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ORIGINAL RESEARCH

Biventricular Repair of Univentricular Heart Lowers Risk of Liver Disease Compared With the Fontan Operation

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ABSTRACT

BACKGROUND The Fontan operation is associated with chronic venous hypertension, liver and renal disease, and several other sequelae. The alterative surgical approach, when feasible, a biventricular conversion (BiV), may diminish some of these long-term risks.

OBJECTIVES The aim of this study was to compare long-term outcomes of patients undergoing BiV with those undergoing a destination Fontan operation.

METHODS We identified all patients with univentricular physiology cared for at Boston Children's Hospital between 2007 and 2022 and divided them into those who received BiV or Fontan operations. Outcomes included 10-year incidences of modified major adverse cardiovascular events (MACE), liver dysfunction, renal dysfunction, and transplant-free survival. Outcomes in the 2 groups were compared using propensity matching.

RESULTS A total of 927 patients were evaluated, 341 BiV and 586 Fontan. Following propensity matching, 258 patients from each group were compared. There were no differences between groups in estimated 10-year freedom from MACE ($P = 0.70$), transplant-free survival ($P = 0.70$), or freedom from renal disease ($P = 0.60$). However, estimated 10-year freedom from liver disease was greater in BiV patients (82% BiV vs 71% Fontan, $P = 0.02$). Incidence rate per 100 person-years follow-up of surgical interventions and readmissions was higher among BiV patients (10.11 vs 1.85, $P < 0.001$ and 13.09 vs 9.6, $P = 0.002$), while catheter-based interventions were higher among Fontan patients (8.41 vs 4.63, $P < 0.001$).

CONCLUSIONS Among a contemporary cohort of patients with single ventricle anatomy, BiV provide comparable long-term survival and lower risk of liver disease when compared to patients who have undergoing Fontan operations. (JACC Adv. 2025;4:101429) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ASD = absolute standardized difference

AVM = arteriovenous malformation

AVV = atrioventricular valve

BiV = biventricular conversion

CHD = congenital heart disease

EFE = endocardial fibroelastosis

FALD = Fontan-associated liver disease

ICU = intensive care unit

MACE = major adverse cardiovascular events

PB = plastic bronchitis

PLE = protein-losing enteropathy

PSM = propensity score matching

PVS = pulmonary vein stenosis

The Fontan circulation is often considered for patients with complex intracardiac anatomy. Although more than 40% of such patients survive into the fourth decade of life,[1] survivors are plagued by significant, life-altering morbidity. It is noteworthy, though, that many of these patients were operated on in the 1970s and 1980s, and significant advances have been made that have since improved long-term outcomes. Physiologically, the Fontan imposes a venous flow resistor, causing venous congestion and diminished flow,[2] perturbations with significant clinical sequelae. First, impaired ventricular filling results in the inability to recruit stroke work during exercise.[3] This compromises peak exercise oxygen consumption, ventilatory anaerobic threshold, and exercise capacity, which are below population norms in patients with Fontan.[4,5] Second, even with modern surgical techniques (ie, lateral tunnel or extracardiac conduit), the incidence of atrial arrhythmias within the first decade approaches 40%, a finding also associated with thromboembolic events.[6] Third, increased systemic venous pressure leads to increased mesenteric capillary pressure and increased lymphatic pressure, which are thought to be the central drivers of protein-losing enteropathy (PLE).[7] Finally, hepatic vein hypertension is thought to drive hepatic fibrosis and cirrhosis, which are nearly universal findings following the Fontan operation in a time-dependent fashion.[8]

A biventricular conversion (BiV) directs systemic venous return to the atrium rather than the pulmonary circulation. When the atrioventricular valves (AVVs) and ventricles are sufficiently functional, a biventricular circulation may diminish venous hypertension, augment cardiac output, and protect against some of the medium- and long-term sequelae of the Fontan. Reports of outcomes following BiV have shown evidence of ventricular growth and favorable near-term outcomes.[9-14] The purpose of this study was to compare 10-year outcomes of patients undergoing BiV with those undergoing a Fontan operations in a large cohort of patients with complex congenital heart disease (CHD) at a single institution.

METHODS

We retrospectively identified all patients with complex CHD, ie, patients with significant ventricular or AVV hypoplasia, abnormal ventricular looping, or complex outflow tract anatomy that precludes a standard neonatal biventricular repair, who underwent neonatal univentricular palliative strategies (eg, pulmonary artery banding, stage 1 palliation, etc), followed by either BiV or Fontan as a destination circulation between January 1, 2007, and July 1, 2022. The study was approved by the Institutional Review Board. A combined 966 patients were identified, 377 patients in the BiV group and 589 patients in the Fontan group. Patients are selected for BiV based on anatomic considerations and preoperative hemodynamics by a multidisciplinary team at the Boston Children's Hospital Complex Biventricular Repair Program.[15,16] **Table 1** lists the broad anatomy classes for each group. Patients were identified based on diagnostic and surgical (ie, Fyler) codes. We divided patients into 2 cohorts: those who ultimately received BiV, and those whose destination circulation was a Fontan. Either the ultimate BiV or destination Fontan was considered the index operation. Patients undergoing 1.5 ventricles repair were excluded. Boston Children's Hospital 1.5 ventricles repair experience has been previously published.[17]

IDENTIFICATION OF PROPENSITY FACTORS. In order to account for various preoperative risk factors that may have influenced the likelihood of undergoing a BiV, we identified the presence of the 13 variables. Propensity factors known from 1 year prior to the index operation until 24 hours prior to surgery were considered.

1. Pulmonary vein stenosis (PVS) intervention, stent or surgery;
2. Atrioventricular valve regurgitation, moderate or worse;
3. Pulmonary hypertension diagnosis, by echocardiogram or catheterization;
4. Tracheostomy;
5. Permanent pacemaker;
6. Systemic ventricular systolic dysfunction, moderate or worse;
7. Aortic or neoaortic valve regurgitation, moderate or worse;
8. Lung disease, defined as the presence of a single lung, hypoplastic lung, agenesis lung, or pulmonary venous atresia;
9. Renal disease (creatinine laboratory value > upper limit of normal for age);
10. Liver disease (aspartate aminotransferase, alanine transaminase, or direct bilirubin values > upper limit of normal for age);
11. Heterotaxy syndrome;
12. Age at the time of surgery;
13. Weight at the time of surgery.

TABLE 1 Anatomic Subtypes and Latest Palliation Prior to Index Operation in Both Aggregate and Propensity-Matched Cohort

	Aggregate			Propensity Matched		
	BiV (n = 377)	Fontan (n = 589)	*P* Value	BiV (n = 258)	Fontan (n = 258)	*P* Value
Age, y	2.3	2.8	0.15	2.8	2.8	0.99
Weight, kg	11.1	12.9	0.07	12.6	13.2	0.15
Male	54%	59%		55%	60%	
Native anatomy						
Hypoplastic left heart	50 (13%)	250 (42%)	<0.001	34 (13%)	99 (38%)	<0.001
Unbalanced atrioventricular canal defect	82 (22%)	53 (9.0%)	<0.001	39 (15%)	39 (15%)	1.00
Double outlet right ventricle	69 (18%)	50 (8.5%)	<0.001	52 (20%)	23 (8.9%)	<0.001
Double outlet right ventricle with complete atrioventricular canal defect	57 (15%)	11 (1.9%)	<0.001	38 (15%)	11 (4.3%)	<0.001
L-transposition of the great arteries	70 (19%)		<0.001	60 (23%)		<0.001
D-transposition of the great arteries with VSD	13 (3.4%)	4 (0.7%)	0.002	9 (3.5%)	3 (1.2%)	0.141
Tetralogy of Fallot with atrioventricular canal defect	7 (1.9%)		0.001	4 (1.6%)		0.124
Coarctation of aorta/VSD	6 (1.6%)		0.003	5 (1.9%)		0.061
Pulmonary atresia/intact ventricular septum	4 (1.1%)	37 (6.3%)	<0.001	3 (1.2%)	12 (4.7%)	0.033
Ebstein's anomaly	3 (0.8%)	1 (0.2%)	0.305	3 (1.2%)		0.249
Interrupted aortic arch/VSD	3 (0.8%)		0.059	1 (0.4%)		1.00
Tricuspid atresia	3 (0.8%)	102 (17%)	<0.001	2 (0.8%)	36 (14%)	<0.001
Aortic atresia	2 (0.5%)		0.152	1 (0.4%)		1.00
Aortic stenosis/VSD	2 (0.5%)		0.152	1 (0.4%)		1.00
Hypoplastic right heart	2 (0.5%)	2 (0.3%)	0.646	2 (0.8%)	1 (0.4%)	1.00
Multiple VSDs	2 (0.5%)		0.152	2 (0.8%)		0.499
Anomalous pulmonary veins	1 (0.3%)		0.39	1 (0.4%)		1.00
Double inlet left ventricle	1 (0.3%)	76 (13%)	<0.001	1 (0.4%)	32 (12%)	<0.001
Other		3 (0.5%)	0.285		2 (0.8%)	0.499
Most recent palliation						
Bidirectional Glenn	94 (25%)	589 (100%)	<0.001	78 (30%)	258 (100%)	<0.001
Pulmonary artery band	95 (25%)			63 (24%)		
Stage 1 palliation	78 (21%)			41 (16%)		
Ventricular recruitment[a]	53 (14%)			36 (14%)		
Fontan	24 (6.4%)			13 (5.0%)		
No prior palliation	18 (4.8%)			15 (5.8%)		
PDA stent +/− pulmonary arteries banding	15 (4.0%)			12 (4.7%)		

Values are n (%). [a]Ventricular recruitment procedures included a bidirectional Glenn with aortopulmonary shunt and/or staging operation, such as atrial septal restriction.
PDA = patent ductus arteriosus; VSD = ventricular septal defect.

Additional risk factors, including preoperative abnormal junctional rhythm, pulmonary arteriovenous malformation (AVM), hemoptysis, and trisomy 21 were considered, but ultimately excluded as they were not present in both groups. Instead, the 35 patients with these factors were removed before matching. An additional 4 patients were removed due to missing data. This has brought the ultimate total number of patients to 927, with 341 in the BiV group and 586 in the Fontan group.

OUTCOMES. Our primary outcome was the 10-year incidence of a composite variable of time to the earliest occurrence of any major adverse cardiovascular events (MACE) that are commonly found in either population. The timing of MACE was defined as the first occurrence after hospital discharge of any of the following (except for death or transplant, which were included any time following the index operation):

1. PLE diagnosis;
2. Plastic bronchitis (PB) diagnosis;
3. Hemoptysis diagnosis;
4. Arrhythmia including ventricular tachycardia, junctional rhythm, atrial flutter, atrial fibrillation, or automatic ectopic atrial tachycardia;
5. New postoperative diagnosis of pulmonary AVM;
6. New tracheostomy;
7. Heart transplant at any time after surgery; or
8. Death at any time after surgery

Each of these was identified by a detailed diagnostic code at our institution and was confirmed by a

TABLE 2 Comparison of Preoperative Risk Factors Between Groups Prior to and Following Propensity Matching

	Aggregate Cohort					Propensity-Matched Cohort				
	BiV (N = 341)	Fontan (N = 586)	Overall (N = 927)	*P* Value	ASD	BiV (N = 258)	Fontan (N = 258)	Overall (N = 516)	*P* Value	ASD
PVS	18 (5.3%)	16 (2.7%)	34 (3.7%)	0.07	0.13	9 (3.5%)	15 (5.8%)	24 (4.7%)	0.30	0.11
AVV regurgitation	80 (23.5%)	61 (10.4%)	141 (15.2%)	0.00	0.35	44 (17.1%)	37 (14.3%)	81 (15.7%)	0.47	0.07
Pulmonary HTN	4 (1.2%)	1 (0.2%)	5 (0.5%)	0.06	0.12	1 (0.4%)	1 (0.4%)	2 (0.4%)	1.00	0.00
Tracheostomy	6 (1.8%)	1 (0.2%)	7 (0.8%)	0.01	0.16	3 (1.2%)	1 (0.4%)	4 (0.8%)	0.62	0.09
Pacemaker	16 (4.7%)	11 (1.9%)	27 (2.9%)	0.02	0.16	10 (3.9%)	8 (3.1%)	18 (3.5%)	0.81	0.04
Ventricular dysfunction	26 (7.6%)	47 (8.0%)	73 (7.9%)	0.90	0.01	16 (6.2%)	16 (6.2%)	32 (6.2%)	1.00	0.00
Aortic regurgitation	9 (2.6%)	6 (1.0%)	15 (1.6%)	0.10	0.12	4 (1.6%)	6 (2.3%)	10 (1.9%)	0.75	0.06
Lung disease	4 (1.2%)	6 (1.0%)	10 (1.1%)	1.00	0.01	4 (1.6%)	5 (1.9%)	9 (1.7%)	1.00	0.03
Renal dysfunction	55 (16.1%)	10 (1.7%)	65 (7.0%)	0.00	0.52	6 (2.3%)	9 (3.5%)	15 (2.9%)	0.86	0.07
Liver dysfunction	53 (15.5%)	23 (3.9%)	76 (8.2%)	0.00	0.40	17 (6.6%)	15 (5.8%)	32 (6.2%)	0.60	0.03
Heterotaxy	70 (20.5%)	65 (11.1%)	135 (14.6%)	0.00	0.26	42 (16.3%)	55 (21.3%)	97 (18.8%)	0.18	0.13
Weight, kg	14.1 ± 10.4	14.7 ± 8.65	14.5 ± 9.33	0.35	0.07	14.5 ± 10.5	16.2 ± 10.9	15.4 ± 10.8	0.07	0.16
Age, y	3.4 ± 3.4	3.7 ± 4.2	3.6 ± 3.1	0.29	0.06	3.5 ± 3.3	4.2 ± 4.3	3.9 ± 3.8	0.07	0.16

Values are n (%) or mean ± SD. *P* values are based on Fisher exact tests for categorical variables and independent sample *t*-tests for continuous variables.
ASD = absolute standardized difference; AVV = atrioventricular valve; BiV = biventricular conversion; HTN = hypertension; PVS = pulmonary vein stenosis.

chart review of a random subset of patients (10%). Events were recorded for 10 years after surgery, and follow-up time after 10 years was censored.

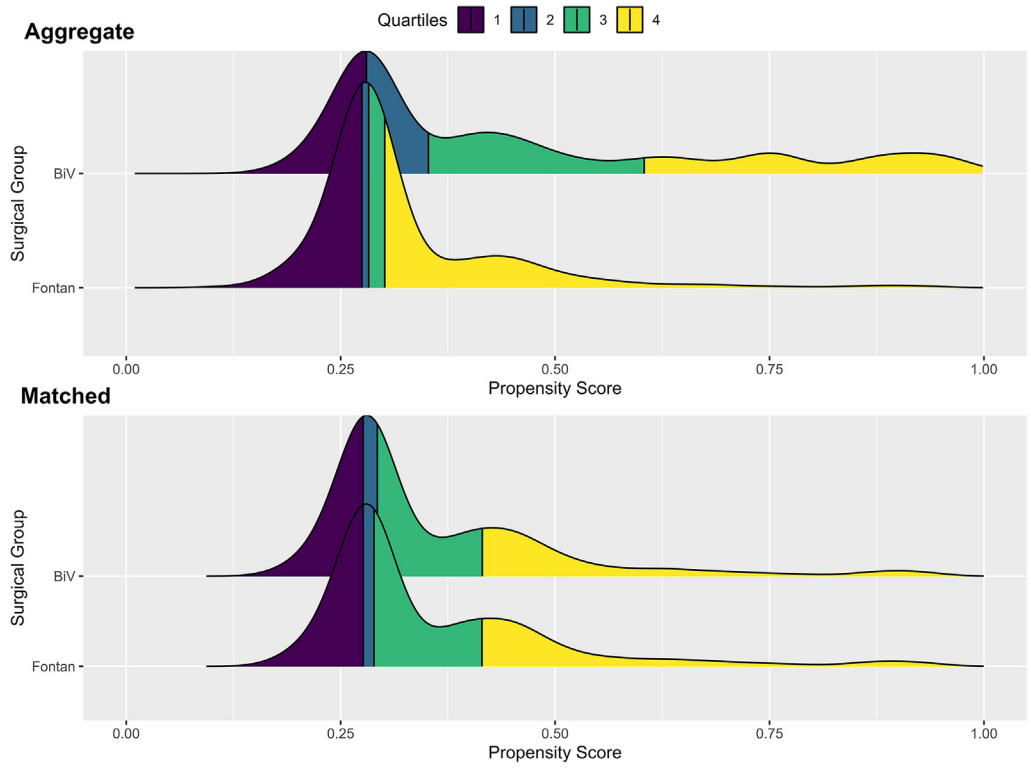
Secondary outcomes included a composite of death and transplant, referred to here as 10-year transplant-free survival time, time to new-onset liver dysfunction, time to new-onset renal dysfunction, survival to hospital discharge, intensive care unit (ICU) length of stay, number of surgical and catheter-based reinterventions, readmission rate, valvular and ventricular dysfunction at most recent follow-up. Freedom from MACE in each group based on presence of preexisting endocardial fibroelastosis (EFE) was also analyzed as a secondary outcome.

STATISTICAL ANALYSIS. Descriptive statistics were calculated using mean ± SD for normally distributed continuous variables or median (IQR) for non-normally distributed continuous variables. Categorical variables were described using frequency and proportion. Differences in continuous variables between groups were compared using Student's *t*-tests or Wilcoxon rank sum tests, and differences in categorical variables between groups were compared using chi-square or Fisher exact tests. A *P* value of <0.05 was considered statistically significant.

In order to minimize differences in risk factor variables between the 2 groups, we performed propensity score matching (PSM). Propensity scores were calculated using a multivariable logistic regression model with the aforementioned 13 predictors as independent variables to estimate the probability of undergoing a BiV (Table 2). Patients in the 2 groups were matched in a 1:1 ratio according to propensity score by nearest-neighbor matching with a max caliper width of 0.05 times the standard deviation of the logit of the propensity score and without replacement.[18] In order to assess matching, we used Fisher exact tests for categorical variables and Student's *t*-tests for continuous variables. We also measured absolute standardized difference (ASD) for continuous and binary variables, respectively (Supplemental Figure 2). Reduction in pseudo R^2 of each model was also measured. Since all Fisher exact tests and Students' *t*-tests were nonsignificant, ASDs between groups for all factors that had a significant impact on days free from MACE were less than our cutoff value of 0.1, and pseudo R^2 was reduced to close to 0, we determined that matching was satisfactory and no further adjustment was made for confounders.[18] Subjects with similar propensity scores were treated as independent, not paired, observations.

The relationship between group and time free from MACE was estimated using Kaplan-Meier methodology and quantified using log-rank tests. Cox modeling with a time dependent coefficient was performed to determine the impact of surgery on time free from MACE during distinct follow-up periods: 0 to 5 years after surgery and >5 years after surgery. Freedom from MACE in each surgical group based on preexisting EFE was estimated in the aggregate cohort using the same Kaplan-Meier methodology after performing Cox modeling to determine the interaction of surgical group and EFE. Associations between

FIGURE 1 Propensity Score for BiV Surgery in Each Surgical Group, in Both the Aggregate and Propensity Score Matched Cohort



other secondary outcomes were assessed using Student's *t*-tests, Fisher exact tests, and exact Poisson tests as appropriate. ICU length of stay was log transformed before significance testing in order to approach normality.

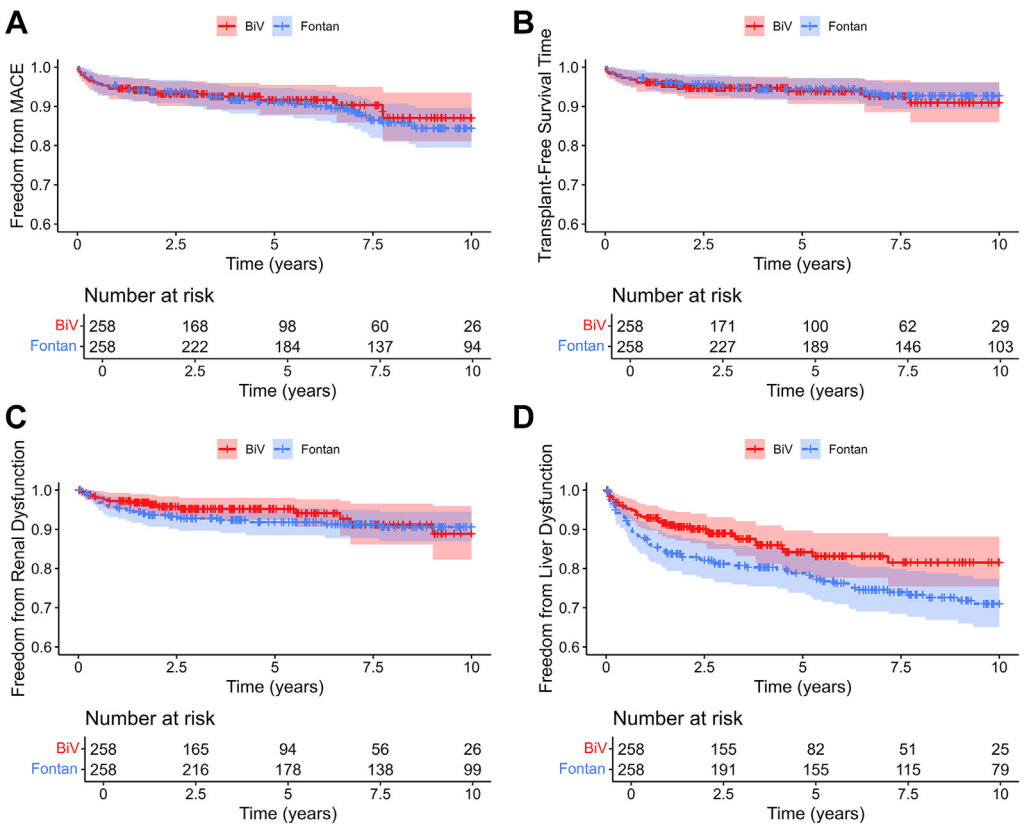
RESULTS

Among the 927 patients, anatomic diagnoses were different between groups (**Table 1**). None of the patients in the BiV cohort underwent BiV in the neonatal period, and the vast majority (95%) underwent univentricular palliations leading to a variable preconversion destination (**Table 1**). The relationship between the most recent palliation prior to index operation as related to underlying anatomy is shown in Supplemental Table 1. The median age at the time of index operation was 2.7 (IQR: 2.1-3.7) years.

Prior to propensity matching, BiV patients had a greater preoperative prevalence of moderate or more AVV regurgitation (23.5%), tracheostomy (1.8%), pacemaker (4.7%), liver dysfunction (15.5%), renal dysfunction (16.1%), and heterotaxy syndrome (20.5%) than did those with Fontan as their destination (**Table 2**). The groups did not differ by the presence of PVS, pulmonary hypertension, ventricular dysfunction, aortic regurgitation, lung disease, age, or weight. In the aggregate cohort, there was no difference in estimated 10-year freedom from MACE, new-onset renal dysfunction, or freedom from new-onset liver dysfunction. However, there was a difference in transplant-free survival (Supplemental Figure 1).

The model used for PSM is shown in Supplemental Table 2. Factors were included regardless of significance of the difference between groups or impact on outcome variables.[19] Following PSM, differences in propensity factors were all nonsignificant (**Table 2**), as was the distribution of propensity scores (**Figure 1**). A total of 258 patients from each group were matched. The ASD for each risk factor was ≤0.1 after matching, with the exception of PVS, heterotaxy, weight, and age (**Table 2**). The pseudo R2 was reduced from 0.169 to 0.029 after matching. The median follow-up time overall was 7.0 (IQR: 3.7-11.1) years, and the follow-up time in the Fontan group was greater than that in the BiV group (4.8 [IQR: 3.0-8.0] vs 9.6 [IQR: 5.7-13.1] years, $P < 0.001$). The distributions of year of surgery differed for the 2 surgical groups, and year of surgery was also associated with study outcomes. Covariate-

FIGURE 2 Kaplan-Meier Curves for Estimated 10-Year Transplant-Free Survival and Freedom From MACE, New Onset Renal and Liver Dysfunction in PSM Cohort



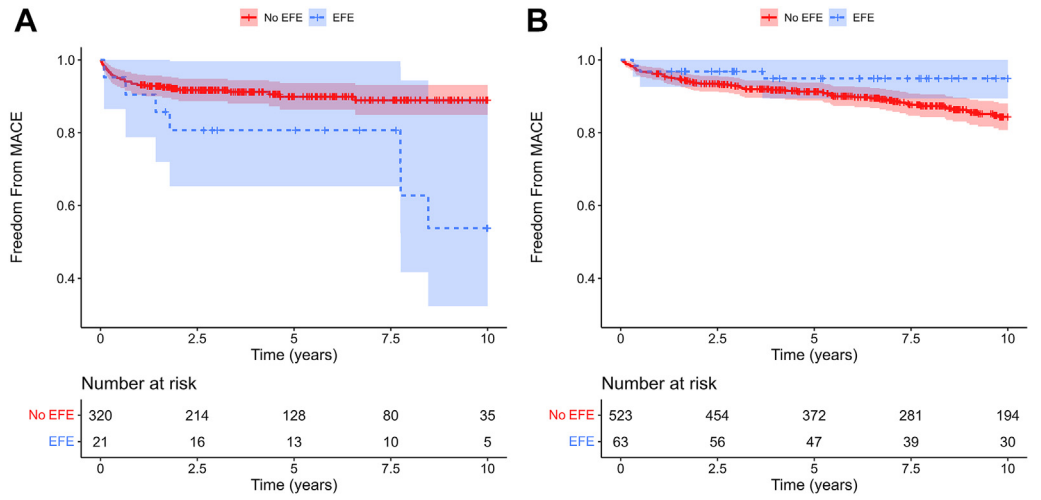
In the PSM cohort, there was no difference in estimated 10-year freedom from (A) MACE (BiV 87% [81%-94%] vs Fontan 84% [80%-90%], $P = 0.70$), (B) transplant-free survival (BiV 91% [86%-96%] vs Fontan 93% [89%-96%], $P = 0.70$), or (C) new-onset renal dysfunction (BiV 89% [82%-96%] vs Fontan 91% [87%-94%], $P = 0.60$). (D) There was an increase in freedom from new-onset liver dysfunction (BiV 82% [75%-88%] vs Fontan 71% [65%-77%], $P = 0.02$). PSM = propensity score matching.

adjusted analyses on the propensity-matched cohort were performed with year of surgery as a covariate, and inferences were unchanged. The following results describe PSM cohort comparisons.

PRIMARY OUTCOME. The estimated 10-year rate of freedom from MACE was 87.1% (95% CI: 81.1%-93.5%) in the BiV group and 84.4% (95% CI: 79.5%-89.6%) in the Fontan group ($P = 0.70$, log-rank test, **Figure 2A**; HR 1.13 [95% CI: 0.65-1.96] Fontan vs BiV, $P = 0.70$). A test of interaction was performed to compare estimates of the final destination surgery effect change over time (<5 years vs ≥5 years postprocedure), and the interaction was not significant ($P = 0.77$), suggesting that there was not a differential effect of BiV vs Fontan surgery according to time postprocedure (or there was insufficient power to declare the 2 effects as different). The breakdown of the first MACE encountered in each cohort is shown in Supplemental Table 3.

SECONDARY OUTCOMES. There were no differences between cohorts with respect to transplant-free survival time ($P = 0.7$, log-rank test; HR 0.87 [95% CI: 0.43-1.73] Fontan vs BiV, $P = 0.70$) (**Figure 2B**) or freedom from new-onset renal dysfunction ($P = 0.60$, log-rank test; HR: 1.20 [95% CI: 0.62-2.33] Fontan vs BiV, $P = 0.60$) (**Figure 2C**). However, estimated 10-year freedom from new-onset liver dysfunction was higher in BiV patients than Fontan patients (BiV 82% [75%-88%] vs Fontan 71% [65%-77%], $P = 0.02$ log-rank test; HR: 1.63 [95% CI: 1.07-2.48] in Fontan vs BiV, $P = 0.02$) (**Figure 2D**). The groups had different log length of stays in the ICU (BiV 7.9 days [log value of 2.1] vs Fontan 3.2 days [log 1.2], $P < 0.001$) (Supplemental Table 5). The groups did not differ in

FIGURE 3 Kaplan-Meier Curves for Estimated 10-Year Freedom From MACE for Each Aggregate Surgical Group With and Without EFE



In the aggregate cohort (A) BiV patients with EFE had a lower rate of estimated 10-year freedom from MACE (54% [32%-89%] vs 89% [85%-93%], $P = 0.003$, log-rank test; HR: 3.24 [95% CI: 1.42-7.40] for EFE vs non-EFE, $P = 0.005$). The interaction of surgical group and EFE had a significant impact on time free from MACE ($P = 0.003$). (B) There was no difference in time free from MACE between Fontan patients with vs without EFE (EFE 95% [89%-100%], no EFE 84% [81%-88%], $P = 0.07$ log-rank test; HR: 0.36 [95% CI: 0.11-1.15] for EFE vs non-EFE, $P = 0.085$). EFE = endocardial fibroelastosis.

survival to discharge (98.1% for BiV vs 98.8% for Fontan, $P = 0.7$). No patient in the BiV cohort experienced PLE, PB, or pulmonary AVMs during the observation period, and no patient in the Fontan cohort experienced tracheostomy (Supplemental Table 4).

READMISSION AND REINTERVENTION RATES. The incidence of readmissions (>2 days stay) following the index encounter was higher among BiV patients relative to Fontan (13.0 vs 9.6 admissions per 100 person-years of follow-up, $P = 0.002$). The incidence of surgical reinterventions was higher following BiV relative to Fontan (10.0 vs 1.8 reinterventions per 100 person-years of follow-up, $P < 0.001$); the most common surgical reinterventions in the BiV group were atrioventricular valve repair and conduit exchange. The incidence of catheter-based interventions was lower following BiV (4.6 vs 8.4 interventions per 100 person-years of follow-up, $P < 0.001$); the most common catheter-based reinterventions in the Fontan group were coiling of collaterals and fenestration device closure. A complete breakdown of interventions is provided in Supplemental Table 5.

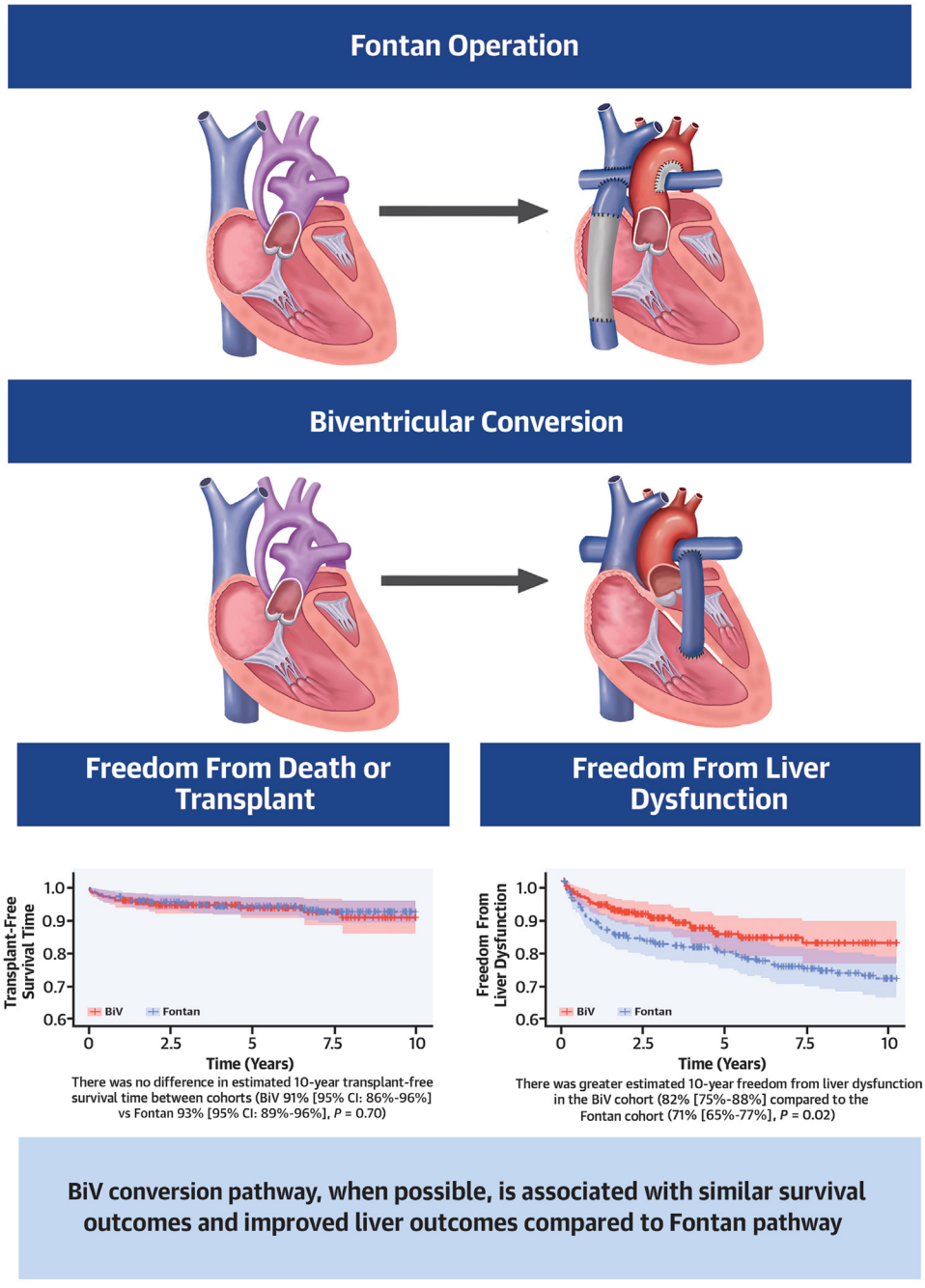
VENTRICULAR SYSTOLIC DYSFUNCTION AND VALVULAR REGURGITATION. At most recent follow-up as of July 2, 2024, the incidence of moderate or more systolic ventricular dysfunction was higher among patients in the Fontan group (BiV 6.6% vs Fontan 17.1%, $P < 0.001$). The incidence of moderate or more AVV regurgitation (either mitral or tricuspid) was no different among patients in both groups (BiV 9.3% vs Fontan 6.2%, $P = 0.249$) (Supplemental Table 6).

ASSOCIATION OF ENDOCARDIAL FIBROELASTOSIS AND OUTCOME. The interaction of surgical group and EFE had a significant impact on time free from MACE ($P = 0.003$). Among the BiV patients in aggregate, the presence of pre-existing EFE was associated with lower estimated 10-year survival from MACE (54% [32%-89%] vs 89% [85%-93%], $P = 0.003$); this was not the case in patients treated with Fontan (EFE 95% [89%-100%], no EFE 84% [81%-88%], $P = 0.07$) (**Figure 3**).

DISCUSSION

In a propensity-matched, contemporary cohort of patients with complex CHD treated at a single center, we have shown that patients undergoing BiV have a similar 10-year freedom from MACE, death or transplant, and renal dysfunction, and a lower incidence of liver dysfunction when compared with patients undergoing Fontan as their destination physiology. As evidenced in the aggregate cohort, patients

CENTRAL ILLUSTRATION **Fontan vs Biventricular Conversion Long-Term Outcomes**



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undergoing BiV were generally sicker, with a higher incidence of pre-existing AVV regurgitation, renal dysfunction, liver dysfunction, and heterotaxy, among others. While these factors were adequately matched in the PSM, this finding is indicative that BiV at our institution is still frequently used in patients who are at high risk for Fontan. Relatedly, BiV patients with other clinically significant risk factors, including pulmonary AVMs, pre-existing hemoptysis, and trisomy 21 had to be excluded from the PSM cohort, as they were not present in any Fontan patient. Even with these limitations, these data

demonstrate that among propensity-matched cohorts, BiV at our institution is associated with similar mortality and transplant-free survival as Fontan and reduces the incidence of liver dysfunction, a major source of morbidity following the Fontan procedure. The ICU length of stay was higher among the BiV patients, readmission rate as well as the surgical reintervention rate, while the cath reintervention rate was higher among the Fontan patients.

At the outset, we hypothesized that BiV patients would have a lower incidence of MACE over time, as several of the MACE events are considered prototypical complications of the Fontan circulation. Although this was not the case in composite, it is noteworthy that no patients in the BiV group experienced PLE, PB, or pulmonary AVMs, and fewer experienced hemoptysis, all complications that can be life-altering and associated with high mortality.[20-22] It is possible that as patients are followed into subsequent decades that these differences will become statistically significant.

Fontan-associated liver disease (FALD) is a well-recognized and important sequela of the Fontan circulation. Surveillance biopsies demonstrate that virtually 100% of patients exhibit hepatic fibrosis by adolescence.[8,23] As the Fontan population ages, reports of advanced liver disease, including cirrhosis, bridging fibrosis, and hepatocellular carcinoma are of increasing prevalence, at times requiring combined heart-liver transplantation.[23] Chronic venous hypertension and hepatic congestion due to absence of a subpulmonary ventricle, combined with diminished cardiac output and hypoxemia, are thought to be the primary drivers of sinusoidal dilation and fibrosis associated with FALD.[24] Thus, attenuation of hepatic injury in the BiV group likely represented the cumulative effect of a diminution of hepatic venous pressure over time.

Also noteworthy was the impact of the presence of EFE, a finding almost exclusive to patients with hypoplastic left heart syndrome. In the aggregate cohorts, conversion to a BiV was associated with a lower 10-year freedom from MACE. This finding is consistent with earlier reports from our institution demonstrating worse outcomes of BiV in patients with hypoplastic left heart syndrome and EFE compared to those without EFE.[14,15,25-28] Based upon the findings of this study, patients with EFE are more likely to undergo alternative palliations at our institution, including Fontan operation, nonanatomic biventricular, or 1.5 V repair by a reverse double switch operation (**Central Illustration**).[29]

STUDY LIMITATIONS. First, there was a selection bias toward sicker patients in the BiV group. While PSM effectively matched groups based on known risk factors, it is possible that unaccounted for risk factors were imbalanced between groups. Second, the differences in liver disease may have been underestimated, given that hepatic enzymes are known to have limited sensitivity as a screening tool for FALD[23]; this was a known tradeoff given the paucity biopsies and other screening tests for FALD in both groups within the postoperative 10-year timeframe. Third, an examination of anatomic inclusion criteria and hospitalization costs were outside the scope of this analysis. Finally, the impact of a BiV on other important endpoints, including quality of life and exercise capacity, could not be assessed in this study due to the paucity of data available. Efforts to study these endpoints prospectively in both cohorts are well underway.

CONCLUSIONS

Among a contemporary propensity-matched cohort of patients with single ventricle anatomy, patients with BiV have comparable 10-year survival and lower risk of liver disease when compared to those with Fontan operations. The frequency of MACE in patients with EFE may be higher with BiV, a population in whom Fontan may still be considered.

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Dr del Nido reports ownership interest/partnership/principal for Autus Valve Technologies Inc, Nido Surgical. Dr Sleeper has received consultant fees/honoraria from Bayer AG Germany, Tenaya Therapeutics. Dr Emani has received consultant fees/honoraria from Chiesi Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY OF MEDICAL KNOWLEDGE: The paper should help cardiologists, cardiac surgeons, other health care providers, patients, and families better appreciate the potential long-term outcomes for biventricular conversion, when feasible, which could be crucial for decision making.

TRANSLATIONAL OUTLOOK: Fontan associated liver disease remains one of the long term complications of Fontan operation. Mitigating the long-term risk for this disease is highly recommended.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.