ONLINE FIRST

Outcome of Patients Who Refuse Transfusion After Cardiac Surgery

A Natural Experiment With Severe Blood Conservation

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Background: Jehovah's Witness patients (Witnesses) who undergo cardiac surgery provide a unique natural experiment in severe blood conservation because anemia, transfusion, erythropoietin, and antifibrinolytics have attendant risks. Our objective was to compare morbidity and long-term survival of Witnesses undergoing cardiac surgery with a similarly matched group of patients who received transfusions.

Methods: A total of 322 Witnesses and 87 453 non-Witnesses underwent cardiac surgery at our center from January 1, 1983, to January 1, 2011. All Witnesses prospectively refused blood transfusions. Among non-Witnesses, 38 467 did not receive blood transfusions and 48 986 did. We used propensity methods to match patient groups and parametric multiphase hazard methods to assess long-term survival. Our main outcome measures were postoperative morbidity complications, in-hospital mortality, and long-term survival.

Results: Witnesses had fewer acute complications and shorter length of stay than matched patients who received transfusions: myocardial infarction, 0.31% vs 2.8% ($P=.01$); additional operation for bleeding, 3.7% vs 7.1% ($P=.03$); prolonged ventilation, 6% vs 16% ($P<.001$); intensive care unit length of stay (15th, 50th, and 85th percentiles), 24, 25, and 72 vs 24, 48, and 162 hours ($P<.001$); and hospital length of stay (15th, 50th, and 85th percentiles), 5, 7, and 11 vs 6, 8, and 16 days ($P<.001$). Witnesses had better 1-year survival (95%; 95% CI, 93%-96%; vs 89%; 95% CI, 87%-90%; $P=.007$) but similar 20-year survival (34%; 95% CI, 31%-38%; vs 32% 95% CI, 28%-35%; $P=.90$).

Conclusions: Witnesses do not appear to be at increased risk for surgical complications or long-term mortality when comparisons are properly made by transfusion status. Thus, current extreme blood management strategies do not appear to place patients at heightened risk for reduced long-term survival.

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RED BLOOD CELLS (RBCs) not only are in short supply but are also associated with increased morbidity and reduced survival after cardiac surgery.[1-3] Jehovah's Witness patients (Witnesses) hold beliefs that disallow blood product transfusion and therefore offer a natural experiment in severe blood conservation. Their beliefs encourage the use of a number of blood conservation practices, including preoperative use of erythropoietin and iron and B-complex vitamins, hemoconcentration, and minimal crystalloid use; intraoperative use of antifibrinolytics and cell-saver and smaller cardiopulmonary bypass circuits; and postoperative liberal use of additional operation for bleeding along with tolerance of low hematocrit levels postoperatively. Although some of these practices may be beneficial to all cardiac surgical patients, others are associated with well-documented morbidity,[4-6] and their effect on long-term survival is uncertain.

See Invited Commentary at end of article

Although prior investigators compared immediate postoperative outcomes between Witnesses and non-Witnesses,[7-16] comparisons of long-term survival are lacking. Comparison is hampered, however, by impossibility of randomization to religious preference or blood transfusion, typical of any natural experiment. We have therefore used propensity-based comparative effectiveness tools[17-19]

to compare morbidity and long-term survival of Witnesses undergoing cardiac surgery with a propensity-matched group of patients who received transfusions.

METHODS

STUDY PATIENTS

A total of 96 162 adult patients underwent cardiac surgery at Cleveland Clinic from January 1, 1983, to January 1, 2011. For this analysis, we excluded patients undergoing placement of ventricular assist devices, those undergoing heart transplantation, or those who required extracorporeal membrane oxygenation (n=2526). We defined Witness status as prospectively documented refusal of RBCs, platelets, plasma, and cryoprecipitate (n=359); we excluded 32 Witnesses whose preoperative documentation of refusal was not found. In addition, 300 non-Witnesses and 5 Witnesses with missing information about blood transfusions were excluded. Only the first operation during the study period was considered, which eliminated 5524 operations. After exclusions, we identified 87 775 consecutive cardiac surgery patients, among whom 322 were Witnesses and 87 453 were non-Witnesses. Among the non-Witnesses, 48 986 (56.0%) received RBC transfusion and 38 467 (44.0%) did not. Thus, the trial cohort consisted of 322 Witnesses and 48 986 non-Witnesses who received transfusions (**Figure 1** and eAppendix 1; available at http://www.archinternmed.com).

We obtained blood transfusion data along with clinical data and outcomes from the Cardiovascular Information Registry (CVIR), a prospective database updated concurrently with patient care. The CVIR receives electronic laboratory and echocardiographic data, but most of its more than 500 variables per patient are abstracted by a team of full-time nurses trained in cardiothoracic surgery or medicine. One hundred percent of outcomes are audited, and a random 10% of cases are reabstracted and data compared and adjudicated. These data form the basis for national reporting, local quality initiatives, and research. The Cleveland Clinic institutional review board approved use of these data for research, with individual patient consent waived. Baseline and perioperative factors for non-Witnesses and Witnesses are listed in eAppendix 2.

END POINTS

We considered in-hospital complications (acute complications) for which the Society of Thoracic Surgeons has provided benchmarks, including return to the operating room for bleeding, stroke, atrial fibrillation, myocardial infarction, renal failure, respiratory insufficiency, sepsis, and in-hospital death. These end points were defined according to standards of the Society of Thoracic Surgeons Adult Cardiac Surgery Database (http: //www .ctsnet .org /file /rptDataSpecifications252 _1 _ForVendorsPGS.pdf).

We determined time-related all-cause mortality by querying the Social Security Death Master File using a closing date of February 6, 2011, and by querying follow-up data collected systematically from the CVIR. Only 1 patient (a Witness) was lost to follow-up.

Witnesses had 3003 patient-years of follow-up (mean [SD] follow-up, 9.6 [7.1] years; median, 8.5 years; 10% of survivors were followed up for more than 20 years). Non-Witnesses who received transfusions had 378 188 patient-years of follow-up (mean [SD] follow-up, 8.6 [7.2] years; median, 7.3 years; 10% of survivors were followed up for more than 19 years).

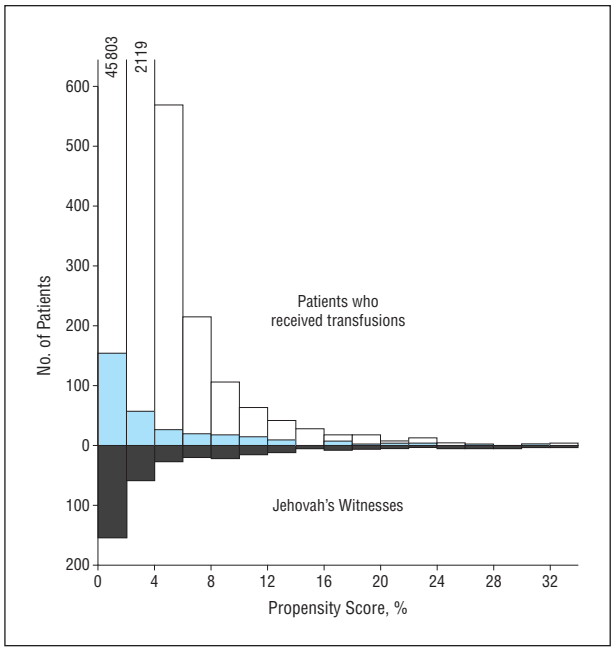

Figure 1. Mirrored histogram of propensity scores. Shaded areas show the distribution of propensity scores in matched patients. Patients who received transfusions are shown above the horizontal line at 0 and Jehovah's Witnesses are shown below. Fifteen patients who received transfusions and 5 Jehovah's Witnesses had a propensity score greater than 32%.

STATISTICAL ANALYSIS

Because neither religious preference nor receipt of blood transfusion among non-Witnesses could be randomized, we expected to find differences in the distribution of preoperative and operative characteristics of Witnesses and non-Witnesses. Using logistic regression analysis, in which being a Witness was the dependent variable, we constructed a model of the probability of being a Witness (as opposed to a non-Witness) with non-Witnesses who received transfusions, considering all preoperative and selected operative variables listed in eAppendix 3.

Initially, we used bagging to identify reliable predictors of being a Witness with random resampling and automated stepwise selection with an entry criterion of $P \leq .10$ and retention criterion of $P \leq .05$.[20] Variables or clusters of variables that entered 50% of 500 models were chosen for the final model (Breiman median rule, devised to balance type I and type II errors). During the study, new variables were introduced in 1990, 1993, and 1997. Therefore, 4 bootstrap models were run: one with variables available for all years using all data, another with variables available for all years plus those available after 1990 using only those patients operated on after 1990, another with variables available for all years plus those available after 1993 using only those patients operated on after 1993, and, finally, one with variables available for all years plus those available after 1997 using only those patients operated on after 1997. We synthesized information from these 4 bootstrap models to create a single parsimonious model. Variables missing during an extended period were treated as interactions with time and thus set to zero for that period. Values missing at random were filled using mean imputation (SAS PROC STANDARD; SAS Institute Inc), and missing value flags were forced into the final model.

Next, we augmented the parsimonious model with the most reliable predictors from clinically relevant groups to form propensity models (see eAppendix 3 for variables included in each propensity model).[17-19] For each patient, a propensity score was

generated, representing the probability that the patient would be a Witness. Using the propensity score and preoperative hematocrit, we matched (using a "greedy" approach[21]) each Witness with a non-Witness who received a transfusion.

We assessed association of Witness status with long-term mortality using a wholly parametric multiphase hazard method.[22] We selected this method because it nonarbitrarily decomposes hazard into time-overlapping temporal components based on the data and permits simultaneous assessment of risk factors (such as Witness vs non-Witness) in discrete time-based phases. The method enabled us to assess nonproportional hazards, a feature common to interventional procedures that carry transiently high early risk that subsides to considerably lower levels after a variable duration of recovery. Details regarding hazard function models and graphics are available at http://my.clevelandclinic.org/professionals/software/hazard/default.aspx).

Unadjusted hospital outcomes were compared using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables, and comparisons between Witnesses and propensity-matched non-Witnesses who received transfusions (adjusted comparison) were performed using the paired McNemar test for categorical variables and paired *t* test for continuous variables.

All analyses were performed using SAS statistical software, version 9.1 (SAS Inc). All *P* values are 2-sided, with a value of .05 considered significant.

PRESENTATION

Categorical variables are summarized by frequencies and percentages and continuous variables by means and standard deviations or 15th, 50th, and 85th percentiles when values are skewed. Asymmetric confidence limits of nonparametric survival estimates and confidence bands around parametric estimates are equivalent to ±1 SE (68%). Comparison of outcomes of propensity-matched pairs used the McNemar test for binary variables and paired *t* test for continuous variables.

RESULTS

ASSESSING THE NATURAL EXPERIMENT

Witnesses, compared with non-Witnesses who received transfusions, were older; more likely to be women, black, more symptomatic, and nonsmokers; and had a higher preoperative hematocrit (eAppendix 4 and eTable). If the patients underwent coronary artery bypass grafting, surgeons were less likely to use the internal thoracic artery as a conduit. Propensity matching, which accounted for these differences, resulted in a group of non-Witnesses who received transfusions well matched to Witnesses (**Table 1**, Figure 1, eAppendix 4, and eFigure 1).

NON-WITNESSES WHO RECEIVED TRANSFUSIONS VS WITNESSES

In unadjusted analyses, Witnesses had similar hospital mortality compared with non-Witnesses who received transfusions yet had statistically significantly lower occurrence of additional operation for bleeding, renal failure, and sepsis (**Table 2**).

After propensity matching, Witnesses and non-Witnesses who received transfusions had similar risks of in-hospital mortality, stroke, atrial fibrillation, and renal failure. However, Witnesses had lower occurrence of postoperative myocardial infarction, prolonged ventilation, and additional operation for bleeding; they also had shorter intensive care unit and postoperative lengths of stay (**Table 3**).

Survival estimates of Witnesses were 86%, 69%, 51%, and 34% at 5, 10, 15, and 20 years after surgery, respectively, vs 74%, 53%, 35%, and 23% among non-Witnesses who received transfusions. In unadjusted analyses, Witnesses had a lower hazard for death in the early and late hazard phases ($P < .001$; **Figure 2**). After propensity matching, Witnesses had a lower risk of death in the early hazard phase ($P = .007$) but a similar risk of death in the late phase ($P = .90$) (**Figure 3**).

COMMENT

PRINCIPAL FINDINGS

In a large cohort of Witnesses undergoing cardiac surgery, Witnesses had fewer in-hospital complications and better early and similar late survival compared with a matched group of cardiac surgical patients who received RBC transfusions (see eFigures 1-3 [http://www.archinternmed.com] for similar comparisons with non-Witnesses who did not receive transfusions).

Witnesses offered us a unique natural experiment of the short- and long-term effects of severe blood conservation. We took into account perioperative transfusions by comparing immediate and long-term survival in Witnesses with those who received transfusions. In previous studies, investigators demonstrated that RBC transfusion is associated with increased risk for in-hospital morbidity and reduced short- and long-term survival.[1,2,23,24]

In our unadjusted comparisons, we found that Witnesses were at lower risk for adverse postoperative outcomes. Propensity-matched comparisons between Witnesses and patients who received transfusions yielded lower risks for selected postoperative outcomes in Witnesses. Witnesses had fewer postoperative myocardial infarctions, fewer episodes of postoperative ventilator support beyond 24 hours, fewer additional operations for bleeding, shorter intensive care unit and postoperative lengths of stay, and a lower hazard for in-hospital death.

CLINICAL IMPLICATIONS

It is important to examine care of a patient population managed differently not only out of concern for morbidity risk but also for possible adoption of management strategies that may benefit other patient groups. These strategies include routine use of erythropoietin, but this has been reported to be linked to increased risk of thromboembolic complications.[4] Extremes of anemia also have associated morbidity risk,[5,6] as does additional operation for bleeding.[25]

STUDY LIMITATIONS

Like all observational studies, our analyses have limitations. We chose to use propensity matching and to

Table 1. Baseline Characteristics of the Propensity-Matched Patients

Characteristic	Jehovah's Witnesses		Non-Witnesses Who Received Transfusions	
	Total No. of Patients[a]	Value[b]	Total No. of Patients[a]	Value[b]
Demographics				
Age, mean (SD), y	322	62 (13)	322	61 (14)
Female sex	322	134 (41.6)	322	134 (41.6)
Race	321		319	
White		253 (78.8)		249 (78.1)
Black		62 (19.3)		60 (18.8)
Other		6 (1.9)		10 (3.1)
Body mass index, mean (SD)[c]	266	29 (5.9)	278	30 (6.6)
Clinical status				
NYHA class	225		244	
I		39 (17.3)		55 (22.5)
II		91 (40.4)		102 (41.8)
III		50 (22.2)		32 (13.1)
IV		45 (20.0)		55 (22.5)
Heart failure	322	56 (17.4)	322	57 (17.7)
Cardiac comorbidity				
Left ventricular dysfunction				
None	265	180 (67.9)	273	194 (71.1)
Mild		35 (13.2)		25 (9.2)
Moderate		33 (12.5)		35 (12.8)
Severe		17 (6.4)		19 (6.8)
Previous myocardial infarction	322	118 (36.6)	322	114 (35.4)
Atrial fibrillation or flutter on ECG	266	19 (7.1)	282	25 (8.9)
Previous cardiac operation	322	50 (15.5)	322	53 (16.5)
Emergency operation	322	5 (1.6)	322	8 (2.5)
Mitral valve stenosis	322	33 (10.2)	322	34 (10.6)
No. of systems diseased[d]	282		282	
0		75 (26.6)		75 (26.6)
1		35 (12.4)		40 (14.2)
2		59 (20.9)		43 (15.2)
3		113 (40.1)		124 (44.0)
Left main disease	271	40 (14.8)	262	25 (9.5)
Noncardiac comorbidity				
Smoking before 1990	248	116 (46.8)	250	131 (52.4)
Smoking after 1990	63	12 (19.0)	61	13 (21.3)
Hypertension	258	170 (65.9)	260	169 (65.0)
Treated diabetes mellitus	307	81 (26.4)	305	85 (27.9)
Peripheral arterial disease	322	17 (5.3)	322	16 (5.0)
Hematocrit, mean (SD), %	218	43 (4.6)	218	43 (4.6)
Dialysis	178	6 (3.4)	155	4 (2.6)
Preoperative BUN, mean (SD), mg/dL	247	19 (8.1)	252	20 (11)
Preoperative creatinine, mean (SD), mg/dL	247	1.2 (1.2)	252	1.3 (1.2)
Surgical characteristics				
Surgeon				
Surgeon 1	322	79 (24.5)	322	84 (26.1)
Surgeon 2	322	33 (10.2)	322	41 (12.7)
Surgeon 3	322	20 (6.2)	322	15 (4.7)
Surgeon 4	322	24 (7.5)	322	16 (5.0)
Surgeon 5	322	18 (5.6)	322	19 (5.9)
Surgical procedure				
CABG	322	209 (64.9)	322	215 (66.8)
AV repair or replacement	322	88 (27.3)	322	91 (28.3)
MV repair or replacement	322	69 (21.4)	322	68 (21.1)
Proximal aorta surgery	322	16 (5.0)	322	18 (5.6)
Cardiopulmonary bypass	222	206 (92.8)	227	209 (92.1)
Aortic clamping	222	198 (89.2)	227	204 (89.9)
Circulatory arrest	222	4 (1.8)	227	15 (6.6)
Years since January 1, 1983, mean (SD)	322	15 (7.9)	322	14 (7.3)

Abbreviations: AV, aortic valve; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; ECG, electrocardiogram; MV, mitral valve; NYHA, New York Heart Association.

SI conversion factors: To convert BUN to millimoles per liter, multiply by 0.357; to convert creatinine to micromoles per liter, multiply by 88.4.

[a] Patients with data available.

[b] Data are presented as number (percentage) of patients unless otherwise indicated.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Stenosis of 50% or greater.

Table 2. In-Hospital Complications: Unadjusted Comparison

Variable	Jehovah's Witnesses		Non-Witnesses Who Received Transfusions		
	Total No. of Patients	Value[a]	Total No. of Patients	Value[a]	*P* Value
Additional operation for bleeding or tamponade	322	12 (3.7)	48 986	3596 (7.3)	.01
Additional operation for graft occlusion[b]	105	0	15 465	15 (1.0)	>.99
Cardiac reoperation excluding valve dysfunction and graft occlusion	322	0	48 986	476 (1.0)	.08
Additional operation for valve dysfunction[b]	102	0	14 700	85 (0.6)	>.99
Other noncardiac operations[c]	116	0	15 022	815 (5.4)	.003
Permanent stroke	322	7 (2.2)	48 986	1415 (2.9)	.6
Perioperative MI	322	1 (0.3)	48 986	765 (1.6)	.07
Atrial fibrillation	258	64 (24.8)	40 810	12 234 (30.0)	.08
Respiratory failure[c]	322	20 (6.2)	48 986	8056 (16.4)	<.001
Postoperative hematocrit, %[d]	150	25/31/37	19 238	25/31/37	.02
Renal failure	322	14 (4.3)	48 986	3385 (6.9)	.08
Renal failure requiring dialysis[b]	173	2 (1.2)	24 191	1554 (6.4)	.002
Septicemia[e]	258	3 (1.2)	38 560	1727 (4.5)	.006
Deep sternal wound infection	322	0	48 986	445 (0.9)	.13
Operative length of stay, 15th/50th/85th percentiles	322	5.1/7.0/11	48 982	6.0/8.0/16	<.001
ICU length of stay, 15th/50th/85th percentiles, h[e]	258	24/25/72	38 530	24/48/144	<.001
Hospital death	322	10 (3.1)	48 986	2216 (4.5)	.30

Abbreviations: ICU, intensive care unit; MI, myocardial infarction.
[a] Data are presented as number (percentage) of patients unless otherwise indicated.
[b] Available January 1, 1997, or after.
[c] Definition changed on January 1, 1997, January 1, 2002, or January 1, 2008.
[d] Available January 1, 2007, or after.
[e] Available January 1, 1990, or after.

Table 3. In-Hospital Complications: Matched Comparison

Variable	Jehovah's Witnesses		Non-Witnesses Who Received Transfusions		
	Total No. of Patients	Value[a]	Total No. of Patients	Value[a]	*P* Value[b]
Additional operation for bleeding or tamponade	322	12 (3.7)	322	23 (7.1)	.03
Additional operation for graft occlusion[c]	105	0	91	0	
Cardiac reoperation excluding valve dysfunction and graft occlusion	322	0	322	3 (0.9)	
Reoperation for valve dysfunction[c]	102	0	87	0	
Other noncardiac operations[d]	116	0	101	3 (2.9)	
Permanent stroke	322	7 (2.2)	322	9 (2.8)	.60
Perioperative MI	322	1 (0.3)	322	9 (2.8)	.01
Atrial fibrillation	258	64 (24.8)	270	81 (30.0)	.20
Respiratory failure[d]	322	20 (6.2)	322	52 (16.1)	<.001
Postoperative hematocrit[e]	150	25/31/37	133	26/30/34	.20
Renal failure	322	14 (4.3)	322	16 (5.0)	.70
Renal failure requiring dialysis[c]	173	2 (1.2)	156	9 (5.8)	
Septicemia[f]	258	3 (1.2)	260	9 (3.5)	.13
Deep sternal wound infection	322	0	322	3 (0.9)	
Operative length of stay, 15th/50th/85th percentiles	322	5.1/7.1/11	322	6.0/8.0/16	<.001
ICU length of stay, 15th/50th/85th percentiles, h[f]	258	24/25/72	260	24/48/162	<.001
Hospital death	322	10 (3.1)	322	14 (4.3)	.40

Abbreviations: ICU, intensive care unit; MI, myocardial infarction.
[a] Data are presented as number (percentage) of patients unless otherwise indicated.
[b] Logarithmic transformation was used in the paired *t* test. In certain cases, comparison tests could not be applied to propensity-matched pairs.
[c] Available January 1, 1997, or after.
[d] Definition changed on January 1, 1997, January 1, 2002, or January 1, 2008.
[e] Available January 1, 2007, or after.
[f] Available January 1, 1990, or after.

identify a control group that received transfusions to minimize selection and referral biases. Nonetheless, propensity methods can account only for those variables that were available and properly recorded. We did not record data on many Witness care-specific practice variables that may have changed over time. Thus, our analyses do not allow us to identify which practices may have contributed to the outcomes. Finally, Witnesses

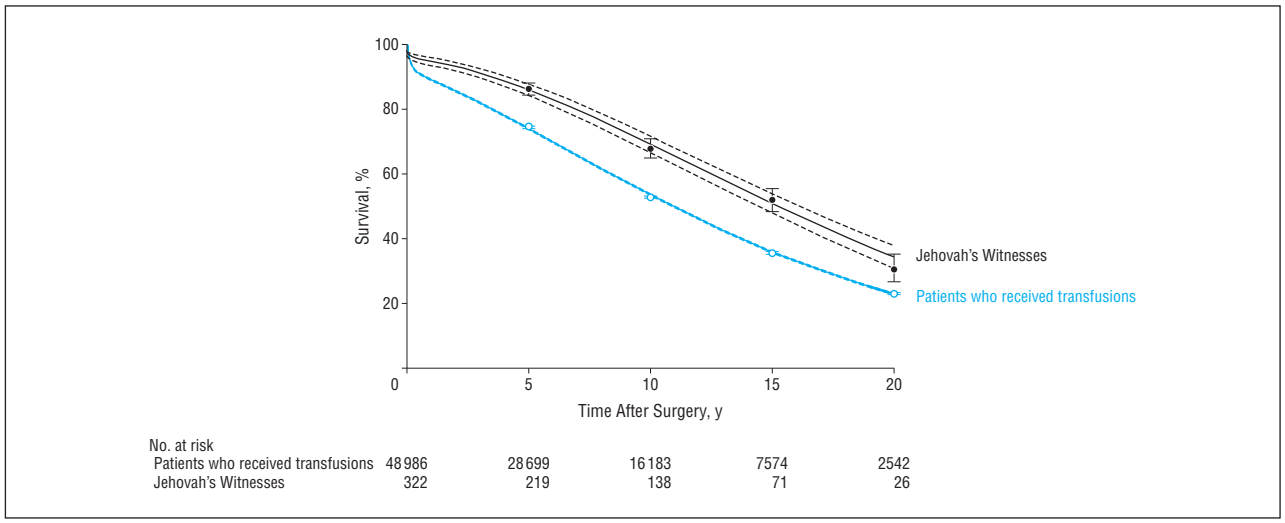

Figure 2. Unadjusted survival after cardiac surgery in Jehovah's Witnesses and patients who received transfusions. Error bars indicate Kaplan-Meier estimates at 5, 10, 15, and 20 years after surgery.

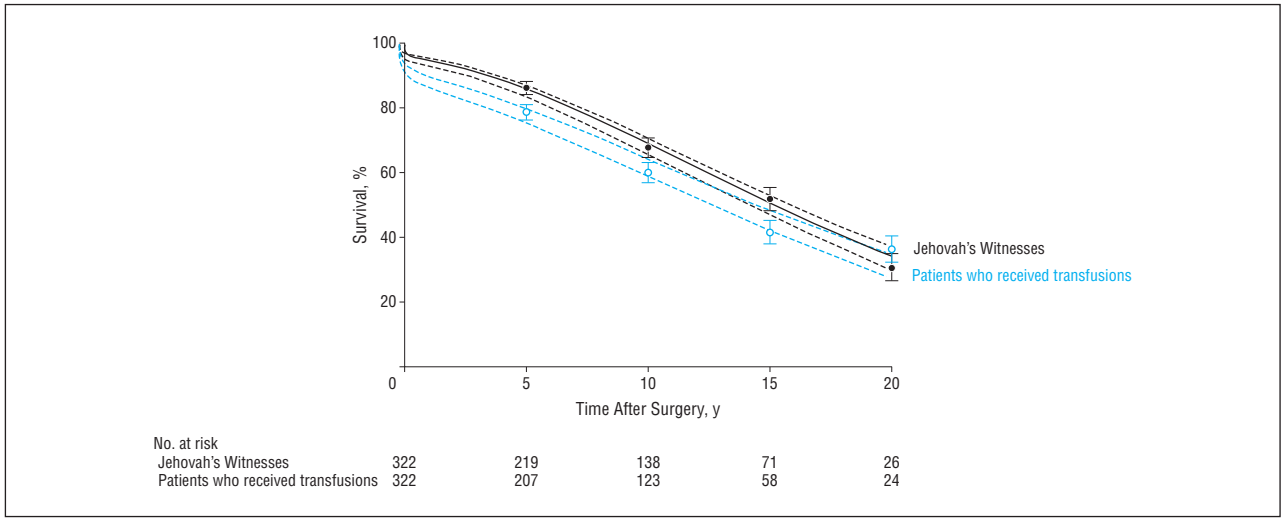

Figure 3. Survival of matched patients. Error bars indicate Kaplan-Meier estimates at 5, 10, 15, and 20 years after surgery.

who came to our center and who were accepted by our surgeons likely represent a select group who might have been expected by their physicians to have better outcomes.

CONCLUSION

In a unique natural experiment of severe blood conservation, Witnesses undergoing cardiac surgery at one major center experienced similar or even better short- and long-term survival than non-Witnesses. These patients differentiate themselves by specific process-of-care management strategies aimed at avoiding extreme anemia. Unique management of the Witnesses may have attendant risks; however, RBC transfusion carries risk as well. Although we found differences in complications among Witnesses and control groups that received transfusions, current extreme blood management strategies do not appear to place patients at heightened risk for reduced long-term survival.

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Online-Only Material: The eAppendix, eTable, and eFigures are available at http://www.archinternmed.com.

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INVITED COMMENTARY

ONLINE FIRST

Severe Blood Conservation

Benefits and Risks

The article by Pattakos and coauthors[1] analyzes outcomes in Jehovah's Witness patients (Witnesses) who do not receive blood transfusion during cardiac operations. They use careful matching statistics to compare Witnesses with a matched group of non-Witnesses who received transfusion. They conclude that no long-term harm accrues to Witnesses as a result of extreme blood conservation interventions.

Witnesses believe that the Bible prohibits ingesting blood and that Christians should therefore not accept blood transfusions or donate or store their own blood for transfusion.[2] Members of the religion who voluntarily accept a transfusion are regarded as having disassociated themselves from the religion by abandoning its doctrines and are subsequently shunned by members of the organization.

Witnesses are taught that the use of fractions, such as albumin, immunoglobulins, and hemophiliac preparations, are not prohibited, and accepting these blood fractions is a matter of personal choice (**Table**). Although accepted by most Witnesses, a few do not endorse this doctrine, and this group adamantly refuses any blood component or fraction.

Surgeons who operate on Witnesses need to understand the nuances of Witnesses' beliefs and use any or all of the interventions listed in the Table if accepted by Witnesses. Witnesses contemplating cardiac operations need to have a specific and individual discussion about surgical options. Few publications that report outcomes of cardiac operations in Witnesses give a complete description of the alternative blood fractions or the