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The Fontan Patient: Inconsistencies in Medication Therapy Across Seven Pediatric Heart Network Centers

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Abstract

Patients who have undergone the Fontan procedure are at risk for thrombosis, ventricular dysfunction, and valve regurgitation, but data to guide the medical treatment and prevention of these adverse outcomes in this population are lacking. This analysis examined medication usage among Fontan patients by putative indication and by study center. The medical history and current medications of 546 Fontan subjects, ages 6–18 years, were assessed in a Pediatric Heart Network multicenter cross-sectional study. Cardiac imaging was performed within 3 months of enrollment. The majority of the subjects (64%) were taking two or more medications. Antithrombotics were taken by 86% of those with a history of stroke, thrombosis, or both and 67% of those without such a history ($P = 0.01$). Conversely, 14% of those with a history of stroke, thrombosis, or both were taking no antithrombotic. Angiotensin-converting enzyme inhibitor (ACEi) therapy was

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independently associated with moderate or severe atrioventricular valve regurgitation ($P = 0.004$), right ventricular morphology ($P < 0.001$), and shorter time since Fontan ($P = 0.004$) but not with ventricular systolic dysfunction. Glycoside therapy and diuretic therapy each was associated with older age at Fontan ($P = 0.001$ and $P = 0.023$, respectively) and a history of post-Fontan arrhythmia ($P < 0.001$ and $P = 0.003$, respectively) but not with ventricular systolic dysfunction. Medication use rates varied widely among the centers, even with controls for center differences in patient characteristics. Prospective therapeutic trials are needed to guide the medical treatment of Fontan patients.

Keywords

Congenital; Drugs; Fontan procedure; Heart defects; Morbidity; Pediatrics

The Fontan procedure has provided excellent palliation for many patients with single ventricle cardiac malformations [10]. However, these individuals are at risk for important complications including thromboembolism, ventricular dysfunction, and valve regurgitation [2,4,7,8,11,13,17,19]. Definitive approaches to treat and prevent these conditions, to maintain exercise capacity, and to improve functional status remain to be established.

The Pediatric Heart Network (Appendix) carried out a prospective cross-sectional study of 546 Fontan subjects, the largest such study to date [20]. The overarching aim of this study was to collect information to facilitate the development of future clinical trials in this population [1]. The goals of the current analysis were to describe current medication therapy, to examine center variation in medication usage, to identify surgical, demographic, and medical condition correlates of medication therapy, and to consider medication therapy in the context of putative clinical indications.

Materials and Methods

Patient Sample

The design of the Pediatric Heart Network Fontan Cross-Sectional Study has been reported previously [20]. The records of 1,078 children at the seven Network centers who had undergone a Fontan procedure were screened. This screening found 644 children fully eligible for the study, and 546 subjects ages 6 through 18 years were enrolled beginning in March 2003 and ending in April 2004. Local institutional review board or ethics committee approval was obtained at each center, and all subjects and/or their parents gave informed consent.

Medical History

The age of the study subjects at enrollment, their age at Fontan surgery, and the type of Fontan procedure were recorded. At study entry, a detailed medical record review was performed to identify history of thrombosis and history of stroke. For purposes of analysis, "history of stroke and/or thrombosis" was defined as a history of stroke, thrombosis, or both. Peripheral vein and artery thromboses were excluded.

Imaging Studies

The subjects underwent transthoracic echocardiography within 3 months of enrollment. Of the 546 subjects, 161 also underwent cardiac magnetic resonance imaging (cMRI). All imaging data were acquired according to uniform study protocols then analyzed in respective echocardiography and cMRI core laboratories. Ventricular anatomy was characterized by echocardiography as left (LV), right (RV), or mixed (e.g., unbalanced

atrioventricular canal). The echocardiographic methods and criteria for severity of semilunar and atrioventricular (AV) valve regurgitation have been published previously [1].

For purposes of the current analysis, *AV valve regurgitation* was defined as moderate or severe AV valve regurgitation, *semilunar valve regurgitation* as moderate or severe semilunar valve regurgitation, and *valve regurgitation* as moderate or severe AV valve and/or semilunar valve regurgitation. Ventricular systolic dysfunction, whether LV or RV, was considered present if the ejection fraction was less than 55% by echocardiogram or cMRI, and was definitively determined for 486 subjects. Ventricular diastolic function was assessed by echocardiography using two grading systems: restrictive pattern present versus absent and grades of 0 (no impairment) to 3 (greatest impairment) in diastolic filling [15].

Medication Therapy

For each subject, a complete list of active cardiac and noncardiac medications was ascertained at enrollment by interview and review of the medical record. Cardiac medications were grouped as antithrombotics, angiotensin-converting enzyme inhibitors (ACEi), glycosides, diuretics, calcium channel blockers, β -adrenoreceptor blockers, and antiarrhythmic agents. For analysis purposes, antithrombotic therapy was defined as none, aspirin or clopidogrel alone, or intensive (warfarin, low molecular weight heparin, or unfractionated heparin with or without other antithrombotics).

Statistical Analysis

Chi-square and Fisher's exact tests were used to compare medication use rates by absence or presence of medical complications, specifically, history of stroke, history of thrombosis, history of stroke and/or thrombosis, AV valve regurgitation, semilunar valve regurgitation, valve regurgitation, ventricular systolic dysfunction, and valve regurgitation and/or ventricular systolic dysfunction. For antithrombotic therapy (none vs. aspirin or clopidogrel vs. warfarin with or without other antithrombotics), a multinomial regression model was used due to the presence of nonproportional odds. Medication use rates by center were compared univariately using the chi-square and Fisher's exact tests. Multivariable logistic regression was used to compare medication use by center adjusted for covariates including medical complications, age at Fontan, years since Fontan, age at enrollment, gender, race/ethnicity, ventricular morphologic type, type of Fontan, history of arrhythmia after Fontan, and median number of interventional cardiac catheterizations and surgical interventions since completion of Fontan. These covariates were included in the multivariable model if they differed by center or between those receiving and those not receiving medication.

Results

Demographics

Table 1 provides the demographics and characteristics of the subjects. The centers varied significantly in distribution of race/ethnicity ($P < 0.001$), age at Fontan ($P < 0.001$), and years since Fontan at time of enrollment ($P < 0.001$), as well as in the median number of interventional cardiac catheterizations ($P < 0.001$) and surgical interventions ($P = 0.003$) since Fontan. Ventricular type also varied among centers ($P = 0.004$), with ranges of 35–60% for LV, 25–43% for RV, and 12–27% for mixed type.

Medical Complications

After the Fontan, a history of stroke, thrombosis, or both was present in 8% of the subjects, ventricular systolic dysfunction in 37%, AV valve regurgitation in 19%, semilunar valve regurgitation in 9%, and valve regurgitation in 33% (Fig. 1). No significant differences in the prevalence of these medical complications were found among the centers, although there

was a trend toward a difference in the prevalence of AV valve regurgitation (9–31%; $P = 0.056$).

Current Medications

Most of the subjects (89%) were taking at least one medication, and 64% were taking two or more medications. More than half (54%) were taking two or more cardiac medications (i.e., antithrombotics, ACEi, glycosides, and diuretics; Fig. 2). The noncardiac medications included anticonvulsants, gastrointestinal medications, bronchodilators, hormonal agents, and biologics.

Antithrombotics—Of the 546 subjects, 295 (54%) were taking aspirin or clopidogrel alone, 77 (14%) were taking intensive antithrombotics (69 of these were taking warfarin alone), and 174 (32%) were taking no antithrombotics (Table 2 and Fig. 3). The majority of the subjects with a history of stroke, thrombosis, or both (86%) were taking at least one antithrombotic compared with 67% of the subjects without such history ($P = 0.01$). Conversely, 14% of those with a history of stroke, thrombosis, or both were taking no antithrombotic. Multivariable analysis showed that intensive antithrombotic therapy was most strongly associated with a history of stroke, thrombosis, or both (odds ratio, 26 vs. no antithrombotic and 19 vs. aspirin or clopidogrel alone; $P < 0.001$). It was more weakly associated with the number of surgical interventions after Fontan ($P = 0.008$) and negatively associated with years since Fontan ($P < 0.001$). Notably, intensive antithrombotic use was more common among the subjects with a history of arrhythmia after Fontan (30/111, 27%) than among those without such history (48/434, 11%). However, a history of arrhythmia was not an independent predictor of antithrombotic use ($P = 0.06$) when added to the model in Table 2, due to its positive correlation with number of surgical interventions after Fontan (mean, 1.0 ± 1.5 vs. 0.2 ± 0.7 surgical interventions for subjects with vs. those without a history of arrhythmia, respectively).

ACEi—A majority of the subjects (57%) were taking an ACEi, namely, enalapril, lisinopril, captopril, fosinopril, enalaprilat, benazepril, or ramipril. In multivariable modeling, three independent correlates of ACEi therapy emerged (Table 3): RV morphology ($P < 0.001$), AV valve regurgitation ($P = 0.004$), and shorter time since Fontan ($P = 0.004$). Neither ventricular systolic nor diastolic dysfunction correlated with ACEi therapy (comprehensive analysis of ventricular function by echocardiography and MRI for this cohort has been reported previously) [1,16].

Cardiac Glycosides—A minority of the subjects (26%) were taking a cardiac glycoside, either digoxin ($n = 142$) or digitoxin ($n = 2$). In multivariable modeling, glycoside therapy was independently associated with older age at the time of Fontan ($P = 0.001$), greater numbers of surgical interventions since the Fontan ($P = 0.004$), and history of post-Fontan arrhythmia ($P < 0.001$), but not with valve regurgitation or ventricular function (Table 4).

Diuretics—A minority of the subjects (16%) were taking diuretics including ethacrynic acid, furosemide, aldactone, and hydrochlorothiazide. In multivariable analysis, diuretic therapy was associated with greater numbers of surgical interventions ($P = 0.001$) and interventional cardiac catheterizations ($p = 0.001$) since Fontan, history of post-Fontan arrhythmia ($P = 0.003$), and older age at the time of Fontan ($P = 0.023$; Table 5).

Other Cardiac Medications—The numbers of subjects taking a beta blocker ($n = 19$), a calcium channel blocker ($n = 1$), or other antiarrhythmic agents ($n = 19$) were too small to analyze meaningfully.

Medication Therapy by Center

The number of cardiac medications that subjects were taking at study entry varied widely among the seven centers. The percentage of subjects at each center taking no cardiac medication ranged from 0 to 26%. Those taking one cardiac medication ranged from 5 to 40%, and those taking two or more cardiac medications ranged from 34 to 95%. Similarly, the use of specific medicine classes varied significantly across the different centers (Fig. 4). Univariate analysis showed the subjects' medication usage ranged from 33 to 97% for antithrombotics ($P < 0.01$), 32 to 76% for ACEi ($P < 0.001$), 22 to 55% for glycosides ($P < 0.005$), and 7 to 45% for diuretics ($P < 0.001$).

We reexamined center usage with attention to demographic and medical history factors that differed by center and between those receiving and those not receiving medication. After adjustment for these factors, center usage of antithrombotics, ACEi, and diuretics still differed significantly ($P < 0.001$), whereas center use of glycosides did not ($P = 0.17$).

Discussion

Patients with Fontan palliation of single ventricle heart disease may experience a range of important complications including thromboembolism, ventricular dysfunction, and valve regurgitation [2,4,7,8,11,13,17,19]. Currently, there is a paucity of data to guide the use of medications to treat and prevent these adverse outcomes in this population [5]. The empiric use of anticoagulant and antiplatelet agents has been based on the well-documented risk of thrombotic complications for Fontan patients, but these complications still occur for patients receiving such preventive therapy, and neither retrospective nor prospective studies have proven efficacy [8,14]. In Fontan patients, ACEi may improve vascular endothelial function but not cardiac output or exercise capacity [9,12]. Published guidelines for ACEi and digoxin treatment of single ventricle dysfunction are based on limited evidence [6,18]. The merits of ACEi therapy for valve regurgitation for single ventricle patients have not been studied [3,6].

In the current study, we sought to characterize current medication usage as part of a multicenter cross-sectional analysis of 546 Fontan subjects, the largest such study to date. The findings show that a majority of the subjects were taking two or more cardiac medications including antithrombotics, ACEi, cardiac glycosides, and diuretics. As noted, no definitive evidence-based indications currently exist for the use of any of these classes of medicines by Fontan patients. However, to the extent that putative indications can be inferred, prescribed therapy has correlated with a putative indication for some of these medicines but not for others. In this study, antithrombotic use was associated with a history of stroke, thrombosis, or both, and ACEi use was associated with AV valve regurgitation. However, digoxin use was not associated with either valve regurgitation or ventricular systolic dysfunction, although it was associated with a history of post-Fontan arrhythmia.

Furthermore, where correlation between medication use and putative indication could be demonstrated, the aforementioned correlation was imperfect. For example, substantial numbers of subjects with no history of stroke or thrombosis were taking antithrombotics, whereas others with such a history were not. The use of antithrombotics with patients who had no history of stroke or thrombosis, and similarly the use of ACEi and digoxin with patients who had no valve regurgitation or ventricular dysfunction may well have been aimed at primary prevention of these conditions, however unproven.

The findings also show striking differences in the use of these medicines across the different centers. For example, the proportion of patients taking antithrombotics ranged from a low of 33% at one center to a high of 97% at another center. Similar disparities were found for

ACEi, glycosides, and diuretics. For the most part, these disparities could not be accounted for by center differences in patient demographics or medical history.

Both the imperfect correlation between medication use and putative indication and the center variation in medication use undoubtedly reflect the fact that clinical scientific evidence on which to base prescription decisions for the Fontan population is lacking. Indeed, few published guidelines of any kind exist to inform these decisions [18]. Thus, it is perhaps not surprising that practitioners at any one center might evolve parochial prescribing practices based on local anecdotes and individual biases. The findings reported in this article highlight the need for rigorous, prospective therapeutic trials with the growing population of Fontan patients.

Study Limitations

The cross-sectional design of this study had inherent limitations. The sample cohort was necessarily biased in that it included only survivors. Medication use for individual patients may have changed over time but was recorded only at study enrollment. The extent to which medicines may have prevented outcomes such as stroke or improved others such as ventricular function in this population is unknown. Possible indications for medication usage have been inferred, but no data on the prescribers' actual rationales were collected.

Conclusions

A majority of the study subjects were taking two or more cardiac medications at enrollment in this cross-sectional study. There was imperfect correlation between medication use and possible therapeutic indications, although some medicines may have been prescribed for preventive reasons. There was striking variation in the use of these medicines across the seven centers.

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Appendix: Pediatric Heart Network Membership

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Fig. 1. Distribution of post-Fontan complications by center and the percentage of Fontan subjects at each of the seven centers with a history of thrombosis and/or stroke, with ventricular dysfunction, and with moderate or severe valve regurgitation. Each center is represented by a color

Fig. 2.
Percentage of Fontan subjects taking no medication (*hatched bar*), one medication (*open bar*), or two or more medications (*black bar*) for all medications and for cardiac medications

Fig. 3. Percentage of Fontan subjects taking no antithrombotic (*hatched bar*), aspirin or clopidogrel only (*open bar*), or intensive antithrombotics (*solid bar*), by history of thrombosis and/or stroke

Fig. 4. Medication usage by study center and percentages of Fontan subjects taking each class of medication at each center. The color designation for each center is identical to that in Fig. 1

Table 1

Fontan cross-sectional study subject characteristics and therapies (*P* values reflect differences among study centers)

Characteristic at enrollment	<i>n</i> (%)	<i>P</i> value
<i>n</i>	546	
Age (years)	11.9 ± 3.4	0.24
Males	329 (60.3)	0.56
Race/ethnicity		< 0.001
Hispanic	35 (6.4)	
Non-Hispanic, white	397 (72.7)	
Non-Hispanic, black	50 (9.2)	
Non-Hispanic, other	35 (6.4)	
Unknown	29 (5.3)	
Ventricular type		0.004
Left	265 (48.5)	
Mixed	184 (33.7)	
Right	97 (17.8)	
Age at Fontan (years)	3.4 ± 2.1	< 0.001
Years since Fontan	8.6 ± 3.4	< 0.001
Catheterization interventions: median (range) ^a	0 (0–8)	< 0.001
Surgical interventions: median (range) ^a	0 (0–9)	0.003
Current medications		< 0.001
No medication	60 (11.0)	
One medication	136 (24.9)	
Two or more medications	350 (64.1)	
Current cardiac medications		< 0.001
No medication	73 (13.4)	
One medication	177 (32.4)	
Two or more medications	296 (54.2)	
Any antithrombotic	372 (68.1)	< 0.001
Aspirin or clopidogrel only	295 (54.0)	
Intensive ^b	77 (14.1)	
ACEi	313 (57.3)	< 0.001
Glycoside	144 (26.4)	0.01
Diuretics	85 (15.6)	< 0.001

ACEi angiotensin-converting enzyme inhibitor

^aNo. of procedures since Fontan completion

^bWarfarin, heparin, low molecular weight heparin, dipyridamole, tirofiban

Table 2Correlates of antithrombotic usage (*P* values are from multinomial logistic regression modeling)

Predictor	Outcome			<i>P</i> Value
	Intensive antithrombotic	Aspirin/clopidogrel	No antithrombotic	
<i>n</i>	77	295	174	
Center				< 0.001
Male (%)	49.4	62.7	60.9	0.25
Ethnicity (%)				0.56
Hispanic	9.5	6.4	6.3	
Non-Hispanic, black	5.4	12.0	7.5	
Non-Hispanic, other	6.8	5.3	9.4	
Non-Hispanic, white	78.4	76.3	76.9	
Age at Fontan (years)	4.0 ± 2.6	3.4 ± 2.1	3.2 ± 1.9	0.03
Years since Fontan	8.7 ± 4.2	8.1 ± 3.4	9.3 ± 3.1	< 0.001
Age at enrollment (years)	12.6 ± 4.0	11.3 ± 3.3	12.4 ± 3.2	< 0.001
Ventricular type (%)				0.34
Left	59.7	45.1	49.4	
Mixed	16.9	19.7	14.9	
Right	23.4	35.3	35.6	
No. of surgical interventions ^a	1.0 ± 1.6	0.3 ± 0.7	0.3 ± 0.9	< 0.001
Number of catheterization interventions ^a	1.1 ± 1.4	0.8 ± 1.1	0.8 ± 0.2	0.31
History of thrombosis ^a (%)	32.5	2.7	2.9	< 0.001
History of stroke ^a (%)	9.1	1.0	0.6	< 0.001
History of stroke/thrombosis ^a (%)	37.7	3.1	3.5	< 0.001

Multivariable model	OR (95% CI)			
	Intensive antithrombotic vs. no antithrombotic	Intensive antithrombotic vs. aspirin/clopidogrel	Aspirin/clopidogrel vs. no antithrombotic	
Center				< 0.001
History of stroke/thrombosis ^a	26.06 ^b (8.62–78.79)	18.95 ^b (7.44–48.26)	1.38 (0.41–4.60)	< 0.001
Years since Fontan	0.90 ^b (0.82–1.00)	1.05 (0.96–1.14)	0.86 ^b (0.80–0.93)	< 0.001
No. of surgical interventions ^a	1.52 ^b (1.13–2.05)	1.43 ^b (1.09–1.87)	1.07 (0.80–1.43)	0.008

^aNumber of procedures and history of thrombosis and stroke since Fontan completion^bOdds ratio differs from one (*P* < 0.05)

OR odds ratio, CI confidence interval, AV atrioventricular

Table 3

Correlates of angiotensin-converting enzyme inhibitor (ACEi) usage (*P* values are from logistic regression modeling)

Predictor	ACEi use	No ACEi use	OR (95% CI)	<i>P</i> value
<i>n</i> ^a	313	233		
Center (%)				< 0.001
Male	62.6	57.1	1.26 (0.89–1.78)	0.19
Ethnicity (%)				0.11
Hispanic	7.8	5.4	1.35 (0.65–2.79)	NS
Non-Hispanic, black	8.1	11.7	0.65 (0.36–1.17)	NS
Non-Hispanic, other	5.1	9.0	0.53 (0.26–1.06)	NS
Non-Hispanic, white	79.0	73.9	1.00	–
Age at Fontan (years)	3.5 ± 2.3	3.3 ± 1.9	1.05 (0.96–1.14)	0.30
Years since Fontan	8.3 ± 3.5	8.9 ± 3.4	0.95 (0.90–0.99)	0.03
Age at enrollment (years)	11.7 ± 3.4	12.1 ± 3.4	0.96 (0.92–1.01)	0.13
Ventricular type (%)				< 0.001
Left	42.5	56.7	0.40 (0.27–0.59)	< 0.001
Mixed	15.3	21.0	0.39 (0.23–0.64)	< 0.001
Right	42.2	22.3	1.00	–
No. of surgical interventions ^b	0.4 ± 1.0	0.4 ± 1.0	1.09 (0.91–1.31)	0.37
No. of catheter interventions ^b	0.9 ± 1.2	0.8 ± 1.1	1.12 (0.96–1.30)	0.14
History of arrhythmia ^b (%)	24.4	15.0	1.73 (1.12–2.69)	0.015
AV valve regurgitation ^c (%)	22.8	13.8	1.85 (1.16–2.94)	0.01
Semilunar valve regurgitation ^c (%)	9.3	8.3	1.13 (0.51–2.51)	0.78
Valve regurgitation ^c (%)	38.4	25.7	1.80 (1.12–2.88)	0.02
Vent. systolic dysfunction ^c (%)	39.4	34.1	1.26 (0.87–1.82)	0.23
Valve regurgitation and/or vent. dysfunction ^c (%)	67.0	58.9	1.41 (0.93–2.14)	0.10
Vent diastolic dysfunction ^c (%)	65.9	60.6	1.25 (0.80–1.97)	0.33
Valve regurgitation and/or vent. systolic and/or diastolic dysfunction ^c (%)	93.2	89.2	1.66 (0.82–3.37)	0.16

Multivariable model (<i>n</i> = 528; <i>R</i> ² = 0.16)	OR (95% CI)		<i>P</i> value
	ACEi use vs. no ACEi		
Center			< 0.001
Ventricular type			< 0.001
Left	0.40	(0.25–0.62)	
Mixed	0.25	(0.14–0.45)	
Right	1.00	–	
Years since Fontan	0.92	(0.87–0.97)	0.004
AV valve regurgitation	2.12	(1.26–3.55)	0.004

^aSample size may be smaller for some predictors

^b No. of procedures or positive history since Fontan completion

^c Measured at study enrollment

OR odds ratio, *CI* confidence interval, *AV* atrioventricular

Table 4Correlates of glycoside usage (*P* values are from logistic regression)

Predictor	Glycoside use	No glycoside use	OR (95% CI)	<i>P</i> value
<i>n</i> ^a	144	402		
Center (%)				0.01
Male	54.9	62.2	0.74 (0.50–1.09)	0.12
Ethnicity (%)				0.38
Hispanic	9.4	5.8	1.62 (0.79–3.34)	NS
Non-Hispanic, black	7.2	10.6	0.69 (0.33–1.42)	NS
Non-Hispanic, other	7.2	6.6	1.10 (0.51–2.36)	NS
Non-Hispanic, white	76.3	77.0	1.00	–
Age at Fontan (years)	3.9 ± 2.4	3.3 ± 2.0	1.14 (1.04–1.24)	0.003
Years since Fontan	9.0 ± 3.9	8.4 ± 3.2	1.05 (1.00–1.11)	0.07
Age at enrollment (years)	12.8 ± 3.8	11.5 ± 3.2	1.11 (1.05–1.17)	< 0.001
Ventricular type (%)				0.88
Left	47.2	49.0	0.90 (0.59–1.38)	NS
Mixed	17.4	17.9	0.91 (0.52–1.58)	NS
Right	35.4	33.1	1.00	–
No. of surgical interventions ^b	0.8 ± 1.4	0.3 ± 0.7	1.65 (1.33–2.03)	< 0.001
No. of catheter interventions ^b	0.9 ± 1.4	0.8 ± 1.1	1.11 (0.95–1.30)	0.20
History of arrhythmia ^b	41.7	12.7	4.90 (3.15, 7.63)	< 0.001
AV valve regurgitation ^c	21.6	18.0	1.25 (0.78–2.03)	0.36
Semilunar valve regurgitation ^c	10.8	8.2	1.36 (0.59–3.13)	0.47
Valve regurgitation ^c	38.7	31.2	1.39 (0.85–2.28)	0.19
Ventricular systolic dysfunction ^c	41.1	35.6	1.26 (0.83–1.92)	0.27
Valve regurgitation and/or ventricular dysfunction ^e	68.3	61.8	1.33 (0.83–2.15)	0.24

Multivariable model (<i>n</i> = 545; <i>R</i> ² = 0.12)	OR (95% CI)		<i>P</i> value
	Glycoside use vs. no glycoside use		
No. of surgical interventions	1.38	(1.11–1.71)	0.004
Age at Fontan (years)	1.16	(1.06–1.26)	0.001
History of arrhythmia ^b	3.99	(2.48–6.40)	< 0.001

^aSample size may be smaller for some predictors^bNo. of procedures or positive history since Fontan completion^cMeasured at study enrollment

Table 5Correlates of diuretics usage (*P* values are from logistic regression)

Predictor	Diuretics use	No diuretics use	OR (95% CI)	<i>P</i> value
<i>n</i> ^a	85	461		
Center (%)				< 0.001
Male	57.7	60.7	0.88 (0.55–1.41)	0.59
Ethnicity (%)				0.34
Hispanic	9.9	6.2	1.77 (0.77–4.08)	NS
Non-Hispanic, black	13.6	8.9	1.68 (0.81–3.48)	NS
Non-Hispanic, other	6.2	6.9	0.99 (0.37–2.67)	NS
Non-Hispanic, white	70.4	78.0	1.00	–
Age at Fontan (years)	4.0 ± 2.3	3.3 ± 2.1	1.14 (1.03–1.25)	0.008
Years since Fontan	8.1 ± 4.3	8.6 ± 3.3	0.96 (0.90–1.03)	0.21
Age at enrollment (years)	12.0 ± 3.8	11.8 ± 3.3	1.02 (0.95–1.09)	0.67
Ventricular type (%)				0.23
Left	40.0	50.1	0.65 (0.39–1.09)	NS
Mixed	20.0	17.4	0.64 (0.49–1.78)	NS
Right	40.0	32.5	1.00	–
No. of surgical interventions ^b	0.9 ± 1.5	0.3 ± 0.8	1.60 (1.31–1.97)	< 0.001
No. of catheter interventions ^b	1.2 ± 1.5	0.8 ± 1.1	1.31 (1.10–1.55)	0.003
History of arrhythmia ^b (%)	40.0	16.7	3.32 (2.02–5.46)	< 0.001
AV valve regurgitation ^c (%)	28.1	17.3	1.87 (1.09–3.21)	0.024
Semilunar valve regurgitation ^c (%)	11.4	8.5	1.38 (0.49–3.84)	0.54
Valve regurgitation ^c (%)	47.3	30.6	2.04 (1.13–3.65)	0.017
Ventricular systolic dysfunction ^c (%)	42.3	36.1	1.29 (0.78–2.16)	0.33
Valve regurgitation and/or ventricular dysfunction ^c (%)	72.9	61.8	1.66 (1.90–3.07)	0.11

Multivariable model (<i>n</i> = 545; <i>R</i> ² = 0.13)	OR (95% CI)		<i>P</i> value
	Diuretics use vs. no diuretics		
Center			< 0.001
No. of surgical interventions ^{<i>b</i>}	1.46	(1.17–1.82)	0.001
No. of catheter interventions ^{<i>b</i>}	1.44	(1.16–1.78)	0.001
Age at Fontan (years)	1.13	(1.02–1.26)	0.023
History of arrhythmia ^{<i>b</i>}	2.42	(1.35–4.33)	0.003

^aSample size may be smaller for some predictors^bNo. of procedures or positive history since Fontan completion^cMeasured at study enrollment

OR odds ratio, CI confidence interval, AV atrioventricular