049$, respectivement). La principale différence numérique dans les causes de décès entre les stratégies restrictive et libérale était la mort par IC à 30 jours (4 vs 11).

Conclusions : L'IC est fréquente chez les patients atteints d'IAM et d'anémie, et elle est associée à un risque plus élevé d'ECIM (y compris le décès toutes causes confondues) et de nouvelle IC non fatale. Bien qu'il n'y ait pas eu d'interaction entre l'IC et l'effet de la stratégie de transfusion sur les ECIM, une stratégie de transfusion libérale a été associée à un risque plus élevé de décès toutes causes confondues, qui semble être dû à un risque plus élevé de décès précoce causé par l'IC.

Enregistrement de l'essai : NCT02648113.

The benefit of red blood cell (RBC) transfusion strategies in patients with acute myocardial infarction (AMI) and anaemia remains debated, with observational studies yielding conflicting results.[1-3] In the **Re**strictive **a**nd **Li**beral **T**ransfusion Strategies in Patients With Acute M**y**ocardial Infarction (REALITY) trial, a restrictive transfusion strategy (transfusion triggered by haemoglobin concentration $\leq$ 80 g/L) was noninferior to a liberal transfusion strategy (triggered by haemoglobin concentration $\leq$ 100 g/L) at 30 days,[4] but noninferiority was no longer present at 1 year.[5] The population of patients with AMI and anemia is, however, heterogeneous. One potential concern with RBC transfusion is the risk of fluid overload and acute heart failure (HF).[6] The balance of benefits and risks of transfusion strategies may therefore differ between patients with vs without HF. Hence, we sought to evaluate the potential interaction between HF and transfusion strategies on outcomes in patients with AMI.

Received for publication October 25, 2023. Accepted February 18, 2024.

‡The REALITY investigators are listed online at https://jamanetwork.com/journals/jama/fullarticle/2776201.

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See page 1713 for disclosure information.

Methods

Study population

REALITY (NCT02648113) was an open-label randomized trial conducted in France and Spain including 668 patients with AMI and hemoglobin concentrations between 70 and 100 g/L. Patients were randomized (1:1) to either a restrictive transfusion strategy, in which transfusions were withheld unless hemoglobin was $\leq$ 80 g/L, with a target hemoglobin concentration of 80 to100 g/L, or a liberal transfusion strategy, in which transfusions were allowed as soon as hemoglobin was $\leq$ 100 g/L, with a target hemoglobin of $\geq$ 110 g/L. The study was performed according to the Declaration of Helsinki and Good Clinical Practice and was approved by the Comité de Protection des Personnes, Île de France-I, France, and the ethics committee of Hospital Clinic, Barcelona, Spain. All patients provided written informed consent.

Patient baseline characteristics and transfusion management are described according to HF status, with HF defined as a history of HF or Killip class $>$ 1 at randomization.

Outcomes

The primary outcome of major adverse cardiovascular events (MACE) was defined as the composite of all-cause death, nonfatal stroke, nonfatal recurrent myocardial infarction, or emergency revascularization prompted by ischemia. Secondary exploratory outcomes were MACE at 1 year, the

individual components of MACE, nonfatal new-onset HF (defined as congestive HF or cardiogenic shock) and overall new-onset HF (defined as nonfatal new-onset HF and death caused by congestive HF or cardiogenic shock) at 30 days and 1 year. Both MACE and HF events were adjudicated by a critical event committee blinded to treatment assignment.

Statistical analysis

The current post hoc analysis was based on the intention to treat (ITT) population with available data on HF status. Sensitivity analyses were conducted comparing Killip class 1 with class > 1 patients, irrespective of a previous history of HF. The main analysis was post hoc, whereas the sensitivity analysis was prespecified.[7] Baseline characteristics are expressed as numbers and percentages for categorical variables and as means $\pm$ standard deviations (SDs) or medians (quartile 1, quartile 3) for continuous variables, depending on their distribution. Groups according to HF status were compared using Pearson's χ^2 test or Fisher's exact test for categorical variables, depending on validity conditions, and Student's *t*-test or Wilcoxon's rank-sum test for continuous variables, depending on their distribution.

Relative risk (RR), defined as p_1/p_2, with $p_1 = n_{11}/n_1$ and $p_2 = n_{21}/n_2$, in which n_{11} is the event number and n_1 is the total number of patients in the restrictive group and n_{21} is the event number and n_2 is the total number of patients in the liberal group. Ninety-five percent confidence intervals (CIs) were estimated using the Wald method. The interaction among groups according to HF status and transfusion strategy was tested using logistic regression.

Survival was estimated using the Kaplan-Meier method. A stratified Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% CIs for the effect of transfusion strategy according to HF status on MACE-free survival and overall survival at 30 days and at 1 year. Data for patients with no evidence of an event were censored at 30 days or 1 year. The risk-proportionality hypothesis was verified by testing the interaction between interest variable and time.

All superiority tests and 95% CIs were 2-sided, and *P* values < 0.05 were considered significant. No adjustment was planned for multiplicity. Because of the potential for type I error caused by multiple comparisons, analyses should be interpreted as exploratory. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

The **Con**solidated **S**tandards **o**f **R**eporting **T**rials (CONSORT) checklist is included in Supplemental Appendix S1.

Results

Baseline characteristics

Among 666 patients randomized in the REALITY trial, 8 had no information on Killip class on admission or history of HF and were excluded from this analysis, leaving 658 patients in the study population. Of these, 311 patients (47.3%) had HF at baseline (Fig. 1).

Briefly, patients with HF were older (median 78 vs 76 years) and more likely to be male (65.6% vs 50.7%) (Table 1). They had more comorbidities, with a higher prevalence of diabetes, history of acute coronary syndrome, percutaneous coronary intervention, and renal failure (Table 1). Non–ST-segment elevation myocardial infarction (NSTEMI) was more common among patients with HF (76.5% vs 63.7%, respectively). The detailed baseline characteristics of patients with HF according to inclusion status (history of HF vs Killip class > 1) are shown in Supplemental Table S1. Baseline characteristics of HF patients according to the allocated strategy (restrictive vs liberal) are provided in Supplemental Table S2.

Outcomes

The distribution of packed RBC units received according to HF status and treatment group is shown in Table 2. As expected, there was a major difference in the rate of transfusions between randomized arms, with fewer transfusions in the restrictive arm; this difference was consistent for patients with vs without HF (38.8% vs 99.3% and 33.5% vs 100.0%, respectively).

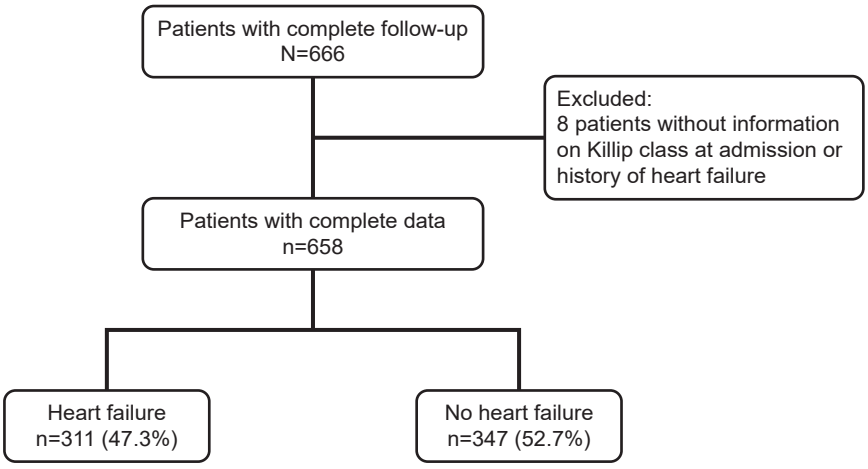


Figure 1. Flow chart of the study population.

Table 1. Characteristics at admission according to HF status

Characteristic	HF (n = 311)	No HF (n = 347)	*P* value
Age, years	78 (70, 86)	76 (67, 83)	0.007*
Male sex	204 (65.6)	176 (50.7)	< 0.0001†
Race‡	(n = 308)	(n = 342)	0.60§
White	269 (87.3)	288 (84.2)	
North Africa	25 (8.1)	39 (11.4)	
African/Caribbean	8 (2.6)	8 (2.3)	
Indian	4 (1.3)	3 (0.9)	
Other Asian	2 (0.6)	4 (1.2)	
Body mass index, kg/m^2	(n = 301)	(n = 342)	0.83¶
	26.7 ± 5.5	26.6 ± 4.9	
Risk factors#			
Hypertension	251 (80.7)	272 (78.4)	0.46†
Dyslipidemia	176 (56.6)	212 (61.1)	0.24†
Diabetes	174 (55.9)	154 (44.4)	0.003†
Tobacco smoking	(n = 281)	(n = 320)	0.14†
Never	132 (47.0)	153 (47.8)	
Current	35 (12.5)	56 (17.5)	
Former	114 (40.6)	111 (34.7)	
Family history of coronary artery disease	(n = 305)	(n = 346)	0.08†
	34 (11.1)	55 (15.9)	
Cardiac history# before index event			
Acute coronary syndrome	137 (44.1)	100 (28.8)	< 0.0001†
Percutaneous coronary intervention	127 (40.8)	95 (27.4)	0.0003†
Angina	50 (16.1)	48 (13.8)	0.42†
Atrial fibrillation	71 (22.8)	47 (13.5)	0.002†
Coronary artery bypass graft	43 (13.8)	43 (12.4)	0.59†
Congestive HF	82 (26.4)	0 (0.0)	< 0.0001†
Internal cardiac defibrillator	13 (4.2)	9 (2.6)	0.26†
Noncardiac medical history#			
Chronic anemia**	62 (19.9)	59 (17.0)	0.33†
Cancer, previously treated	(n = 310)	43 (12.4)	0.51†
	42 (13.5)		
Cancer, under treatment	23 (7.4)	19 (5.5)	
Chronic obstructive pulmonary disease	38 (12.2)	35 (10.1)	0.38†
Dialysis	30 (9.6)	25 (7.2)	0.26†
History of bleeding requiring hospitalization and transfusion	22 (7.1)	21 (6.1)	0.60†
Index hospitalization			
MI type			0.0003†
NSTEMI	238 (76.5)	221 (63.7)	
STEMI	73 (23.5)	126 (36.3)	
Killip class†† at admission	(n = 310)		< 0.0001†
I	25 (8.1)	347 (100%)	
II	175 (56.5)	0 (0.0)	
III	93 (30.0)	0 (0.0)	
IV	17 (5.5)	0 (0.0)	
Delay between admission and randomization, days	(n = 305)	(n = 338)	0.013¶
	1.9 (0.9, 3.9)	1.6 (0.8, 3.3)	
Active bleeding‡‡	30 (9.6)	55 (15.9)	0.018†
Creatinine clearance at randomization,§§ mL/min/1.73 m^2	(n = 306)	(n = 345)	< 0.0001*
	35.2 (21.1, 57.4)	57.3 (33.3, 81.4)	

Values are n (%), mean ± standard deviation, or median (quartile 1, quartile 3). Percentages may not add to 100 because of rounding.
HF, heart failure; MI, myocardial infarction; NSTEMI, non–ST-segment elevation MI; STEMI, ST-segment elevation MI.
* Wilcoxon's rank sum test.
† Pearson's χ^2 test.
‡ Self-reported.
§ Fisher's exact test.
¶ Student's *t*-test.
# Collected through chart review.
** Pre-existing anemia not caused by acute bleeding.
†† Killip class was determined by investigators according to clinical examination: class I: no sign of congestion; class II: basal rales on auscultation; class III: acute pulmonary oedema; class IV: cardiogenic shock.
‡‡ Active bleeding identified and documented during the index admission before randomization.
§§ According to the Chronic Kidney Disease Epidemiology Collaboration formula.

At 30 days, patients with HF had higher rates of MACE (12.9% vs 8.1%), nonfatal new-onset HF (5.5% vs 1.7%), and all-cause death (9.7% vs 4.6%) than patients without HF. Similar observations were made at 1 year (Supplemental Table S3).

There were no differences in rates of MACE between restrictive and liberal groups in patients with HF at 30 days (RR, 0.62; 95% CI, 0.34-1.12) or at 1 year (RR, 1.08; 95% CI, 0.82-1.44) as well as in patients without HF at 30 days

Table 2. Transfusions in patients with and without HF according to a restrictive or liberal transfusion strategy (intention-to-treat population)

	HF population		No HF population	
	Restrictive (n = 160)	Liberal (n = 151)	Restrictive (n = 176)	Liberal (n = 171)
Received transfusion	62 (38.8)	150 (99.3)	59 (33.5)	171 (100.0)
Units of packed red blood cells transfused				
0	98 (61.3)	1 (0.7)	117 (66.5)	0 (0.0)
1	19 (11.9)	26 (17.2)	7 (4.0)	30 (17.5)
2	23 (14.4)	60 (39.7)	38 (21.6)	71 (41.5)
3	6 (3.8)	24 (15.9)	6 (3.4)	25 (14.6)
≥ 4	12 (7.5)	27 (17.9)	8 (4.5)	31 (18.1)
≥ 1 but exact number not available	2 (1.3)	13 (8.6)	0 (0.0)	14 (8.2)

Values are n (%). Percentages may not add to 100 because of rounding.
HF, heart failure.

(RR, 1.12; 95% CI, 0.55-2.28) or at 1 year (RR, 1.21; 95% CI, 0.80-1.83). In addition, there was no interaction between HF and the effect of randomized assignment on MACE ($P_{interaction}$ = 0.20 at 30 days and 0.76 at 1 year). Similar observations were made for nonfatal new-onset HF ($P_{interaction}$ = 0.44 at 30 days and 0.43 at 1 year) as well as for overall new-onset HF ($P_{interaction}$ = 0.77 at 30 days and 0.23 at 1 year).

A liberal transfusion strategy was associated with an increased risk of all-cause death in patients with HF and a reduced risk in patients without HF at both 30 days and 1 year ($P_{interaction}$ = 0.009 and P = 0.049, respectively) (Fig. 2 and Table 3). A sensitivity analysis performed according to Killip class yielded similar results, although the increase in all-cause death did not reach statistical significance at 1 year (P = 0.06) (Supplemental Fig. S1). Analysis of outcomes adjusted

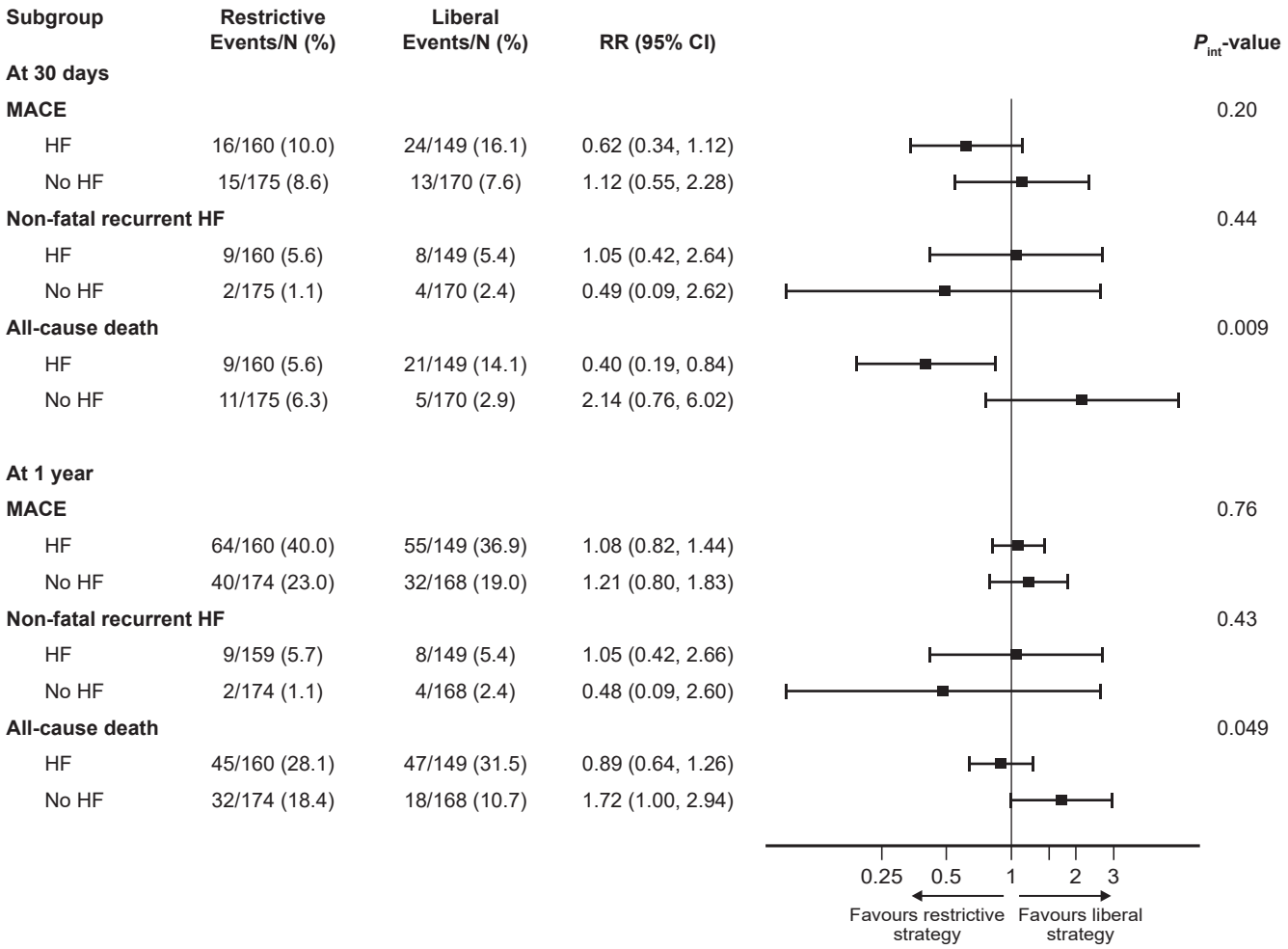


Figure 2. Outcomes according to treatment group and HF status. CI, confidence interval; HF, heart failure; MACE, major adverse cardiovascular events; RR, relative risk.

Table 3. Outcomes in patients with and without HF according to a restrictive or liberal transfusion strategy

Outcome	HF population		No HF population		$P_{interaction}$
	Restrictive (n = 160)	Liberal (n = 151)	Restrictive (n = 176)	Liberal (n = 171)	
At 30 days					
Primary outcome: MACE	16 (10.0)	(n = 149) 24 (16.1)	(n = 175) 15 (8.6)	(n = 170) 13 (7.6)	0.20
All-cause death	9 (5.6)	(n = 149) 21 (14.1)	(n = 175) 11 (6.3)	(n = 170) 5 (2.9)	0.009
Nonfatal recurrent MI	4 (2.5)	(n = 149) 4 (2.7)	(n = 175) 3 (1.7)	(n = 170) 6 (3.5)	0.51
Emergency revascularization	4 (2.5)	(n = 149) 4 (2.7)	(n = 175) 1 (0.6)	(n = 170) 2 (1.2)	0.65
Nonfatal ischemic stroke	2 (1.3)	(n = 149) 0 (0.0)	(n = 175) 0 (0.0)	(n = 170) 2 (1.2)	0.92
Nonfatal new-onset HF	9 (5.6)	(n = 149) 8 (5.4)	(n = 175) 2 (1.1)	(n = 170) 4 (2.4)	0.44
Overall new-onset HF	13 (8.1)	(n = 148) 18 (12.2)	(n = 174) 2 (1.1)	(n = 170) 4 (2.4)	0.77
At 1 year					
Primary outcome: MACE	64 (40.0)	(n = 149) 55 (36.9)	(n = 174) 40 (23.0)	(n = 168) 32 (19.0)	0.76
All-cause death	45 (28.1)	(n = 149) 47 (31.5)	(n = 174) 32 (18.4)	(n = 168) 18 (10.7)	0.049
Nonfatal recurrent MI	15 (9.4)	(n = 149) 8 (5.4)	(n = 174) 8 (4.6)	(n = 168) 12 (7.1)	0.10
Emergency revascularization	(n = 159) 13 (8.2)	(n = 149) 6 (4.0)	(n = 174) 4 (2.3)	(n = 168) 7 (4.2)	0.093
Nonfatal ischemic stroke	(n = 159) 5 (3.1)	(n = 149) 3 (2.0)	(n = 174) 2 (1.1)	(n = 168) 3 (1.8)	0.44
Nonfatal new-onset HF	(n = 159) 9 (5.7)	(n = 149) 8 (5.4)	(n = 174) 2 (1.1)	(n = 168) 4 (2.4)	0.43
Overall new-onset HF	(n = 152) 21 (13.8)	(n = 144) 21 (14.6)	(n = 165) 2 (1.2)	(n = 167) 6 (3.6)	0.24

Values are n (%).
HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction.

on main covariates associated with both HF status and assigned treatment strategy also yielded results consistent with the main analysis (Supplemental Table S4). A per-protocol analysis was performed (Supplemental Table S5) and showed a greater all-cause mortality rate in the liberal transfusion HF group at 30 days.

Causes of death are detailed in Table 4. At 30 days, deaths were predominantly cardiovascular in the HF group: 7 cardiovascular deaths (77.8%) in the restrictive group vs 20 (95.2%) in the liberal group, whereas causes of death were more balanced in patients without HF. In the HF group, the main numerical difference in cause of death between the restrictive and liberal strategy groups was for death caused by new onset of HF (congestive HF or cardiogenic shock): 4 vs 11 events.

Kaplan-Meier curves for MACE and all-cause death according to HF and assignment group are presented in Figure 3.

Discussion

In this subgroup analysis from the randomized REALITY trial, patients with HF represented an important subset of those with AMI and anemia. Patients with HF had a higher risk of MACE, nonfatal new-onset HF, and death. Importantly, in patients with HF, a liberal transfusion strategy was associated with a higher rate of all-cause death than a restrictive strategy at both 30 days and 1 year.

We observed no interaction between HF and the effect of randomized assignment on the primary outcome or nonfatal new-onset HF. Similarly, in the recently published **M**yocardial **I**schemia a**n**d **T**ransfusion (MINT) trial,[8] the largest randomized trial on transfusion strategies in patients with AMI, there was no interaction among congestive HF, acute HF, and low left ventricular ejection fraction and the effect of randomized strategy on a composite outcome of recurrent myocardial infarction or all-cause death.

The population of patients with anemia and AMI is heterogeneous, and it is likely that the benefit-to-risk balance of transfusion strategies varies according to individual clinical characteristics. If tailoring transfusion strategies according to each patient's individual characteristics is not feasible, the largest subgroups deserve special attention. Indeed, the subgroup with HF represents nearly one-half of all patients.

There is a rationale to consider that the subgroup of patients with HF could have a different benefit-to-risk balance of transfusion strategies than the remaining population because the risk of transfusion-associated circulatory overload (TACO) is a special concern in this population. TACO incidence has been reported to be > 10%, depending on the population transfused,[9] with a mortality of approximately 5%.[10,11] In 2011, a report from the US Food and Drug Administration indicated that transfusion-associated fluid overload was the second most commonly reported cause of death associated with transfusion (15% of transfusion-related deaths) after

Table 4. Causes of death in patients with and without HF according to a restrictive or liberal transfusion strategy

Outcome	HF population		No HF population		$P_{interaction}$
	Restrictive transfusion strategy (n = 160)	Liberal transfusion strategy (n = 151)	Restrictive transfusion strategy (n = 176)	Liberal transfusion strategy (n = 171)	
At 30 days					
All-cause death	9 (5.6)	(n = 149) 21 (14.1)	(n = 175) 11 (6.3)	(n = 170) 5 (2.9)	0.009
Cardiovascular	7/9 (77.8)	20/21 (95.2)	7/11 (63.6)	2/5 (40.0)	
Noncardiovascular	2/9 (22.2)	0/21 (0.0)	3/11 (27.3)	3/5 (60.0)	
Unknown	0/9 (0.0)	1/21 (4.8)	1/11 (9.1)	0/5 (0.0)	
If cardiovascular					
Acute MI	3/7 (42.9)	4/20 (20.0)	2/7 (28.6)	1/2 (50.0)	
Sudden cardiac death	0/7 (0.0)	2/20 (10.0)	4/7 (57.1)	1/2 (50.0)	
Congestive HF or cardiogenic shock	4/7 (57.1)	11/20 (55.0)	0/7 (0.0)	0/2 (0.0)	
Cardiovascular procedure	0/7 (0.0)	2/20 (10.0)	1/7 (14.3)	0/2 (0.0)	
Other cardiovascular cause	0/7 (0.0)	1/20 (5.0)	0/7 (0.0)	0/2 (0.0)	
If noncardiovascular primary cause of death					
Pulmonary	1/2 (50.0)	0/0 (0.0)	1/3 (33.3)	2/3 (66.7)	
Renal	0/2 (0.0)	0/0 (0.0)	1/3 (33.3)	0/3 (0.0)	
Neurologic process that is not a stroke or haemorrhage	0/2 (0.0)	0/0 (0.0)	1/3 (33.3)	0/3 (0.0)	
Other noncardiovascular	1/2 (50.0)	0/0 (0.0)	0/3 (0.0)	1/3 (33.3)	
At 1 year					
All-cause death	45 (28.1)	(n = 149) 47 (31.5)	(n = 174) 32 (18.4)	(n = 168) 18 (10.7)	0.049
Cardiovascular	22/45 (48.9)	28/47 (59.6)	10/32 (31.3)	5/18 (27.8)	
Noncardiovascular	16/45 (35.6)	14/47 (29.8)	13/32 (40.6)	12/18 (66.7)	
Unknown	7/45 (15.6)	5/47 (10.6)	9/32 (28.1)	1/18 (5.6)	
If cardiovascular					
Acute MI	3/22 (13.6)	4/28 (14.3)	3/10 (30.0)	1/5 (20.0)	
Sudden cardiac death	6/22 (27.3)	3/28 (10.7)	6/10 (60.0)	1/5 (20.0)	
Congestive HF or cardiogenic shock	12/22 (54.5)	15/28 (53.6)	0/10 (0.0)	3/5 (60.0)	
Stroke (ischemic)	1/22 (4.5)	0/28 (0.0)	0/10 (0.0)	0/5 (0.0)	
Stroke (type undetermined)	0/22 (0.0)	1/28 (3.6)	0/10 (0.0)	0/5 (0.0)	
Cardiovascular procedure	0/22 (0.0)	4/28 (14.3)	1/10 (10.0)	0/5 (0.0)	
Other cardiovascular cause	0/22 (0.0)	1/28 (3.6)	0/10 (0.0)	0/5 (0.0)	
If noncardiovascular primary cause of death					
Pulmonary	2/16 (12.5)	4/14 (28.6)	3/13 (23.1)	6/12 (50.0)	
Renal	0/16 (0.0)	2/14 (14.3)	2/13 (15.4)	2/12 (16.7)	
Gastrointestinal	2/16 (12.5)	1/14 (7.1)	3/13 (23.1)	0/12 (0.0)	
Hemorrhage (excluding hemorrhagic stroke and cardiovascular hemorrhage)	2/16 (12.5)	2/14 (14.3)	0/13 (0.0)	1/12 (8.3)	
Noncardiovascular procedure or surgery	0/16 (0.0)	0/14 (0.0)	1/13 (7.7)	0/12 (0.0)	
Neurologic process that is not a stroke or hemorrhage	0/16 (0.0)	0/14 (0.0)	3/13 (23.1)	0/12 (0.0)	
Accidental (physical accident or drug overdose) or trauma	1/16 (6.3)	0/14 (0.0)	0/13 (0.0)	0/12 (0.0)	
Other noncardiovascular	9/16 (56.3)	5/14 (35.7)	1/13 (7.7)	3/12 (25.0)	

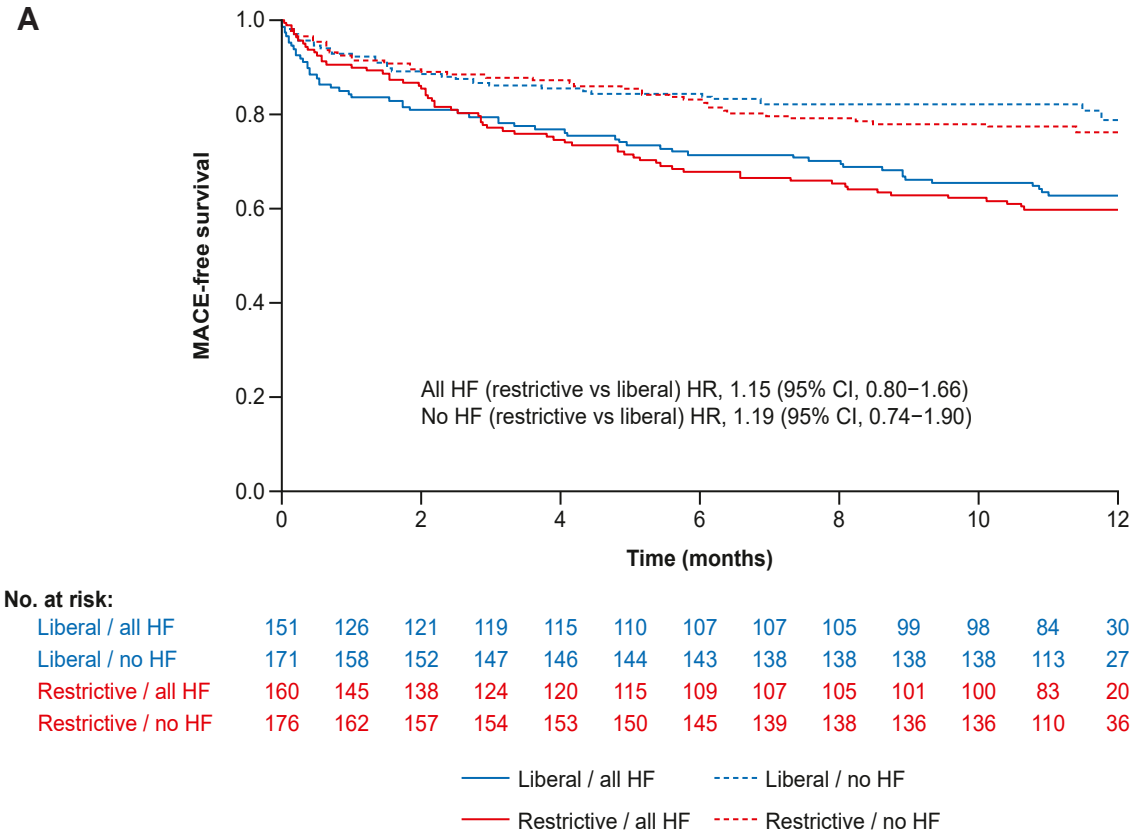
Values are n (%) or n/n (%). Percentages may not add to 100 because of rounding.
HF, heart failure; MI, myocardial infarction.

acute lung injury.[6] The pathophysiology explaining the occurrence of TACO and its severity remains incompletely understood.[12] However, HF is consistently reported as being a risk factor for TACO.[13]

An observational study conducted in intensive care units found that the subgroup of patients with left ventricular dysfunction was at 8-fold higher risk of developing TACO.[14] The **C**onservative vs Liberal **R**ed Cell Transfusion in Myocardial **I**nfarction **T**rial (CRIT) trial,[15] published in 2011, was a pilot randomized trial of 45 patients comparing a liberal vs a conservative transfusion strategy in patients with anemia and myocardial infarction. The study showed an important increase in in-hospital new or worsening HF in patients assigned to the liberal strategy (38% vs 8%; $P = 0.03$), with no excess of mortality in the liberal transfusion group.

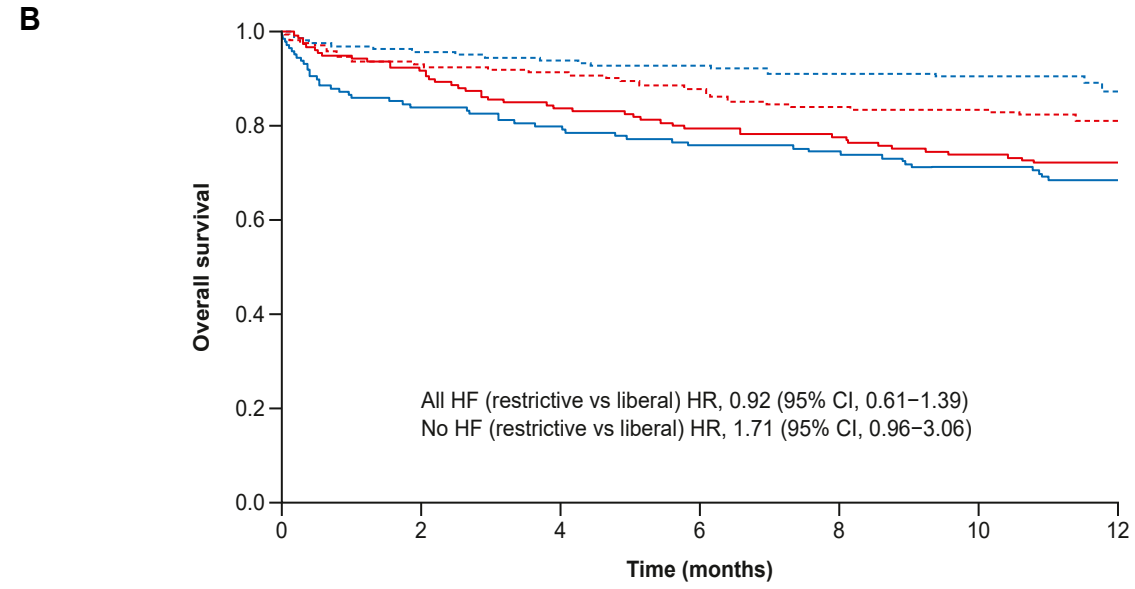
Surprisingly, in the current analysis, we found no interaction between HF and transfusion strategy in the risk of new-onset HF. It is likely that physicians now have greater expertise in preventing fluid overload in high-risk patients with use of diuretic therapy[6] and slow rates of transfusion. Those aspects were left to investigator discretion in the REALITY trial.

Compared with the restrictive strategy, the liberal transfusion strategy was, however, associated with higher all-cause death, at both 30 days and 1 year. This finding was consistent regardless of how HF was defined. Of note, this increase appeared to be driven by cardiovascular death and, in particular, death caused by HF or cardiogenic shock in the first 30 days. These findings suggest that a liberal transfusion strategy in patients with HF is associated with a higher risk of HF, leading to death. This could be perceived as



No. at risk:

Liberal / all HF	151	126	121	119	115	110	107	107	105	99	98	84	30
Liberal / no HF	171	158	152	147	146	144	143	138	138	138	138	113	27
Restrictive / all HF	160	145	138	124	120	115	109	107	105	101	100	83	20
Restrictive / no HF	176	162	157	154	153	150	145	139	138	136	136	110	36



No. at risk:

Liberal / all HF	151	129	125	123	119	115	113	113	111	107	106	92	35
Liberal / no HF	171	165	163	161	160	158	157	153	153	153	152	125	32
Restrictive / all HF	160	152	147	137	134	132	127	125	124	120	118	98	24
Restrictive / no HF	176	166	163	161	160	157	153	147	146	145	145	117	38

Figure 3. (**A**) Rates of MACE at 1 year for restrictive and liberal transfusion strategies in patients with and without HF. (**B**) Kaplan-Meier curves for deaths at 1 year in patients with and without HF at baseline for a liberal vs a restrictive transfusion strategy. CI, confidence interval; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events.

contradictory, with the lack of increase in nonfatal HF. However, it is possible that the most severely ill patients have refractory HF associated with fluid overload.

TACO was not specifically captured in REALITY, but in MINT,[8] despite a similar risk of heart failure at 30 days, more TACO occurred in the liberal arm. Another hypothesis is therefore that some patients develop hydrostatic pulmonary edema triggered by fluid overload that can be easily managed, whereas others have more complex mechanisms with cytokine involvement, such as described in TACO, which can be more difficult to treat.[12]

Our observation has potential clinical implications. If confirmed, clinicians should avoid performing transfusions in patients with HF and myocardial infarction, and—if absolutely necessary—should pay attention to prevent TACO.[6]

Limitations

The current analysis has several limitations. First, we considered HF as a whole entity regardless of phenotype.[16] As such, ejection fraction was not captured in the REALITY trial, precluding analysis of outcomes according to reduced vs preserved ejection fraction. Second, we did not formally test the difference in causes of death because of the risk of multiplicity in this relatively small trial. Third, comprehensive data on medication use were not captured, and diuretics may have mitigated the effect of volume overload among those with heart failure. Fourth, the current analysis is from a subgroup of a randomized trial that was not powered for subgroup analyses. The ongoing MINT trial (NCT02981407) is evaluating transfusion strategies in a similar but substantially larger population and thus will provide important information on the optimal transfusion strategy in the context of AMI and anemia in general but also in common subgroups such as HF.

Conclusions

HF is frequent in patients with AMI and anemia (nearly one-half of the population) and is associated with higher risks of MACE and nonfatal new-onset HF. Although there was no interaction of HF with the effect of transfusion strategy on the primary outcome of MACE, a liberal transfusion strategy was associated with higher risk of all-cause death at both 30 days and 1 year. This higher rate of death appears to be driven primarily by a higher risk of early death caused by HF.

Acknowledgements

Editorial support was provided by Sophie K. Rushton-Smith, PhD (MedLink Healthcare Communications, London).

Data Availability

Requests from qualified investigators for data from the trial will be considered by its Executive Steering Committee.

Ethics Statement

REALITY trial was approved by the Comité de Protection des Personnes, Ile de France-I, France and the ethics committee at the Hospital Clinic, Barcelona, Spain. Patients provided written informed consent.

Patient Consent

The authors confirm that patient consent forms have been obtained for this article.

Funding Sources

The REALITY trial was designed by the French Alliance for Cardiovascular Trials and was funded via a grant from the Programme de Recherche Médico-Economique (PRME) 2015 from the French Ministry of Health and a grant from the Instituto de Salud Carlos III (Spanish Ministry of Economy and Competitiveness; grant PI15/01543). There was no industry support. The sponsor of the trial was Délégation à la Recherche Clinique et au Développement, Assistance Publique-Hôpitaux de Paris, Paris, France.

Disclosures

Dr Ducrocq has received speaker or consulting fees from Abbott, Amarin, Amgen, Astra Zeneca, Bayer, Boston Scientific, BMS, Novo Nordisk, and Sanofi; Critical Event Committee, Data Safety Monitoring Board, he has served on steering committees for Amgen, Novo Nordisk, and Janssen and as Proctor for Boston Scientific. Dr Simon has held grants or contracts for Programme de Recherche Medico Economique and the Instituto de Salud Carlos III (PI15/01543) for Spanish centres in the trial and AstraZeneca, Bayer, Boehringer, Daiichi-Sankyo, Eli-Lilly, GSK, Novartis, and Sanofi, and has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events for Servier and Novartis. He has participated on Data Safety Monitoring Boards or Advisory Boards for Ablative Solutions, Air Liquide, AstraZeneca, Sanofi, Novartis, and 4Living Biotech. Dr Lemesle has received personal fees for consulting or conferences and travel support from Alnylam, Amarin, Amgen, Astra Zeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, MSD, Mylan, Novartis, Novo Nordisk, Organon, Pfizer, Recordati, Sanofi Aventis, and Servier. Dr Lattuca has received research grants from Biotronik, Boston Scientific, Daiichi-Sankyo, Fédération Française de Cardiologie, and Institute of CardioMetabolism and Nutrition; consulting fees from Daiichi-Sankyo and Eli Lilly; and lecture fees from AstraZeneca, Medtronic, and Novartis. Dr Silvain has received consulting fees or lecture fees from Astra Zeneca, Bayer HealthCare SAS, CSL Behring SA, Sanofi-Aventis France, and Zoll; he is a stockholder of 4P-Pharma. Dr Lermusier has received consulting and lecture fees from Abbott and Boston Scientific. Dr Coste has received personal fees from Amgen, Astra-Zeneca, Servier, Vifor, and Abiomed. Dr Cottin has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pfizer, BMS, Novartis, Exeltis, and AGEM. Dr Dillinger has received consulting and lecture fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, and Sanofi; grants from Bayer, Bristol-Myers Squibb/Pfizer, and Biosensors. Dr Steg has received grants or contracts from Amarin, Bayer, Sanofi, and Servier; consulting fees from Amgen, AstraZeneca, BMS/Myokardia,

Merck, Novo-Nordisk, and Regeneron Pharmaceuticals; and has served on steering committees or critical event committees for Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Idorsia, Novartis, PhaseBio, Pfizer, Sanofi, and Servier; he has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Novartis, and Novo Nordisk; support for attending meetings or travel from AstraZeneca; and he has participated on data safety monitoring boards or advisory boards for Servier, Sanofi, PHRI, and Monash University. The other authors have no conflicts of interest to disclose.

References

1. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med 2001;345:1230-6.
2. Chatterjee S, Wetterslev J, Sharma A, Lichstein E, Mukherjee D. Association of blood transfusion with increased mortality in myocardial infarction: a meta-analysis and diversity-adjusted study sequential analysis. JAMA Intern Med 2013;173:132-9.
3. Carson JL, Carless PA, Hebert PC. Outcomes using lower vs higher hemoglobin thresholds for red blood cell transfusion. JAMA 2013;309:83-4.
4. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al. Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: the REALITY randomized clinical trial. JAMA 2021;325:552-60.
5. Gonzalez-Juanatey JR, Lemesle G, Puymirat E, et al. One-year major cardiovascular events after restrictive versus liberal blood transfusion strategy in patients with acute myocardial infarction and anemia: the REALITY randomized trial. Circulation 2022;145:486-8.
6. Alam A, Lin Y, Lima A, Hansen M, Callum JL. The prevention of transfusion-associated circulatory overload. Transfus Med Rev 2013;27:105-12.
7. Ducrocq G, Calvo G, Gonzalez-Juanatey JR, et al. Restrictive vs liberal red blood cell transfusion strategies in patients with acute myocardial infarction and anemia: rationale and design of the REALITY trial. Clin Cardiol 2021;44:143-50.
8. Carson JL, Brooks MM, Hebert PC, et al. Restrictive or liberal transfusion strategy in myocardial infarction and anemia. N Engl J Med 2023;389:2446-56.
9. Clifford L, Jia Q, Yadav H, et al. Characterizing the epidemiology of perioperative transfusion-associated circulatory overload. Anesthesiology 2015;122:21-8.
10. Lieberman L, Maskens C, Cserti-Gazdewich C, et al. A retrospective review of patient factors, transfusion practices, and outcomes in patients with transfusion-associated circulatory overload. Transfus Med Rev 2013;27:206-12.
11. Serious Hazards of Transfusion (SHOT): Annual SHOT Report 2017. Available at: https://www.shotuk.org.
12. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. Blood 2019;133:1840-53.
13. Roubinian NH, Hendrickson JE, Triulzi DJ, et al. Contemporary risk factors and outcomes of transfusion-associated circulatory overload. Crit Care Med 2018;46:577-85.
14. Li G, Rachmale S, Kojicic M, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. Transfusion 2011;51:338-43.
15. Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol 2011;108:1108-11.
16. Ducharme A, Zieroth S, Ahooja V, et al. Canadian Cardiovascular Society-Canadian Heart Failure Society focused clinical practice update of patients with differing heart failure phenotypes. Can J Cardiol 2023;39:1030-40.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2024.02.013.