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ORIGINAL RESEARCH

Propensity Score Analysis of Possible Medication Effects on Outcomes in Patients With Systemic Right Ventricles

Amrit Misra, MD,[a,*] Carla P. Rodriguez-Monserrate, MD,[a,*] Kimberlee Gauvreau, PhD,[b] Mikael Dellborg, MD,[c] Flavia Fusco, MD,[d] Tripti Gupta, MD,[e] Joseph Kay, MD,[f] Shelby Kutty, MD,[g] Robert M. Kauling, MD,[h] Jeremy Nicolarsen, MD,[i] Jolien Roos-Hesselink, MD, PhD,[h,j] Anitha S. John, MD, PhD,[k] Joshua Wong, MBBS,[l] Luke J. Burchill, MBBS, PhD,[l] Eric V. Krieger, MD,[m] Adam M. Lubert, MD,[n] Pastora Gallego, MD,[j,o] Marissa Kuo, MD,[p] Jamil Aboulhosn, MD,[q] Jonathan Cramer, MD,[r] Petra Antonova, MD,[s] David Baker, MBBS,[t] Payam Dehghani, MD,[u] Alexander R. Opotowsky, MD, MMSc,[n] Alexandra van Dissel, MD,[v] Jasmine Grewal, MD,[w] Elizabeth Yeung, MD,[f] Susan Fernandes, LPD,[x] Salil Ginde, MD,[y] Paul Khairy, MD, PhD,[z] Frank Han, MD,[aa] Isabelle Vonder Muhll, MD,[bb] William M. Wilson, MBBS,[l] William Aaron Kay, MD,[cc] Stephen Pylypchuk, MD,[bb] Berardo Sarubbi, MD,[d] Clare O'Donnell, MBChB,[dd] Fred Rodriguez III, MD,[p] Pavithra S. Jayadeva, MBBS,[ee] David S. Celermajer, MBBS, PhD,[t] Sangeeta Shah, MD,[ff] Timothy Cotts, MD,[gg] Christopher DeZorzi, MD,[hh] Anthony Magalski, MD,[hh] Anne Marie Valente, MD,[a] Craig S. Broberg, MD, MCR[ii]

ABSTRACT

BACKGROUND Patients with systemic right ventricle (SRV), either d-transposition of the great arteries following an atrial switch procedure or congenitally corrected transposition of the great arteries, develop severe right ventricular dysfunction, prompting appropriate medical therapy. However, the efficacy of beta-blockers and angiotensin receptor blockers or angiotensin-converting enzyme inhibitors (ACEI) in SRV patients is unproven.

OBJECTIVES The objective of this study was to determine the effects of ACEI/ARB and beta-blockers on outcomes in SRV patients after accounting for likely cofounders affecting their use.

METHODS From a retrospective, multicenter study on heart failure-related outcome in individuals with SRV, those who were taking an ACEI/ARB, beta-blocker, or both of these medication were identified. We performed a propensity analysis to match them to those not using these medications at their initial visit. Matching was based on a propensity score, which captured co-morbidities, demographics, and baseline echocardiographic parameters. Primary outcome of death, transplant, or mechanical circulatory support, and secondary outcomes of heart failure hospitalizations/atrial arrhythmias were analyzed respectively.

RESULTS We identified 393 patients taking ACEI/ARB or beta-blocker, or taking both a beta-blocker and ACEI/ARB (62.1% male, median age 31.3 years) and 484 patients (56.4% male, median age of 26.0 years) who were neither on a beta-blocker nor on ACEI/ARB at the time of initial clinic visit. Median follow-up was ~8 years. After propensity matching, medication use was not associated with decreased mortality, heart failure hospitalizations, or arrhythmias. Hazard ratios remained positive for beta blockers, implying potential harm rather than benefit.

CONCLUSIONS In this large multicenter propensity-matched observational study, patients with SRV taking beta-blockers or ACEI/ARB did not have a benefit in survival or reduced hospitalization. The likelihood of demonstrating favorable effects in larger studies appears remote. (JACC Adv. 2025;4:101443) © 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

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

cc-TGA = congenitally corrected transposition of the great arteries

d-TGA/AS = d-loop transposition of the great arteries status post atrial switch

ICD = implantable cardioverter-defibrillator

MCS = mechanical circulatory support

SRV = systemic right ventricle

Patients with a systemic right ventricle (SRV) are at risk for right ventricular (RV) dysfunction due to high RV systolic pressures leading to eccentric free wall hypertrophy, a shift of interventricular septal motion toward the left ventricle, and RV dilation. These changes result in increased ventricular wall stress and dysfunction of the trabecular component, papillary muscles, and valvar apparatus of the tricuspid valve.[1] This leads to progressive myocardial fibrosis and ventricular failure.[2,3] Although it seems plausible that standard heart failure pharmacotherapies would have a favorable impact on this process, limited data in patients with SRV have failed to show benefit of beta-blockers, angiotensin receptor blockers (ARB), and angiotensin-converting enzyme inhibitors (ACEI) on mortality and long-term outcomes.[2,4-7] Some studies have suggested that beta-blockers in the SRV population lead to symptomatic improvement, but they have not been extensively studied, nor examined in combination with ACEI/ARB usage.[8,9] Despite limited evidence for these medications, many SRV patients have empirically been prescribed these agents for treatment of heart failure.[10,11] Data show that prescribing patterns reflect worsening clinical status, and hence their use is likely a marker of disease progression.[10,11]

However, practice patterns differ between institutions and providers, even in specialized care centers, and this heterogeneity amongst a large patient cohort provides opportunities to study the potential medication effects more closely. In this multicenter study, we used propensity score analysis, based on features that would likely motivate choices of medical therapy, to determine whether beta-blockers or ACEI/ARB usage improved clinical outcomes in SRV patients.

METHODS

STUDY DESIGN. This was a planned sub-study of an international, multicenter, retrospective cohort study. Patients included those with either d-loop transposition of the great arteries status postatrial switch (d-TGA/AS) or congenitally corrected

From the [a]Boston Children's Hospital and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [b]Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [c]Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [d]Adult Congenital Heart Disease Unit, Monaldi Hospital, Napoli, Italy; [e]Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [f]Colorado Adult and Teen Congenital Heart (C.A.T.C.H.) Program, Colorado University School of Medicine, Denver, Colorado, USA; [g]Helen B. Taussig Heart Center, Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland, USA; [h]Department of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands; [i]Providence Adult and Teen Congenital Heart Program, Providence Spokane, Spokane, Washington, USA; [j]European Reference Network for Rare, Low Prevalence and Complex Disease of the Heart- ERN-Guard Heart, Amsterdam, the Netherlands; [k]Division of Pediatric Cardiology, Children's National Hospital, Washington, DC, USA; [l]Royal Melbourne Hospital, Department of Medicine, Melbourne, Australia; [m]University of Washington Medical Center and Seattle Children's Hospital, Seattle, Washington, USA; [n]Cincinnati Children's Hospital Medical Center, Heart Institute, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA; [o]Adult Congenital Heart Disease Unit, Hospital Universitario Virgen Del Rocio, Sevilla, Spain; [p]Division of Cardiology, Department of Medicine, Emory University Hospital, Atlanta, Georgia, USA; [q]Division of Cardiology, Department of Medicine, Ahmanson/UCLA Adult Congenital Heart Disease Center, UCLA Medical Center, Los Angeles, California, USA; [r]Children's Hospital, Omaha & University of Nebraska Medical Center, Omaha, Nebraska, USA; [s]Department of Cardiovascular Surgery, 2nd Faculty of Medicine, University Hospital Motol, Prague, Czech Republic; [t]Department of Cardiology, University of Sydney and Royal Prince Alfred Hospital, Sydney, Australia; [u]Department of Cardiology, Regina General Hospital, Regina, Saskatchewan, Canada; [v]Division of Cardiology, Amsterdam University Medical Center, Amsterdam, the Netherlands; [w]St.Paul's Hospital, Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada; [x]Stanford University, School of Medicine, Departments of Pediatrics and Medicine, Palo Alto, California, USA; [y]Division of Cardiology, Children's Hospital of Wisconsin, Milwaukee, Wisconsin, USA; [z]Department of Medicine, Montreal Heart Institute, Montreal Heart Institute, Montreal, Quebec, Canada; [aa]Department of Cardiology, University of Mississippi Medical Center, Jackson, Mississippi, USA; [bb]Internal Medicine/Cardiology, University of Alberta, Edmonton, Alberta, Canada; [cc]Division of Cardiology, Krannert Institute of Cardiology, Indianapolis, Indiana, USA; [dd]Green Lane Paediatric and Congenital Cardiac Service, Auckland City Hospital, Auckland, New Zealand; [ee]Peter Munk Cardiac Center, Toronto General Hospital, University Health Network, University of Toronto, Ontario, Canada; [ff]Department of Cardiology, Ochsner Medical Center, New Orleans, Los Angeles, USA; [gg]Division of Cardiology, University of Michigan Medical Center, Ann Arbor, Michigan, USA; [hh]Division of Cardiology, Saint Luke's Mid America Heart Institute Hospital, Kansas City, Missouri, USA; and the [ii]Knight Cardiovascular Institute, Oregon Health and Science University, Portland, Oregon, USA. *Drs Misra and Rodriguez-Monserrate are co-first authors for this paper.

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transposition of the great arteries (cc-TGA) with biventricular physiology who were seen on at least 2 occasions over at least 12 months. The first visit to a congenital heart outpatient center since January 1, 2002 was considered the initial visit and the most recent outpatient evaluation, prior to death, heart transplant, or need for mechanical circulatory support (MCS) if relevant, was considered the follow up visit. Details about the study design and coordination have been previously published.[10]

DATA COLLECTION. For the purposes of this substudy, our primary exposure variable of interest was the use of these target medications, categorized into the following 4 groups: patients on none of the medications of interest (group 1), on both medication classes (group 2), only beta-blockers (group 3), or only ACEI/ARB (group 4) at the initial visit and follow-up visit. Patients who were started on or taken off these medications between the first and follow-up visit were excluded, as specific dates giving duration of treatment could not be confirmed, and reasons for the changes were unknown. For each patient, data collected included sex, age at initial and follow up visits, presence of a pacemaker or implantable cardioverter-defibrillator (ICD), tobacco smoking status, arrhythmia history (including ventricular tachycardia, atrial flutter or fibrillation), diabetes, hypertension, heart failure hospitalization prior to the study period. Our study period was defined as the time between the initial and most recent follow-up visit, or last contact for deceased patients.

Data regarding patient usage of medications, including beta-blockers, ACEI, ARB, diuretics, and spironolactone in use or newly prescribed at the initial visit and at the most recent follow-up, were collected. The primary outcome was time from first visit to a composite of all-cause mortality, MCS placement, or heart transplantation. Secondary outcomes were time to heart failure hospitalization and onset of arrhythmia.

PROPENSITY SCORE ANALYSIS. In order to control for confounding by indication, propensity scores for medication usage were estimated from a multivariable logistic regression model that included multiple variables that might have an impact on medication choice prior to the initial visit. These variables included age, sex, anatomic morphology, smoking status, diabetes, hypertension, history of atrial flutter/fibrillation, baseline diuretic use, baseline spironolactone use, pacemaker, ICD, previous ventricular tachycardia, RV dysfunction (assessed by a semi-quantitative scale), tricuspid regurgitation, and anatomic complexity (ventricular septal defect, pulmonary stenosis, or situs abnormalities). The anatomic complexity was reflected in complexity score that delineated the total number of these conditions the patient had. For example, a patient with dextrocardia, situs inversus, and ventricular septal defect would have a complexity of score of 3, while a patient with only pulmonary stenosis would have a score of 1. NYHA functional class was not available and thus not included.

The propensity scores were then used in 2 ways. First, the propensity score was used for covariate adjustment in models evaluating the effect of medication use on the primary composite outcome, as well as the secondary outcomes; the treating institution was utilized as a part of the propensity score for these analyses. Second, propensity scores were utilized to create 1:1 matched pairs of patients who were on ACEI/ARB or beta-blockers versus those who were not on any of these medications. Matching was performed using a nearest neighbor algorithm, with a maximum caliper of 0.01 for the propensity score. For the secondary outcome of atrial arrhythmias during follow-up, patients with previous atrial arrhythmias were excluded from the analysis in order to focus on new-onset arrhythmias.

STATISTICAL ANALYSIS. Continuous variables are presented as medians with 25th and 75th percentiles (IQR). Categorical variables are listed as numbers and percentages. Comparisons among groups were performed using Fisher's exact test for categorical variables, and either the Wilcoxon rank sum test or Kruskal-Wallis test for continuous variables. Associations between medication use and the primary and secondary outcomes were evaluated using Cox proportional hazards models, adjusting for propensity score. Schoenfeld residuals were calculated to verify the proportional hazards assumption. Shared frailty models were used for propensity score matched comparisons. Hazard ratios were presented with 95% CIs. Analyses were performed in Stata version 16 (StataCorp).

RESULTS

CHARACTERISTICS OF STUDY COHORT. A total of 877 of 1721 patients (51%) who were either taking or not taking ACEI/ARB or beta blockers consistently during the initial visit and follow up were included in this study. 59% were male with median age at first visit 28.0 years (IQR: 22.3-35.5 years). Group 1 consisted of 484 (55.2%) patients who were not on any medications. Group 2 consisted of 148 patients (16.8%) who were taking a beta-blocker and

TABLE 1 Comparison of Characteristics Among the Groups

	Group 1: No Meds (n = 484)	Group 2: On AA and BB (n = 148)	Group 3: Only on BB (n = 81)	Group 4: Only on AA (n = 164)	*P* Value
Male	273 (56.4%)	93 (62.8%)	42 (51.9%)	109 (66.5%)	0.052
d-TGA	343 (70.9%)	90 (60.8%)	53 (65.4%)	109 (66.5%)	0.13
Baseline smoker	60 (13.7%)	13 (9.6%)	10 (13.0%)	16 (10.5%)	0.55
Diabetes	6 (1.2%)	12 (8.2%)	4 (4.9%)	3 (1.8%)	<0.001
Hypertension	12 (2.5%)	28 (19.1%)	4 (5.0%)	21 (12.8%)	<0.001
History of atrial flutter or fibrillation	72 (14.9%)	71 (48.0%)	45 (55.6%)	36 (22.0%)	<0.001
History of heart failure	14 (2.9%)	31 (21.1%)	11 (13.6%)	11 (6.7%)	<0.001
Baseline diuretic	12 (2.5%)	66 (44.6%)	15 (18.5%)	17 (10.4%)	<0.001
Baseline spironolactone	5 (1.0%)	38 (25.7%)	11 (13.8%)	6 (3.7%)	<0.001
Baseline pacemaker	78 (16.2%)	55 (37.4%)	32 (39.5%)	42 (25.6%)	<0.001
Baseline ICD	4 (0.8%)	20 (13.5%)	11 (13.6%)	7 (4.3%)	<0.001
Baseline VT	12 (2.5%)	22 (15.0%)	14 (17.3%)	9 (5.5%)	<0.001
Baseline RV dysfunction					<0.001
Normal	152 (32.2%)	22 (14.9%)	19 (25.7%)	35 (22.0%)	
Mild	202 (42.8%)	34 (23.0%)	21 (28.4%)	52 (32.7%)	
Moderate	106 (22.5%)	55 (37.2%)	24 (32.4%)	60 (37.7%)	
Severe	12 (2.5%)	37 (25.0%)	10 (13.5%)	12 (7.5%)	
Baseline tricuspid regurgitation					<0.001
None	100 (21.5%)	17 (11.8%)	10 (13.7%)	19 (11.8%)	
Mild	280 (60.2%)	65 (45.1%)	29 (39.7%)	78 (48.4%)	
Moderate	73 (15.7%)	38 (26.4%)	30 (41.1%)	50 (31.1%)	
Severe	12 (2.6%)	24 (16.7%)	4 (5.5%)	14 (8.7%)	
Complexity score					0.042
0	331 (68.4%)	111 (75.0%)	61 (75.3%)	106 (64.6%)	
1	95 (19.6%)	20 (13.5%)	12 (14.8%)	24 (14.6%)	
2	38 (7.9%)	13 (8.8%)	5 (6.2%)	27 (16.5%)	
3	12 (2.5%)	3 (2.0%)	3 (3.7%)	5 (3.0%)	
4	8 (1.7%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	
5	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	
Age at first visit, y	26.0 (21.4-31.4)	35.5 (27.8-46.8)	34.8 (28.8-41.6)	26.7 (21.5-33.9)	<0.001
Follow-up duration, y	8.7 (4.9-14.5)	6.0 (3.6-9.0)	6.0 (2.9-8.8)	8.0 (5.1-12.9)	<0.001
Death	19 (3.9%)	18 (12.2%)	8 (9.9%)	10 (6.1%)	[a]
Transplant	3 (0.6%)	6 (4.1%)	2 (2.5%)	3 (1.8%)	[a]
MCS	2 (0.4%)	2 (1.4%)	1 (1.2%)	1 (0.6%)	[a]
Composite outcome	22 (4.6%)	24 (16.2%)	11 (13.6%)	14 (8.5%)	[a]

Values are n (%) or median (IQR). Comparisons across groups are made using Fisher's exact test for categorical variables, and the Kruskal–Wallis test for continuous variables. Baseline refers to the presence of the parameter at the first visit; that is baseline diuretic means that the patient was on a diuretic at the first visit. [a]Unable to calculate *P* values due to differences in when outcomes occurred between the groups.

A/A = angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker; BB = beta-blocker, d-TGA = dextro-transposition of the great arteries; ICD = implantable cardioverter-defibrillator; MCS = mechanical circulatory support; RV = right ventricle; VT = ventricular tachycardia.

ACEI/ARB. Group 3 was comprised of 81 (9.2%) patients on beta-blockers alone. In group 4, 164 patients (18.7%) received an ACEI/ARB without a beta-blocker. Tables 1 and 2 compare the baseline characteristics of patients who were not medications (Group 1) and who were (Group 2, 3, and 4) on medications. Patients who were on beta-blockers or ACEI, and/or ARB were more likely to have a history of atrial arrhythmias, heart failure hospitalizations, moderate or severe RV dysfunction and/or tricuspid regurgitation, and ICD or pacemaker placement. In a univariable Cox regression model, patients with d-TGA/AS were at lower risk of reaching the primary outcome than those with cc-TGA, with a HR of 0.41 and 95% CI of 0.26-0.66; the type of TGA (cc-TGA vs d-TGA/AS), was not significantly associated with either a difference in time to hospitalization or atrial arrhythmia, with HR of 1.30 (95% CI: 0.82-2.08) and 1.22 (95% CI: 0.82-1.82) respectively.

PROPENSITY SCORE ANALYSIS. In the univariable, unadjusted Cox regression analysis, ACEI/ARB, and/or beta-blocker use was associated with the

primary outcome with a HR of 3.61 (95% CI: 2.17-5.99); Beta-blocker and ACEI/ARB use as well as beta-blocker without ACEI/ARB were also associated with the primary outcome with HR of 6.66 (95% CI: 3.65-12.2) and 4.9 (95% CI: 2.36-10.1), respectively. ACEI/ARB alone was not significantly associated with the primary outcome ($P = 0.087$). As seen in **Table 3**, when adjusted for the propensity score, beta-blockers, ACEI, and/or ARB were not associated with a difference in the composite outcome ($P = 0.82$, HR: 1.07 [95% CI: 0.57-2.02]) or heart failure hospitalizations ($P = 0.48$, HR: 0.81 [95% CI: 0.45-1.46]). Similarly, patients on both beta-blockers and ARB/ACEI did not have a statistically significant difference in heart failure hospitalization (**Table 4**, $P = 0.58$) or composite outcome (**Table 4**) ($P = 0.53$).

Among 393 patients on medications, 207 were able to be matched to patients not medications using the propensity score. The baseline characteristics for the propensity score matched-pair analyses are delineated in Supplemental Table 1; the primary composite outcome occurred in 14 (6.7%) patients who were on either an ACEI/ARB, beta-blocker, or both a beta-blocker and an ACEI/ARB, and in 13 (6.2%) patients who were not taking these medications (Supplemental Table 2). Differences between patients who were and were not matched are summarized in Supplemental Table 3. The propensity-matched group tended to have fewer comorbidities, including lower rates of ventricular dysfunction, atrial fibrillation or flutter, and diuretic use compared to those who were not used in the analysis as a function of matching patients with similar sets of comorbidities.

For the propensity score matched group, there was no significant association between beta-blocker, ACEI/ARB usage during the study period and the composite outcome (**Table 5**) (HR: 1.37 [95% CI: 0.62-3.04], $P = 0.43$). Furthermore, the combination of ACEI/ARB and beta-blockers did not result in a significant difference in the outcome (**Table 5**) (HR: 2.07 [95% CI: 0.61-6.99], $P = 0.24$) (**Central Illustration**).

For analysis of the association between medications and atrial arrhythmias, only patients with no history of atrial arrhythmias were included (n = 652); Supplemental Table 4 delineates the differences between the patients with a history of atrial arrhythmias and those without, which includes higher percentages of medication use. When controlling for propensity score in this subgroup of patients, beta-blockers, ACEI, and/or ARBs were associated with a higher incidence of atrial arrhythmias ($P = 0.032$) (**Table 4**).

TABLE 2 Comparison of Characteristics Between Those With and Without Medications

	Group 1: No Meds (n = 484)	Group 2: On AA and/or BB (n = 393)	*P* Value
Male	273 (56.4%)	244 (62.1%)	0.098
d-TGA	343 (70.9%)	252 (64.1%)	0.035
Baseline smoker (n = 439, n = 364)	60 (13.7%)	39 (10.7%)	0.24
Diabetes (n = 481, n = 392)	6 (1.2%)	19 (4.9%)	0.002
Hypertension (n = 482, n = 391)	12 (2.5%)	53 (13.6%)	<0.001
History of atrial flutter or fibrillation (n = 482, n = 393)	72 (14.9%)	152 (38.7%)	<0.001
History of heart failure	14 (2.9%)	53 (13.5%)	<0.001
Baseline diuretic (n = 480, n = 392)	12 (2.5%)	98 (25.0%)	<0.001
Baseline spironolactone (n = 482, n = 390)	5 (1.0%)	55 (14.1%)	<0.001
Baseline pacemaker (n = 482, n = 392)	78 (16.2%)	129 (32.9%)	<0.001
Baseline ICD (n = 483, n = 393)	4 (0.8%)	38 (9.7%)	<0.001
Baseline VT (n = 482, n = 392)	12 (2.5%)	45 (11.5%)	<0.001
Baseline RV dysfunction (n = 472, n = 381)			<0.001
Normal	152 (32.2%)	76 (20.0%)	
Mild	202 (42.8%)	107 (28.1%)	
Moderate	106 (22.5%)	139 (36.5%)	
Severe	12 (2.5%)	59 (15.5%)	
Baseline tricuspid regurgitation (n = 465, n = 378)			<0.001
None	100 (21.5%)	46 (12.2%)	
Mild	280 (60.2%)	172 (45.5%)	
Moderate	73 (15.7%)	118 (31.2%)	
Severe	12 (2.6%)	42 (11.1%)	
Complexity score			0.048
0	331 (68.4%)	278 (70.7%)	
1	95 (19.6%)	56 (14.3%)	
2	38 (7.9%)	45 (11.5%)	
3	12 (2.5%)	11 (2.8%)	
4	8 (1.7%)	2 (0.5%)	
5	0 (0.0%)	1 (0.3%)	
Age at First Visit, y	26.0 (21.4-31.4)	31.3 (24.0-41.2)	<0.001

Values are n (%) or median (IQR). Baseline refers to the presence of the parameter at the first visit; that is baseline diuretic means that the patient was on a diuretic at the first visit.

A/A = angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker; BB = beta-blocker; d-TGA = dextro-transposition of the great arteries; ICD = implantable cardioverter-defibrillato; MCS = mechanical circulatory support; RV = right ventricle; VT = ventricular tachycardia.

DISCUSSION

In this retrospective propensity score analysis of medication use amongst a large SRV population, there was no detectible improvement in clinical outcomes for patients who were on beta-blockers, and/or ACEI/ARBs. To our knowledge, our study is the first to evaluate the effect of beta-blockers on mortality and hospitalizations in a large propensity-matched cohort of SRV patients attempting to account for multiple likely confounders.

PRIMARY OUTCOMES. Our previous publications found use of these medications was associated with increased mortality, no doubt reflecting higher use in sicker patients.[10,11] Yet, even after efforts to control

TABLE 3 Propensity Adjusted Association Between Clinical Outcomes and Medication Status—Comparison of Patients Not on Medications With Those on Medications

	HR (95% CI)	*P* Value
Medication AA and/or BB		
Mortality, MCS, or Tx	1.07 (0.58, 1.99)	0.82
HF hospitalizations	0.81 (0.45, 1.47)	0.48
Atrial arrhythmias	1.67 (0.91, 3.06)	0.10

AA = angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; BB = beta-blocker; HF = heart failure; MCS = mechanical circulatory support; Tx = transplantation.

TABLE 5 Association of Medication Usage With Composite Outcome of Death, Transplant, or Mechanical Circulatory Support Placement in the Propensity Score Matched Group

	HR (95% CI)	*P* Value
Medication AA and/or BB	1.37 (0.62, 3.04)	0.43
Medication status		
BB and AA	2.07 (0.61, 6.99)	0.24
BB, no AA/ARB	2.48 (0.71, 8.72)	0.16
AA, no BB	0.89 (0.32, 2.43)	0.82
No medications	-	-

A/A = angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; BB = beta-blocker.

for factors likely influencing use of these medications via propensity scoring, there was still no difference in mortality. In fact, the hazard ratio for patients on both ACEI/ARB and beta-blockers trended toward increased mortality on these medications, albeit without achieving statistical significance. Hence, the results suggest that these medications do not have a measurable favorable impact on outcomes in the SRV population, and, in fact, cannot exclude a detrimental impact.

While this is not a randomized prospective study and never be considered a substitute for such, the data do give pause for any advocacy in favor of their routine use. Our study adds credence to previous work that has shown no significant effects of beta-blockers, ARBs, or ACEI on mortality in smaller groups prospectively that were sometimes simply viewed as being underpowered. These medications form the backbone of heart failure therapy for patients without congenital heart disease and left ventricular dysfunction with multiple, albeit larger studies confirming they convey a survival benefit in those with such dysfunction.[12] However, beta-blockers, ACEI, or ARBs have not conclusively been shown to prevent death in the SRV population. For example, van der Boom et al previously described the VALSERVE study in which 88 patients with SRV were randomized to either valsartan 160 mg twice a day or to placebo; at the end of the 3-year study period, valsartan did not confer statistically significant benefits with regard to quality of life, RV ejection fraction, or exercise capacity.[1] A follow-up study on this original cohort showed that, after a median 8 years of follow-up, there was still no difference in the combined clinical outcome of arrhythmia, heart failure, death, and tricuspid valve surgery. However, for symptomatic patients, there was a significant reduction in the primary outcome, suggestive of a potential benefit of valsartan.[5] Yet, the overall patient numbers were small, limiting the generalizability of the study. Similarly, a study of ~350 patients who were on ACEI, ARB, or not on either medication found no mortality benefit after a mean follow up of ~7 years.[6] Overall, these results are consistent with a systemic review and meta-analysis that did not find a mortality benefit for these medications in the SRV patient population.[2] Taken together, the totality of evidence suggests that the pathophysiology of SRV heart failure is different to that involving the left ventricle and that results from trials in patients with systemic left ventricular dysfunction should not be extrapolated to the patient with a systemic RV.

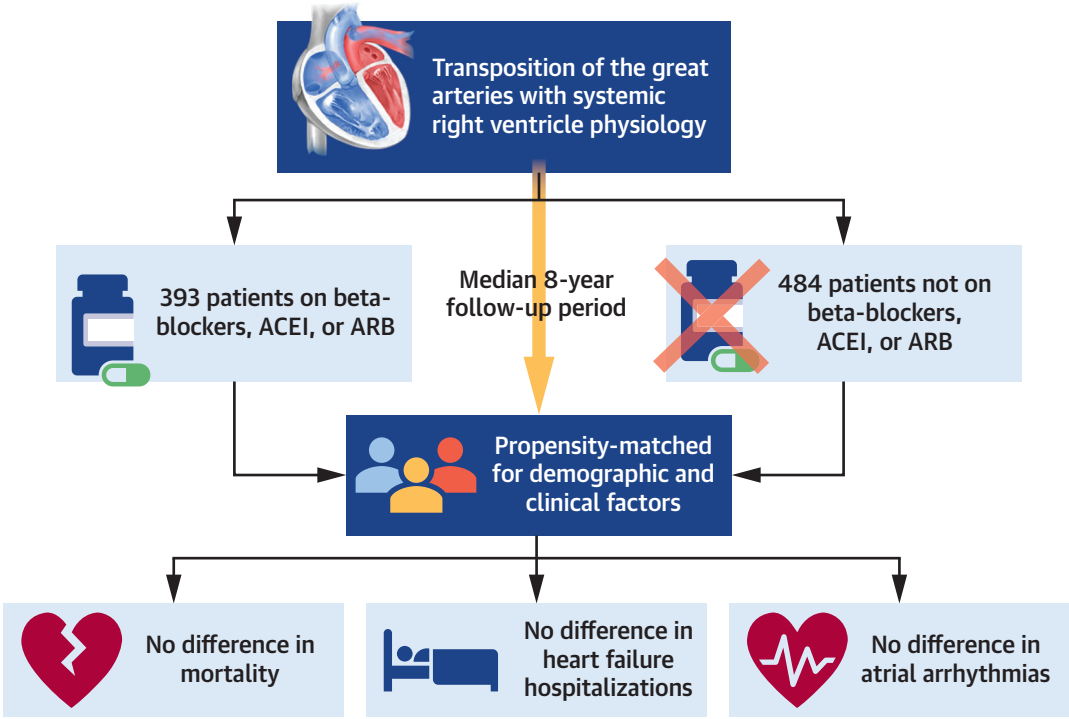
TABLE 4 Propensity Adjusted Association Between Clinical Outcomes and Medication Status: Comparison of Patients Not on Medications as a Reference in Comparison With Those on Beta-Blockers, Angiotensin Converting Enzyme Inhibitors, or Angiotensin Receptor Blockers

	HR (95% CI)	*P* Value
Mortality, MCS, or Tx		
BB and AA/ARB	1.28 (0.54, 3.08)	0.58
BB, no AA/ARB	1.76 (0.92, 3.35)	0.09
AA, no BB	0.77 (0.34, 1.75)	0.53
No medications	-	-
HF hospitalizations		
BB and AA/ARB	0.82 (0.42, 1.60)	0.55
BB, no AA/ARB	1.05 (0.53, 2.08)	0.90
AA, no BB	0.71 (0.33, 1.50)	0.37
No medications	-	-
Atrial arrhythmias		
BB and AA/ARB	2.26 (1.06, 4.82)	0.036
BB, no AA/ARB	3.06 (1.46, 6.44)	0.003
AA, no BB	1.38 (0.65, 2.90)	0.40
No medications	-	-

AA = angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; BB = beta-blocker; HF = heart failure; MCS = mechanical circulatory support; Tx = transplantation.

SECONDARY OUTCOMES. Our study also did not show benefit from ACEI, ARB, or beta-blockers with regard to reducing heart failure hospitalizations.

CENTRAL ILLUSTRATION Clinical Outcomes of Patient Cohort



Misra A, et al. JACC Adv. 2025;4(1):101443.

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker.

Interestingly, the data suggested that these medications were associated with a higher rate of atrial arrhythmias, though this again may be secondary to the presence of other comorbidities which predisposed patients to developing atrial arrhythmias. As previously shown, patients on medications tended to have more significant illness, with a higher percentage having moderate or severe tricuspid regurgitation or RV systemic dysfunction, ICD or pacemaker placement at the time of the first visit, and a history of atrial or ventricular arrhythmias which contributed to their overall increased mortality compared to those who were not on medications.[10] While these predisposing conditions likely contribute to the higher rate of arrhythmias rather than any deleterious effect of the medications themselves with the initiation of medications likely suggestive of an overall more medically complex patient, the findings certainly raise the question of their assumed efficacy in rhythm reduction in this population. Similarly, in the univariable analysis, medication use was associated with the primary outcome. These findings were not seen in the propensity score analysis that was adjusted for propensity scores, suggesting these findings likely represent the initiation of medications for patients who were already high risk.

SYSTEMIC RIGHT VENTRICLE HEART FAILURE PHYSIOLOGY. Due to limited patient numbers, studying the effects of therapeutics for SRV patients with heart failure has been difficult. There have been only 3 randomized controlled trials to our knowledge in the SRV population that have evaluated the effects of ARBs and mineralocorticoid receptor antagonists, with only 1 of the studies using mortality as an endpoint.[4,5,13,14]

Additional mechanistic targets of therapy should be considered given the morphological differences between the systemic RV and the left ventricle, which may explain why standard guideline-directed medical therapy for left ventricular dysfunction may not

be applicable to the SRV population. Patients with SRV develop progressive hypertrophy of the SRV due to the chronic afterload which over time leads to significant fibrosis and eventual dysfunction.[15] The presence of myocardial fibrosis in SRV patients has been shown to correlate with worse clinical outcomes, potentially highlighting a target of therapy.[16] Newer agents, such as combined angiotensin receptor-neprilysin inhibitors, have been shown to improve right ventricular function and quality of life in the short term and may represent further areas of research.[17,18] Randomized controlled trials are required to conclusively demonstrate the benefits of newer medications on morbidity and mortality in the SRV population.

STUDY LIMITATIONS. Importantly, this retrospective and observational study should not be considered a substitute for a randomized prospective trial. Our study design led to the exclusion of patients who may have been started on the medication during the study period, and decreased our statistical power. We attempted to take advantage of the variable practice of prescribing medication among the centers as well as the indications for starting or stopping a medication. Our matching favored metrics that were objective, readily available, and distinctive between those with and without endpoints, which gave greater credibility to the propensity matching. However, propensity matching is imperfect, and it is plausible that residual confounding is at play. After necessary exclusions, some cohorts were relatively small in number. The doses of the medications, titration intervals and adherence patterns were beyond what could be obtained with the study design. The echocardiographic data collected varied between centers and subsequently, the grading of regurgitation or SRV function is subjective and may have differed between centers. Additionally, clinical parameters such as NYHA functional class were not readily available to include in the analysis; the number of patients with other parameters such as brain natriuretic peptide, subpulmonary LV function prior to study period, and cardiac catheterization was limited, making it difficult to analyze them adequately in the propensity score matching.

CONCLUSIONS

Even when accounting for disease severity through propensity score analysis, we were unable to show that the practice of prescribing beta-blockers, ACEI, and ARBs had a favorable impact on mortality in patients with SRV. While not a substitute for a randomized trial, the data suggest that any favorable effect of these medicines in the SRV population is very small, and that larger studies with statistical power, if ever feasible, may only show negative effects. Thus, efforts to find pharmacotherapeutic options for SRV patients may be better targeted elsewhere.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Amrit Misra, Boston Children's Hospital/Brigham and Women's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115, USA. E-mail: amrit.misra@cardio.chboston.org.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND MEDICAL KNOWLEDGE: Patients with SRV are at high risk of developing ventricular dysfunction, leading to significant morbidity and mortality. Current therapeutics for treating SRV patients with heart failure are limited, with most providers using goal directed medical therapy traditionally used for left ventricular dysfunction, including beta-blockers, ACEI, and ARBs. We studied the effects of beta-blockers, ACEI, and ARBs in a multicenter cohort of SRV population, specifically looking at whether these medications improve clinical outcomes such as MCS placement, mortality, or transplantation as well as atrial arrhythmias and heart failure hospitalizations.

TRANSLATIONAL OUTLOOK: Our study did not show an improvement in clinical outcomes for SRV patients on beta-blockers, ACEI, or ARBs, suggesting that alternative therapies are needed to treat heart failure in these patients.

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KEY WORDS congenital heart diseas, congestive heart failure, systemic right ventricle, transposition of the great arteries

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