

Impact of Disease Complexity on Cardiovascular Events after the Transition to an Adult Congenital Heart Disease Specialized Medical Unit

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The follow-up of patients with adult congenital heart disease (ACHD) at a specialized medical unit is necessary for the patients' appropriate medical care. However, limited information is available about cardiovascular events among ACHD patients. Here we investigated the type and frequency of cardiovascular events in ACHD patients in relation to disease complexity. We retrospectively analyzed the cases of 535 patients (median age 35 years) referred to our ACHD center between 2014 and 2017. We divided the patients into 3 groups based on their disease complexity. To evaluate the relationship between disease complexity and cardiovascular events, we performed univariate and multivariate survival analyses. The Simple, moderate, and complex disease groups accounted for 62%, 19%, and 19% of the patients, respectively. Apart from events related to atrial septal defect (ASD) trans-catheter treatment, the frequency of cardiovascular events was dependent on the disease complexity (event-free survival rates at 3 years were 85%, 65%, and 58%, respectively). The hazard ratios were 4.0 and 5.1 in the moderate and complex groups, respectively. With the exception of scheduled transcatheter intervention, cardiovascular events were strongly related to the disease complexity of original heart disease. However, cardiovascular events were not rare even in the simple ACHD group.

Key words: congenital heart defect, congenital in adults, hospitalization, cardiovascular event

Surgical and medical treatments for congenital heart disease (CHD) have improved over time, and nowadays over 90% of pediatric CHD patients are expected to reach adulthood [1,2]. However, despite receiving appropriate treatment in childhood, individuals with adult CHD (ACHD) are not necessarily completely cured [2]. Following up these adult patients is recognized as an important medical and social issue. In Japan, the number of ACHD outpatient clinics operated by cardiologists has increased, but it remains unknown what types of cardiovascular events occur in patients with ACHD. We conducted the present study

to investigate the types and frequency of cardiovascular events in ACHD patients and to assess the influence of the patients' disease complexity on cardiovascular events requiring hospitalization.

Patients and Methods

Patient population. This was a retrospective, observational cohort study. All ACHD patients who were referred from other hospitals or transferred from the departments of pediatric surgery and pediatric cardiology to the ACHD Center of Okayama University Hospital between August 2014 and September 2017

were enrolled in this study. Patients were eligible for the study if they were >18 years of age.

Classification of ACHD complexity. We divided the ACHD patients into 3 groups based on their Bethesda disease complexity classification (complexity of primary diagnosis) [3,4] as follows: the Simple group was comprised of the cases of CHD with only simple lesions such as isolated valve disease (aortic, mitral, or pulmonary stenosis and/or regurgitation), atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), and isolated coronary anomaly. The Moderate group was the patients with CHD with moderate-complexity lesions such as atrioventricular septal defect, coarctation of the aorta, interrupted aortic arch, Ebstein anomaly, tetralogy of Fallot (TOF), and total/partial anomalous pulmonary venous return. The Complex group was the patients with CHD with highly complex lesions such as congenitally corrected transposition of the great arteries, transposition of the great arteries, truncus arteriosus, pulmonary atresia, other congenital complex lesions including single ventricle, tricuspid atresia, and double-outlet ventricles. Patients with Eisenmenger syndrome or Fontan physiology were included in Complex group regardless of their original heart diseases.

Definition of cardiovascular events. We used the patients' chart records in our search for cardiovascular events. Our definition of cardiovascular events included: death, open cardiac surgery and unexpected hospitalizations due to heart failure, arrhythmias, pulmonary hypertension or ischemic heart disease. Hospitalization for a scheduled catheter intervention was excluded as a cardiovascular event. The diagnosis of heart failure was based on the clinical presentation of the modified Framingham Heart Failure criteria [5], and we identified patients with New York Heart Association class 3 or 4 symptoms. Hospitalization for pulmonary hypertension was defined as the worsening of symptoms related to pulmonary hypertension and the addition of pulmonary hypertension-specific drugs [6]. Indications for cardiac surgery were decided on the basis of guidelines of The Japanese Circulation Society (http://www.j-circ.or.jp/guideline/pdf/JCS2017_ichida_h.pdf accessed March 2019), The American Heart Association [3], and The European Society of Cardiology [2].

Statistical analyses. All analyses were performed

with SPSS25 (2017 release software by IBM, Armonk, NY, USA). *P*-values <0.05 were accepted as significant. Continuous variables are presented as the median (25-75% interquartile range [IQR]), and categorical variables are summarized as numbers and percentages. The baseline characteristics of patients at their first visits were determined. We used the Kruskal-Wallis test and the χ^2 -test when comparing multiple continuous variables and binary variables, respectively. Post hoc comparisons were analyzed with the Bonferroni correction.

To investigate the relationship between disease complexity and cardiovascular events, we performed a univariate survival analysis with the log-rank test. We used the Cox proportional hazards model to quantify the effects of disease complexity on the risk of cardiovascular events. For the multivariate analysis, variables were selected in advance of the analysis as clinically meaningful factors including demographic factors (sex, age, referral from other institutions), co-morbidity factors (complication of pulmonary hypertension, history of ventricular arrhythmia), and representative laboratory data, *i.e.*, B-type natriuretic peptide (BNP) and the estimated glomerular filtration rate (eGFR). 'Time zero' was the day of the patient's first visit to our ACHD Center. This study was approved by the Ethical Committee of Okayama University (approval no. 1707-004).

Results

Patient backgrounds. The disease distribution of the patients is shown in Table 1. The 535 ACHD patients who visited the center during this period were classified as the Simple (n=330, 62%), Moderate (n=102, 19%), and Complex (n=103, 19%) groups. ASD patients were the most common and accounted for 43%, followed by TOF and VSD (9% and 8%, respectively). Other diseases accounted for between 0.4% and 5% of the patient series. Four percent of the patients had undergone a Fontan operation. Eisenmenger syndrome patients accounted for 0.5%.

The characteristics of patients are summarized in Table 2. The median age of all patients was 35 years (IQR 22-58 years), and the patients in the Simple group were the oldest. Most of the patients in the Simple group were referred from other hospitals for the catheter treatment of ASD or PDA. Most of the patients in the Moderate and Complex groups were transferred from the pediatric department in our hospital. Two

percent of the patients had a history of ventricular arrhythmia, 4% of the patients had pulmonary hypertension, and 0.6% of the patients had Eisenmenger syndrome. The median BNP level at the first visit was

Table 1 Distribution of disease

Simple	330	62%
ASD	231	43%
VSD	46	8%
Aortic valve disease	15	3%
PDA	13	3%
Pulmonary valve disease/right ventricular outlet stenosis	12	2%
Mitral valve disease	9	2%
Isolated coronary anomaly	4	0.6%
Moderate	102	19%
TOF	49	9%
CoA/IAA	20	4%
AVSD	16	3%
Ebstein	8	2%
TAPVR/PAPVR	6	1%
Other congenital heart diseases with moderate Complexity	3	0.5%
Complex	103	19%
SV/TA/DORV/DOLV	25	5%
Post Fontan procedure	22	4%
TGA	16	3%
cTGA	15	3%
PA-VSD/TOF-PA	13	2%
PA-IVS	7	0.3%
Eisenmenger syndrome	3	0.5%
PTA	2	0.4%

Table 2 Baseline characteristics

	Simple (n = 330)	Moderate (n = 102)	Complex (n = 103)	Total number (n = 535)	p value
Demographic factors					
Age (years old)	49 [27–66]	22 [20–32]	24 [21–37]	35 [22–58]	< 0.001**
Male, n (%)	128 (39)	51 (50)	50 (49)	229 (43)	0.06
Reference from other Institutions, n (%)	253 (77)	20 (20)	36 (35)	309 (58)	< 0.001**
Co-morbidity factors					
Ventricular arrhythmia, n (%)	2 (0.6)	6 (5.9)	5 (4.9)	13 (2.4)	0.002**
Pulmonary hypertension on drug, n (%)	12 (3.6)	2 (1.0)	8 (7.8)	22 (4.1)	0.09
Laboratory data					
BNP (pg/ml)	32.1 [13.7–101.6]	24.2 [10.4–49.5]	36.4 [15.3–96.3]	31.7 [13.7–87.6]	0.01*
eGFR (mL/min/1.73 m ²)	78.2 [63.5–93.7]	94.0 [83.6–109.4]	94.1 [78.1–109.4]	84.7 [69.3–100.0]	< 0.001**

lower in the Moderate group compared to the Simple and Complex groups. However, the eGFR in the Simple group was significantly lower than those in the two other groups, probably due to the Simple group patients' advanced ages at their first visits.

The influence of ACHD complexity on cardiovascular events requiring hospitalization. During the median follow-up of 537 days, corresponding to 787 patient years, 91 (17%) patients had 158 complications in total. Eight percent of the patients in the Simple group, 23% in the Moderate group, and 30% in the Complex group experienced a cardiovascular event during their follow-up.

Figure 1 shows the cardiovascular event-free survival curves from death, open cardiac surgery, or cardiovascular events requiring unexpected hospitalization for treatment. A decrease in cardiovascular event-free survival within the first few months after the patients' first visit was observed in all 3 groups. The cardiovascular event-free survival curve in the Simple group was almost flat after 180 days, whereas the curves in the Moderate and Complex groups progressively decreased. Cardiovascular events were strongly associated with ACHD complexity, and the 3-year cardiovascular event-free rate was significantly lower in the Moderate and Complex groups: 65% in the Moderate group, 58% in the Complex group, and 85% in the Simple group ($p=0.009$ the Simple group vs the Moderate group, $p=0.002$ the Simple group vs the Complex group).

The Cox proportional hazard model revealed that with reference to the Simple group, the adjusted hazard ratio (HR) of ACHD complexity for cardiovascular

events requiring hospitalization was 4.0 (95% confidence interval [CI]: 2.0-7.8, $p < 0.001$) in the Moderate group and 5.1 (95%CI: 2.8-9.3, $p < 0.001$) in the Complex group. The three other significant risk factors were age (adjusted HR 1.3 per 10 years of age; 95%CI: 1.1-1.5, $p = 0.04$), the comorbidity of pulmonary hyper-

tension requiring specific medication (adjusted HR 2.4, 95%CI: 1.3-4.7, $p = 0.008$), and low eGFR (adjusted HR 0.9 per 10 ml/min/1.73 m², 95%CI: 0.8-0.99, $p = 0.03$) (Table 3).

Details of the cardiovascular events. As shown in Fig. 2, the proportion of causes of hospitalization varied by ACHD complexity, but arrhythmia, heart failure, and surgery were the most common cardiovascular events in each of the 3 patient groups. On the whole, these three events accounted for 41%, 33%, and 16% of all of the events, respectively.

Although arrhythmias requiring hospitalization or any treatment were commonly documented in every group, ventricular tachycardia with the risk of sudden death occurred only in the Moderate and Complex groups (one case of TOF, one Ebstein anomaly, one complete transposition of the great arteries, and one pulmonary atresia with VSD). Heart failure, especially in the Complex group, tended to be refractory, and 70% (7 of the 10) patients with heart failure in the Complex group needed hospitalization more than once.

Eight of the 12 cases (75%) with surgery in the Moderate group were for the reconstruction of the right ventricular outflow tract of TOF. Two ischemic heart events occurred in elderly patients with arteriosclerosis risk factors without an anomalous origin of a coronary artery.

Two patients (0.12%) died during the observational period. One was a 67-year-old male with unrepaired TOF. The patient underwent the surgical implantation of a cardiac resynchronization therapy device for

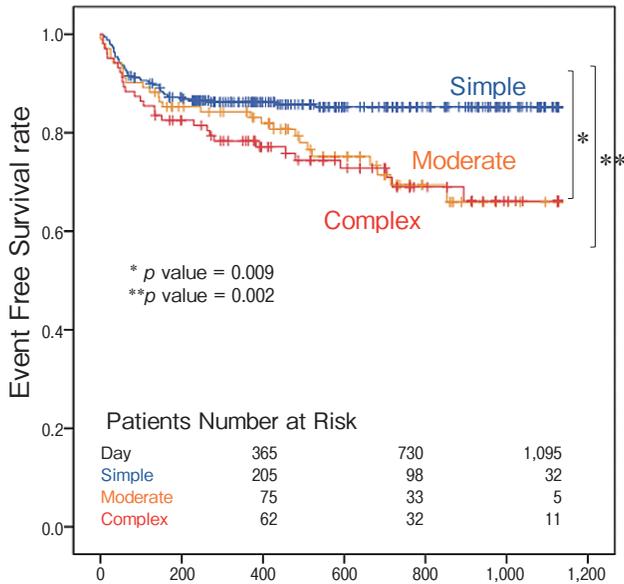


Fig. 1 Event-free survival curves for cardiovascular events requiring hospitalization in relation to ACHD complexity (log-rank test). The cardiovascular event-free survival curves of the Simple, Moderate, and Complex ACHD groups are shown. Events included death, open cardiac surgery, and unexpected hospitalizations due to heart failure, arrhythmias, pulmonary hypertension, or ischemic heart disease.

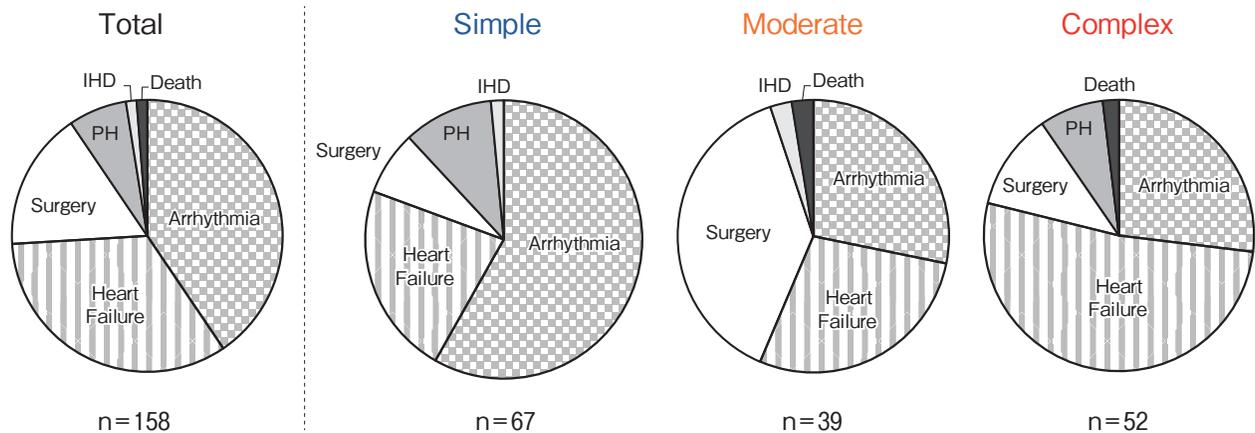


Fig. 2 Causes of hospitalization. The causes of hospitalization depending on ACHD complexity are shown. Transcatheter intervention was the most common cause in the Simple group, with surgery the most common cause in the Moderate group, and heart failure in the Complex group. IHD, ischemic heart disease; PH, pulmonary hypertension.

Table 3 Adjusted hazard ratio of risk factors Influencing cardiac events requiring hospitalization

	AHR	95% upper CI	95% lower CI	p-value
Complexity				
Simple (reference)	1			–
Moderate	3.95	1.99	7.84	< 0.001
Complex	5.14	2.84	9.3	< 0.001
Age (10 years)	1.27	1.08	1.5	0.04
Female	0.85	0.55	1.32	0.47
Referred from other institutions	1.75	0.95	3.21	0.07
Pulmonary hypertension	2.44	1.26	4.72	0.008
Ventricular arrhythmia	0.97	0.37	2.55	0.95
BNP (10 pg/ml)	1	0.99	1.01	0.97
eGFR (10 ml/min/1.73 m ²)	0.9	0.81	0.99	0.03

severely deteriorated left ventricular function. An unexpected massive hemorrhage due to pericardial adhesion occurred during the surgical procedure, and he died 1 month later. The other patient who died was a 44-year-old male with tricuspid atresia and failed Fontan status, complicated with liver cirrhosis and hepatic cancer. The patient was repeatedly hospitalized due to right heart failure, protein-losing enteropathy, and low output syndrome. He died due to multiple organ failure.

Discussion

This was a retrospective observational study of 535 ACHD patients referred to our ACHD center over a 3-year period. We found that increasing complexity of ACHD is associated with a greater risk of comorbidities regardless of ACHD treatment in childhood.

ACHD outpatient clinics have become increasingly widespread in Japan in the past decade [7], and our present findings provide an overview of a single territorial ACHD center. There have been only a few explorative investigations of ACHD complexity and associated cardiovascular events [8,9]. Diller *et al.* evaluated the survival prospects and circumstances of death of ACHD patients, and they reported that the mortality ratio of moderate or complex congenital heart disease ranged from 1.7 to 3.3 compared with a sex- and aged-matched general population [10]. Engelfriet *et al.* reported substantial morbidity among ACHD patients, even with only simple complexity disease [11]. Our present data are consistent with these observations; we observed that the disease complexity of ACHD had a significant

impact on the number of cardiovascular events requiring hospitalization.

We also observed that the details of the patients' cardiovascular events varied depending on ACHD complexity. The Simple group included patients referred to our hospital for trans-catheter ASD/PDA closure. Although it is true that a substantial number of patients need a trans-catheter closure of defects after they develop heart failure or dilation of the right ventricle, we note that in Japan the trans-catheter closure procedure is performed in only a limited number of registered facilities. However, importantly, as many as 15% of the patients in our Simple group had cardiovascular events other than this procedure, suggesting that no ACHD patient should be lost during following-up.

Arrhythmias were commonly observed in every group as in previous studies [12]. More severe arrhythmias occur in complex ACHD patients due to multiple mechanisms such as intra-cardiac repair scars, congenital conduction abnormalities, or persistent hemodynamic abnormalities [13]. However, Bouchardy *et al.* reported that both supraventricular arrhythmias and ventricular arrhythmias influenced mortality [14]. This may indicate that the monitoring of arrhythmias in ACHD patients can be important as a surrogate marker of mortality risk.

Heart failure was also a common reason for hospitalization. Negishi *et al.* reported that 86% of their study's ACHD patients requiring heart failure hospitalization had complex forms of congenital heart disease [15]. Heart failure, especially in more complex disease, emerges as a final expression of various disorders such as uncontrollable arrhythmias, reduced ventricular

function, and/or valvular diseases. Patients with complex lesions tended to have refractory heart failure and repeat hospitalization to receive palliative therapy.

A multidisciplinary approach is the key to the optimal management of ACHD patients, and this approach highlights the need for territorial referral centers in this field. The incidence of heart failure after the Fontan procedure progresses with age, reaching nearly 50% by adulthood [16,17]. Although the patient cohorts of these previous studies cannot be easily compared with our patient series, 23% of the patients with Fontan physiology in our study had heart failure, and thus the incidence of heart failure may increase further as these patients continue to age.

A first or repeat surgery is often required in patients with moderate or complex ACHD. For example, Ebstein anomaly or corrected transposition of the great arteries result in only insignificant symptoms in childhood but require surgery later in life as these conditions develop. The majority of repeat surgeries in the present study were for TOF with severe pulmonary regurgitation. The importance of repeated surgical procedures should thus be recognized, and this also highlights the need for multimodal assessment including CT, MRI, cardiopulmonary exercise, and electrophysiological evaluations at ACHD-specific facilities.

We also evaluated the influence of representative factors on cardiovascular events, and in our cohort, the patient's age at the first visit, the comorbidity of pulmonary hypertension, and the eGFR were detected as independent factors. Although there are unmeasured compounding factors due to CHD variation, these results are reasonable and compatible with previous studies [18-20]. To identify disease-specific risk factors, further investigations using 'big data' with multiple variables are needed.

Limitation. This was a retrospective cohort study from a single center with a relatively small patient population. The follow-up period was limited and it was thus not possible to evaluate the risks of cardiovascular events or mortality in ACHD patients. Each disease classification does not reflect the disease severity completely; rather, each classification reflects a majority of ACHD patients with comorbidity or associated cardiac lesions.

In conclusion, the results of our analyses demonstrate that the disease complexity of ACHD has a significant impact on the number of cardiovascular events

requiring hospitalization during a 3-year observation period. However, cardiovascular events were not rare even in the simple-complexity group. A higher incidence of hospitalization was observed in the patients with higher age, those with pulmonary hypertension, and those with renal dysfunction. Arrhythmia was the most frequent event in the Simple group, surgery in the Moderate, and heart failure in the Complex group. Regular follow-up at specialized ACHD centers and a regional network are essential to monitor these various events in ACHD patients and to supply optimal care. Further studies, including multi-institutional prospective surveys, are expected to identify disease-specific risk factors.

Acknowledgments. We thank Drs. Shingo Kasahara, Kenji Baba, Shinichiro Nakamura, Masaru Kinomura, Hisashi Masuyama, Kazuhiro Ohmori, and all other staff at the ACHD Center in Okayama University Hospital for the management of ACHD patients. We also thank Hanne Gadeberg, PhD, from Edanz Group for editing a draft of this manuscript. This work was partly supported by a grant from the Japan Agency for Medical Research and Development (17ek0210069h0002).

References

1. Moons P, Bovijn L, Budts W, Belmans A and Gewillig M: Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. *Circulation* (2010) 122: 2264-2272.
2. Budts W, Roos-Hesselink J, Radle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, Crespo-Leiro MG, Walker F and Frogoudaki AA: Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J* (2016) 37: 1419-1427.
3. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, Everitt MD, Gatzoulis M, Harris L, Hsu DT, Kuvin JT, Law Y, Martin CM, Murphy AM, Ross HJ, Singh G, Spray TL, American Heart Association Council on Clinical Cardiology CoFG, Translational B, Council on Cardiovascular R and Imaging: Chronic Heart Failure in Congenital Heart Disease: A Scientific Statement From the American Heart Association. *Circulation* (2016) 133: 770-801.
4. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP, Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP and Webb GD: ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation* (2008) 118: e714-833.
5. McKee PA, Castelli WP, McNamara PM and Kannel WB: The natural history of congestive heart failure: the Framingham study. *N Engl J Med* (1971) 285: 1441-1446.

6. Coghlan JG, Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, Kuwana M, McLaughlin VV, Peacock AJ, Simonneau G, Vachieri JL, Blair C, Gillies H, Miller KL, Harris JHN, Langley J, Rubin LJ and investigators A: Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. *Ann Rheum Dis* (2017) 76: 1219–1227.
7. Ochiai R, Kato H, Akiyama N, Ichida F, Yao A, Inuzuka R, Niwa K, Shiraishi I and Nakanishi T: Nationwide Survey of the Transfer of Adults With Congenital Heart Disease From Pediatric Cardiology Departments to Adult Congenital Heart Disease Centers in Japan. *Circ J* (2016) 80: 1242–1250.
8. Opatowsky AR, Siddiqi OK and Webb GD: Trends in hospitalizations for adults with congenital heart disease in the U.S. *J Am Coll Cardiol* (2009) 54: 460–467.
9. Billett J, Majeed A, Gatzoulis M and Cowie M: Trends in hospital admissions, in-hospital case fatality and population mortality from congenital heart disease in England, 1994 to 2004. *Heart* (2008) 94: 342–348.
10. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulos K and Gatzoulis MA: Survival Prospects and Circumstances of Death in Contemporary Adult Congenital Heart Disease Patients Under Follow-Up at a Large Tertiary Centre. *Circulation* (2015) 132: 2118–2125.
11. Engelfriet P, Boersma E, Oechslin E, Tijssen J, Gatzoulis MA, Thilen U, Kaemmerer H, Moons P, Meijboom F, Popelova J, Laforest V, Hirsch R, Daliento L, Thaulow E and Mulder B: The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. *The Euro Heart Survey on adult congenital heart disease. Eur Heart J* (2005) 26: 2325–2333.
12. Somerville J: Management of adults with congenital heart disease: an increasing problem. *Annu Rev Med* (1997) 48: 283–293.
13. Task Force sul Trattamento delle Cardiopatie Congenite dell'Adulto della Societa Europea di C: [Guidelines for the management of grown-up congenital heart disease (new version 2010)]. *G Ital Cardiol (Rome)* (2011) 12: 505–550.
14. Bouchardy J, Therrien J, Pilote L, Ionescu-Iltu R, Martucci G, Bottega N and Marelli AJ: Atrial arrhythmias in adults with congenital heart disease. *Circulation* (2009) 120: 1679–1686.
15. Negishi J, Ohuchi H, Miyazaki A, Tsuda E, Shiraishi I and Kurosaki K: Clinical Characteristics of Adult Patients With Congenital Heart Disease Hospitalized for Acute Heart Failure. *Circ J* (2018) 82: 840–846.
16. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoega M and Buchhorn R: Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. *Am J Cardiol* (2006) 97: 1238–1243.
17. Piran S, Veldtman G, Siu S, Webb GD and Liu PP: Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. *Circulation* (2002) 105: 1189–1194.
18. Barst RJ, Ivy DD, Foreman AJ, McGoon MD and Rosenzweig EB: Four- and seven-year outcomes of patients with congenital heart disease-associated pulmonary arterial hypertension (from the REVEAL Registry). *Am J Cardiol* (2014) 113: 147–155.
19. Lui GK, Saidi A, Bhatt AB, Burchill LJ, Deen JF, Earing MG, Gewitz M, Ginns J, Kay JD, Kim YY, Kovacs AH, Krieger EV, Wu FM, Yoo SJ, American Heart Association Adult Congenital Heart Disease Committee of the Council on Clinical C, Council on Cardiovascular Disease in the Y, Council on Cardiovascular R, Intervention, Council on Quality of C and Outcomes R: Diagnosis and Management of Noncardiac Complications in Adults With Congenital Heart Disease: A Scientific Statement From the American Heart Association. *Circulation* (2017) 136: e348–e392.
20. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulou SA, Babu-Narayan SV, Salukhe TV, Piepoli MF, Poole-Wilson PA, Best N, Francis DP and Gatzoulis MA: Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. *Circulation* (2008) 117: 2320–2328.