The outcome of Eisenmenger patients with trisomy 21 does not differ from patients without trisomy 21

Els TROOST[1], MD; Alexander VAN DE BRUAENE[1], MD; Konstantinos LAMPROPOULOS[1], MD, PhD; Martijn POST[1], MD; Marc GEWILLIG[2], MD, PhD; Philip MOONS[3], RN, PhD; Marion DELCROIX[4], MD, PhD; Werner BUDTS[1], MD, PhD

[1]Congenital and structural cardiology, [2]Paediatric cardiology and [4]Pneumology, University Hospitals Leuven; [3]Centre for Health Services and Nursing Research, Catholic University of Leuven, Leuven, Belgium.

Objective Several patients with trisomy 21 developed the Eisenmenger syndrome (ES) because the underlying congenital heart defect was not corrected. However, little is known about their prognosis. This study aimed at (1) identifying risk factors for worse prognosis in ES patients, and (2) evaluating whether outcome of ES patients with trisomy 21 differs from ES patients without trisomy 21.

Design Data on all Eisenmenger patients in follow-up at the paediatric and adult congenital heart disease clinic of the University Hospitals Leuven were collected for retrospective analysis. Regression analysis was performed where applicable and survival rate was compared between patients with and without trisomy 21.

Results One hundred thirty-four patients (mean age at latest follow-up 33.2 ± 13.6 years, 41.8% male, 44.8% trisomy 21) were included in the study. Complex lesions, right heart failure, impaired renal function, lower transcutaneous saturation and lower body mass index were predictive of impaired outcome. Mean survival of the global ES group was 44.9 ± 2.2 years. However, long-term survival of trisomy 21 patients was not statistically different from patients without trisomy 21 (mean survival 44.5 ± 2.6 years vs 44.5 ± 2.9 years, respectively, $P = 0.80$, log rank test).

Conclusion Long-term survival is markedly reduced in Eisenmenger patients. Complex lesions, right heart failure, impaired renal function, lower transcutaneous saturation and lower body mass index were related to worse prognosis. However, survival of trisomy 21 patients did not differ from patients without trisomy 21.

Keywords *Eisenmenger syndrome – outcome – trisomy 21 – Down – pulmonary arterial hypertension.*

INTRODUCTION

Our current knowledge of Eisenmenger syndrome (ES) has been founded more than 50 years ago by Paul Wood. In his Croonian Lectures he defined Eisenmenger reaction as a new pathophysiological condition of pulmonary hypertension resulting from a reversed or bidirectional shunt in different congenital heart defects[1,2].

Address for correspondence:

Werner Budts MD, PhD; Congenital and structural cardiology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. E-mail: werner.budts@uz.kuleuven.ac.be

Received 18 January 2011; accepted for publication 20 January 2011.

Thanks to advances in the surgical management of congenital heart defects, evolution towards an Eisenmenger physiology can be prevented in most paediatric patients. However, a substantial proportion of congenital heart disease patients have already an ongoing Eisenmenger reaction when first diagnosed, compromising the prognosis of these patients[3-5]. Moreover, as congenital heart defects are frequent in patients with trisomy 21, they might also develop the typical Eisenmenger syndrome.

For several decades treatment options for most ES patients were restricted to palliative support and heart-lung transplantation with relatively poor long-term outcome[6,7]. Recent reports, however, indicate that advanced therapy for pulmonary arterial hypertension is promising for ES patients leading to lower mortality and morbidity[8-11]. Nowadays, also patients with trisomy 21 are

treated with advanced therapy. However, little is known about their natural history, treated or untreated.

This study aimed at (1) identifying risk factors for worse prognosis in ES patients, and (2) evaluating whether outcome of ES patients with trisomy 21 differs from ES patients without trisomy 21.

METHODS

Patient selection

All patients with Eisenmenger physiology in regular follow-up at our department of paediatric and adult congenital cardiology were identified through review of our database.

The database, which includes all patients with a congenital heart defect (N > 25,000) who were evaluated and/or treated in our paediatric and/or congenital cardiology department, was started in 1988 by the department of congenital cardiac surgery, and extended in 1991 by the department of paediatric cardiology. The database runs on Filemaker Pro 4.1 software (FileMaker Inc, Santa Clara, CA, US) and is updated each time a patient comes into contact with paediatric or congenital cardiology (outpatient visit, when seeking professional advice, requiring attestation, intervention, etc.). Administrative data (age, birth date, address, general practitioner, last follow-up data, scheduled out-patient visit, etc.), cardiac interventions and non-cardiac diagnosis are included. A quick and complete search can be done using predefined input fields. In this way, the database is a strong tool to easily identify patient cohorts. For more detailed information of clinical examinations and technical tests, the original patients' records have to be reviewed.

Eisenmenger physiology was defined as pulmonary arterial hypertension associated with a reversed or bidirectional shunt through a large previously unrestrictive defect between the systemic and pulmonary circulation at ventricular, atrial or aorta-pulmonary level, confirmed by echocardiography and/or cardiac catheterization. Patients with progressive or severe pulmonary hypertension after shunt closure or patients with small restrictive defects with disproportionate pulmonary hypertension were excluded. The study protocol was approved by the institutional review board (University Hospitals Leuven).

Patient characteristics and follow-up data

Patient characteristics were obtained by reviewing all records: age, gender, type of congenital defect according to the Venetian classification (simple, combined or complex), age at latest follow-up, physical examination at latest follow-up. Most recent data on laboratory findings, transcutaneous oxygen saturation, electrocardiogram, and medical treatment were reviewed.

Events defined as death, thrombo-embolic pulmonary and cerebral complications, arrhythmias and bleeding complications were recorded. Bleeding complications were classified as major or minor. A bleeding event was defined as major if there was a need for transfusion or an association with hypovolemic shock. Minor bleedings mainly referred to episodes of haemoptysis with clinical benign course and without life-threatening complications.

Statistical analysis

We analysed the data using SPSS® for Windows (version 16, SPSS, Chicago). Continuous variables were tested for normality. Continuous data with normal distribution are reported as means ± standard deviation. Continuous data with non-normal distribution are reported as medians with ranges. Proportions are expressed as numbers and percentages. Cox regression analysis was performed to identify predictors of survival for time-fixed variables such as gender, association with trisomy 21 and complexity of disease. Kaplan-Meier analysis and log-ranking were performed for complexity of the lesions and the presence or absence of trisomy 21. Characteristics of patients with or without trisomy 21 were compared with appropriate comparative statistics (independent *T* test, Mann-Whitney *U* test, and chi square test). For time-dependent variables, consecutive uni- and multivariate binary logistic regression analysis were performed to identify risk factors indicating worse prognosis. The following variables were evaluated: use of diuretics, creatinine level, transcutaneous oxygen saturation, BMI at latest follow-up, bleeding events, arrhythmia, haematocrit, iron reserve, use of warfarin, and use of selective pulmonary vasodilators. The dependent variable was defined as all-cause mortality. All tests were two-sided and $P < 0.05$ was considered statistically significant.

RESULTS

Patient population

Overall, 134 patients (mean age at latest follow-up 33.2 ± 13.6 years, 41.8% male, > 99% Caucasian) were included in the study. According to the Venetian Classification[12], 40 patients (29.9%) had a simple defect, 8 (6.0%) a combined lesion and 86 patients (64.1%) a complex lesion. Complex lesions comprised atrioventricular septal defects (AVSDs), truncus arteriosus, transposition of the great arteries with large VSD and univentricular

Table 1 Demographic and clinical characteristics of the patient population

		All patients (number)	Percentage of total (n = 134)
Gender	male	56	41.8%
	female	78	58.2%
Type of lesion	simple	40	29.9%
	combined	8	6.0%
	complex	86	64.1%
Chromosomal disorder	trisomy 21	60	44.8%
	normal karyotype	74	55.2%
Smoking		10	7.5%
Age at latest follow-up (years, mean ± SD)		33.2±13.6	
BMI > 25 at latest FU		41	30.6%
Medical treatment	diuretics	42	31.3%
	ACE-I/ARB	9	6.7%
	aspirin	19	14.2%
	warfarin	13	9.7%
Advanced therapy	ERA	29	21.6%
	sildenafil	10	7.5%
	epoprostenol	2	1.5%
	treprostinil sodium	9	6.7%
	iloprost	1	0.7%
Bleeding events	minor	26	19.4%
	major	5	3.7%
Thrombotic events	cerebral	12	9.0%
	pulmonary	8	6.0%
Arrhythmia	all types	27	20.1%

BMI: body mass index, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, ERA: endothelin receptor antagonists.

heart anatomy. Trisomy 21 patients were largely represented in this study population (n = 60). Most trisomy 21 patients had complex lesions, mainly AVSDs.

During follow-up, 42 patients (31.3%) needed treatment with diuretics; 9 (6.7%) with angiotensin-converting enzyme (ACE) inhibitors or angiotension receptor blockers (ARB), 19 (14.2%) with aspirin for various reasons (coronary artery disease n = 2, cerebral or peripheral emboli n = 3, atrial arrhythmias n = 2, unknown n = 12) and 13 (9.7%) with warfarin for different indications (cerebral emboli n = 2, atrial fibrillation n = 1, pulmonary thrombi n = 6, unknown n = 4). A substantial number of patients were treated with advanced therapy for pulmonary arterial hypertension: 29 patients (21.6%) were treated with endothelin receptor antagonists (ERA), mainly Bosentan. Treatment with sildenafil was always on top of the use of ERA (n = 9) or prostacyclin analogues as epoprostenol (Flolan®) (n = 1). Prostanoid treatment was in all except one in combination with ERA and/or sildenafil (table 1).

Clinical events during follow-up

During a follow-up time of 33.2 ± 16.6 years, most patients developed symptoms or experienced an aggravation of their functional status. Twenty patients (14.9%) suffered from one or more thrombotic events, cerebral in 12 and pulmonary in 8, but none of these events were fatal. Minor bleeding (haemoptysis) complications occurred in 26 (19.4%) and major bleeding complications occurred in 5 (3.7%). Three patients died as a direct consequence of a major bleeding complication. Arrhythmias were reported in 27 patients (20.1%), mostly atrial fibrillation or flutter (n = 11), but also bradyarrhythmias (n = 5), AV conduction disturbances (n = 3) and other forms of supraventricular arrhythmias (n = 7). One patient had a documented non-sustained ventricular tachycardia. Arrhythmias were diagnosed based on symptoms; no systematic 24-hour Holter monitoring was performed in asymptomatic patients.

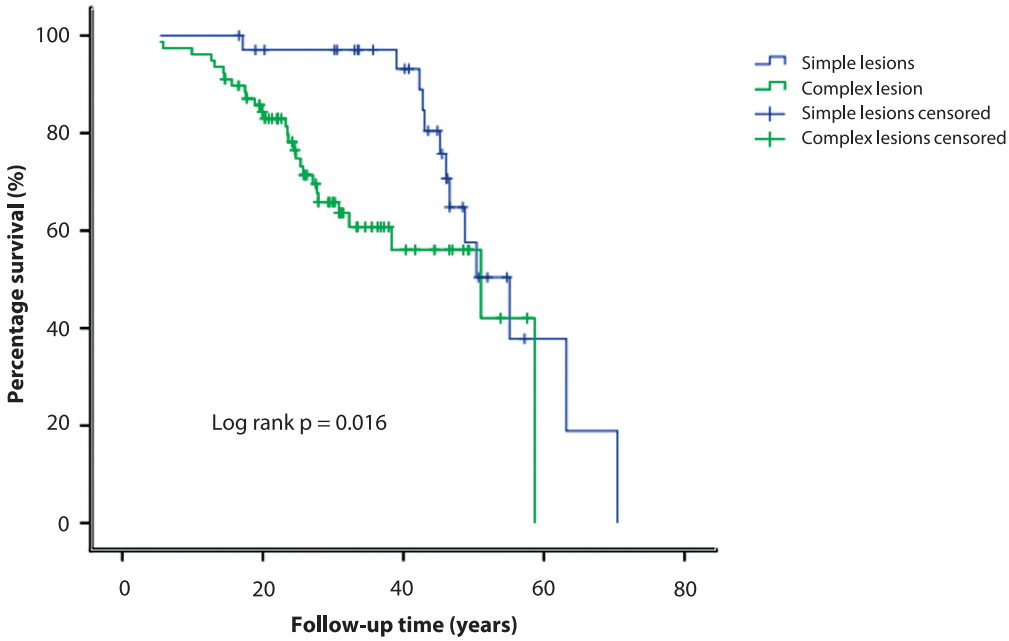

Fig. 1 Kaplan Meier survival analysis of global population with all-cause mortality as endpoint according to complexity of underlying defect. *Only patients with a follow-up date less than one year were included; **data not included in the statistical analysis.

Simple lesions	Numbers at risk	33*	32	24	2
	Number of events	0	1	2	11
Complex lesions	Numbers at risk	77*	60	12	0
	Number of events	0	12	26	28
Combined lesions**					

Table 2 Time-fixed predictors of mortality (univariate Cox regression analysis)

	B	HR	95% CI	*P* value
Type of defect (all types)	–	–	–	0.032
Simple vs combined and complex defects	-0.875	0.42	0.203-0.858	0.018
Combined vs simple and complex defects	-1.402	0.25	0.033-1.823	0.170
Gender	-0.485	0.62	0.338-1.123	0.114
Trisomy 21	0.041	1.04	0.548-1.982	0.900

HR: hazard ratio, CI: confidence interval.

Table 3 Time-dependent predictors of mortality (univariate and multivariate logistic regression analysis)

	OR (univariate)	*P* value (univariate)	OR (multivariate)	*P* value (multivariate)
Diuretics	2.571	0.023	2.312	0.157
Creatinine level	18.271	0.009	10.875	0.017
O2 saturation	0.908	0.003	0.904	0.025
BMI > 25	0.109	0.001	0.173	0.030
Smoking	1.691	0.454	–	–
Haematocrit	0.948	0.062	–	–
Iron reserves	1.00	0.780	–	–
ERA	0.504	0.156	–	–
Warfarin	1.354	0.545	–	–
Bleeding complications	0.988	0.977	–	–
Arrhythmia	1.478	0.155	–	–

OR: odds ratio, BMI: body mass index, ERA: endothelin receptor antagonist.

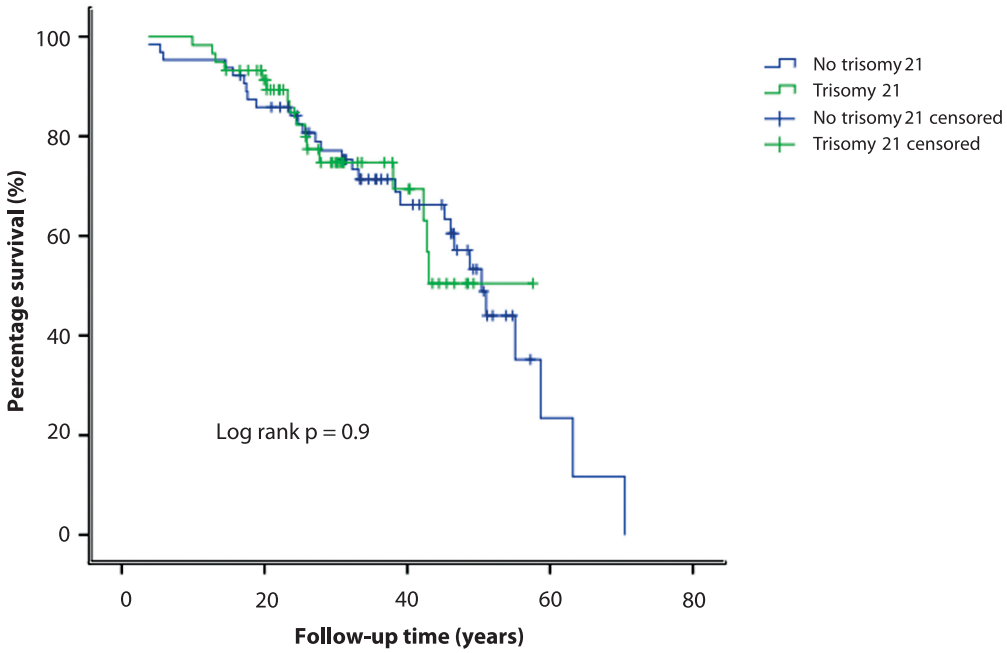

Fig. 2 Kaplan Meier survival analysis of trisomy 21 vs no trisomy 21 population with all-cause mortality as endpoint.
*Only patients with a follow-up date less than one year were included.

Trisomy 21	Numbers at risk	58*	46	13	0
	Number of events	0	5	13	16
No trisomy 21	Numbers at risk	63*	54	26	02
	Number of events	0	9	19	27

Survival analysis

Mean survival of the global ES group was 44.9 ± 2.2 years. During follow-up, 46 patients died. Four patients died in hospital because of refractory end-stage right heart failure, 2 patients because of a witnessed cardiac arrest, 7 patients because of severe infections complicated with septic shock or severe heart failure, 3 because of severe bleeding complications, 6 patients after heart-lung transplantation and 1 young patient because of a rapidly progressive malignancy. The remaining 23 patients died out of hospital, presumably suddenly. Kaplan-Meier analysis showed a significant shorter survival for patients with complex lesions versus simple lesions with a diversion of both curves already at the age of 20 years. However, it was striking that both curves merged again around the age of 55 years with a survival rate of 35-40% in both groups (figure 1).

Predictors of mortality

Cox regression analysis showed that complex lesions were associated with a worse prognosis ($P = 0.032$). However, neither gender nor associated trisomy 21 were predictive of survival (table 2).

For time-dependent variables, univariate logistic regression analysis showed that the use of diuretics (OR = 2.571, $P = 0.023$), impaired renal function (OR = 18.271, $P = 0.009$), lower oxygen saturation (OR = 0.908, $P = 0.003$) and a lower BMI (OR = 0.109, $P = 0.001$), were associated with increased mortality (table 3). Bleeding complications and arrhythmias complicated the course of a lot of patients but were not associated with increased mortality. The use of warfarin or advanced therapy for pulmonary hypertension was not associated with significant changes in survival. On a multivariate analysis, only a lower BMI (OR= 0.173, $P = 0.030$), impaired renal function (OR = 10.875, $P = 0.017$) and lower transcutaneous oxygen saturation (OR = 0.904, $P = 0.025$) were independently associated with increased mortality.

Trisomy 21 patients

Long-term survival of trisomy 21 patients did not differ from non-trisomy 21 patients (mean survival 44.5 ± 2.6 years vs 44.5 ± 2.9 years, $P = 0.8$) (figure 2).

There was no difference according to gender or disease complexity between trisomy 21 and non-trisomy 21 patients. However, trisomy 21 patients were significantly younger at their latest follow-up (28.6 ± 11.1 years vs 36.9 ± 14.4 years) and they were less frequently treated with diuretics (20% vs 40.5%, $P = 0.004$) and vitamin K antagonists (0% vs 17.6%, $P = 0.0001$). However, the proportion of trisomy 21 patients treated with advanced

Table 4 Clinical characteristics and events in trisomy 21 vs non-trisomy 21 patients

		Trisomy 21 number (percentage) (n=60)	No trisomy 21 number (percentage) (n=74)	*P* value
Gender	male	34 (56.7%)	44 (59.5%)	0.744
	female	26 (43.3%)	30 (40.5%)	
Type of lesion	simple	14 (23.3%)	26 (35.1%)	
	combined	2 (3.3%)	6 (8.1%)	0.121
	complex	44 (73.4%)	42 (56.8%)	
Age at latest follow-up (years, mean ± SD)		28.6 ± 11.1	36.9 ± 14.4	0.0001
BMI > 25 at latest FU		28 (46.7%)	13 (17.6%)	0.0001
Conservative therapy	diuretics	12 (20.0%)	30 (40.5%)	0.004
	ACE-I/ARB	2 (3.3%)	7 (9.5%)	0.126
	aspirin	6 (10%)	13 (17.6%)	0.120
	warfarin	0 (0%)	13 (17.6%)	0.0001
Advanced therapy	ERA	11 (18.3%)	18 (24.3%)	0.335
	sildenafil	2 (3.3%)	8 (10.8%)	0.084
Bleeding events	minor	4 (6.7%)	22 (29.7%)	0.003
	major	2 (3.3%)	3 (4.1%)	0.820
Thrombotic events	cerebral	4 (6.7%)	8 (10.8%)	0.402
	pulmonary	2 (3.3%)	6 (8.1%)	0.241
Arrhythmia	all types	7 (11.7%)	20 (19.4%)	0.070

BMI: body mass index, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, ERA: endothelin receptor antagonists.

therapy as endothelin receptor antagonists (ERA) and/or sildenafil was equally distributed when compared with non-trisomy 21 patients (ERA 18.3% vs 24.3%, $P=0.335$; sildenafil 3.3% vs 10.8%, $P=0.084$).

There was no significant difference in event rates for bleeding complications, thrombotic events, cerebrovascular accidents (CVA) and arrhythmias between no trisomy 21 and trisomy 21 patients, except for minor bleeding complications which had a significantly lower incidence in the trisomy 21 group (6.7% vs 29.7%, $P=0.003$) (table 4).

DISCUSSION

This retrospective study presents the outcome of a large Eisenmenger population in follow-up at a tertiary care centre. Complex lesions, high creatinine levels, low body mass index and low transcutaneous oxygen saturation were identified as predictors of adverse outcome. However, survival and late complications of patients with trisomy 21 did not differ from those without it.

Despite advances in the medical and surgical management, long-term survival in patients with Eisenmenger physiology is still markedly reduced and has not changed greatly over the last two decades[6,7,12]. Although short-term prognosis is relatively good, median survival is reduced by approximately 20 years for Eisenmenger syndrome related to simple defects and with an additional 20 years in patients with more complex defects[9]. As more than 60% of our patients were suffering from complex defects, this explains the relative poor outcome in the long run in our total group.

Predictors of outcome and survival of Eisenmenger patients

Of time-fixed variables, complexity of disease was the only predictor of all-cause mortality, which is in line with earlier published data[9-11,13]. Kaplan-Meier curves for simple and complex lesions already diverged from the age of 20 years. Interestingly, both curves came together again at the age of 50 years with a survival rate of 35-40%, which has not yet been described by Daliento et al. and Diller et al.[9,10]. There are several possible explanations. First, more benign lesions, but defined as complex according to the Venetian classification, may have been selected out during follow-up. Secondly, the increased use of advanced therapy for pulmonary arterial hypertension may have affected the course of the curves. At least 20% of our patient group was treated with advanced therapy, compared to only

12% in the group presented by Diller et al.[9]. Thirdly, the low number of patients followed above age 40 may have led to an underpowered statistical analysis.

Of the time-dependent variables, lower oxygen saturation, the use of diuretics, impaired renal function, and lower BMI were associated with worse prognosis. The use of diuretics and eventually impaired renal function reflect progressive right heart failure, whereas a lower BMI probably reflects cardiac cachexia. These findings have been reported by others, indicating that our patients sample is representative[10,14].

Trisomy 21 and outcome

This study specifically aimed at comparing outcome between patients with and without trisomy 21. Trisomy 21 patients mostly present with a more advanced degree of pulmonary hypertension at a younger age, are more disabled, and more often have complex lesions (70% of AVSDs, which are otherwise rare, are diagnosed in this group)[15,16]. However, this study showed that long-term prognosis of patients with trisomy 21 was not different from patients without it. The comparable course of patients with and without trisomy 21 may be supported by a similar incidence of complications such as major bleedings, thrombotic events, cerebrovascular accidents, and arrhythmias in both groups. Although a selection bias may be present (patients with trisomy 21 were younger, had less minor bleeding complications and were less likely to take diuretics), Cox regression analysis could not identify trisomy 21 as a risk factor for death. To our knowledge this is one of the first reports about long-term outcome in such a large group of trisomy 21 patients with Eisenmenger syndrome.

Late complications: arrhythmia, bleeding and thrombotic events

Arrhythmia occurred in 20.1% of the patients during follow-up. No relation between the occurrence of rhythm disturbances and outcome could be identified. The literature also reports conflicting data concerning the effect of arrhythmias in the long-term prognosis[9-11]. The occurrence of arrhythmias in this study may be underestimated because they were diagnosed on a clinical basis. While end-stage heart failure and/or sudden death occurs in more than 50% of cases[10,17], this study only identified heart failure as a risk factor for death. The occurrence of arrhythmia was not related with adverse outcome, making it extremely difficult to predict sudden death in Eisenmenger patients.

Bleeding and thrombotic events occurred in 23.1% and 15% of the patients during follow-up. Eisenmenger syndrome is associated with haematological changes and a paradox of thrombotic problems and bleeding disorders[13,18-21]. Moreover, there is a risk of massive haemoptysis resulting from massive pulmonary infarction due to arterial thrombosis[2]. This study showed no relationship between bleeding complications or thrombotic events and adverse outcome. Although in older series death was attributed to major bleeding complications, in more recent series bleeding complications and haemoptysis were not predictive of survival[9-11,22]. The co-existence of increased bleeding risk and pulmonary thrombosis still poses a difficult clinical dilemma. Although some authors advise anticoagulation for the prevention and treatment of pulmonary thrombosis, we continued to use vitamin K antagonists only on a clinical basis: in case of documented thrombo-embolic complications and/or atrial arrhythmias in patients without a history of significant haemoptysis.

Advanced therapy and Eisenmenger syndrome

There is accumulating evidence of the beneficial effect of advanced therapy for pulmonary hypertension in Eisenmenger patients in terms of lower morbidity, delay of transplantation and mortality[23-25]. However, long-term follow-up data are somewhat conflicting, with some studies showing a persistent beneficial effect of advanced therapies at the long term whereas others studies show a loss of benefit after 1 year with a return to the state at the initiation of advanced therapy[14,26,27]. Even in more complex diseases as well as in trisomy 21 patients these disease targeting therapies are promising in terms of functional and haemodynamic improvement[28-30]. More than 20% of patients (equally distributed among trisomy 21 and non- trisomy 21 patients) were treated with advanced therapy, but this was not related with better outcome. Presumably, treated patients had already more advanced disease.

Limitations of the study

First, this study is a single-centre study which may lead to an important selection bias. However, data found were similar to other reports, suggesting that our study group was a comparable and representative sample. Secondly, numbers were limited which implicates that the study might be underpowered for some statistical analysis, certainly during longer follow-up as few patients with complex lesions are still in follow-up after the age of 40 years. Thirdly, the data were collected on an accurate follow-up database, but the study design remains retrospective with its inconvenient disadvantages.

CONCLUSION

Long-term survival remains markedly reduced in Eisenmenger patients despite the intensive efforts and progress made during the last decades. The outcome in patients with trisomy 21 is not different from patients without trisomy 21, as the incidence of Eisenmenger-related complications is similar. Therefore, treatment options in these patients should be considered in a similar way as for non-trisomy 21 patients.

LIST OF ABBREVIATIONS

ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, AVSD: atrioventricular septal defect, BMI: body mass index, CI: confidence interval, CVA: cerebrovascular accident, ERA: endothelin receptor antagonist, ES: Eisenmenger syndrome, HR: hazard ratio, OR: odds ratio, VSD: ventricular septal defect.

CONFLICT OF INTEREST: none declared.

REFERENCES

1. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. I. *Br Med J* 1958; **2**: 701-9.
2. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. *Br Med J* 1958; **2**: 755-62.
3. Engelfriet PM, Duffels MG, Moller T, Boersma E, Tijssen JG, Thaulow E, Gatzoulis MA, Mulder BJ. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. *Heart* 2007; **93**: 682-7.
4. Kidd L, Driscoll DJ, Gersony WM, Hayes CJ, Keane JF, O'Fallon WM, Pieroni DR, Wolfe RR, Weidman WH. Second natural history study of congenital heart defects. Results of treatment of patients with ventricular septal defects. *Circulation* 1993; **87**(2 Suppl): I38-51.
5. Steele PM, Fuster V, Cohen M, Ritter DG, McGoon DC. Isolated atrial septal defect with pulmonary vascular obstructive disease--long-term follow-up and prediction of outcome after surgical correction. *Circulation* 1987; **76**: 1037-42.
6. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant* 1996; **15**: 100-5.
7. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation* 2005; **112**: 828-35.
8. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. *Circulation* 2007; **115**: 1039-50.
9. Diller GP, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A, Harries C, Goktekin O, Gibbs JS, Gatzoulis MA. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. *Eur Heart J* 2006; **27**: 1737-42.
10. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998; **19**: 1845-55.
11. Cantor WJ, Harrison DA, Moussadji JS, Connelly MS, Webb GD, Liu P, McLaughlin PR, Siu SC. Determinants of survival and length of survival in adults with Eisenmenger syndrome. *Am J Cardiol* 1999; **84**: 677-81.
12. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; **25**: 2243-78.
13. 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, Gatzoulis MA. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. *Circulation* 2008; **117**: 2320-8.
14. Diller GP, Dimopoulos K, Kaya MG, Harries C, Uebing A, Li W, Koltsida E, Gibbs JS, Gatzoulis MA. Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. *Heart* 2007; **93**: 974-6.
15. Weijerman ME, van Furth AM, van der Mooren MD, van Weissenbruch MM, Rammeloo L, Broers CJ, Gemke RJ. Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome. *Eur J Pediatr* 2010; **169**: 1195-9.
16. Freeman SB, Bean LH, Allen EG, Tinker SW, Locke AE, Druschel C, Hobbs CA, Romitti PA, Royle MH, Torfs CP, Dooley KJ, Sherman SL. Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project. *Genet Med* 2008; **10**: 173-80.
17. Niwa K, Perloff JK, Kaplan S, Child JS, Miner PD. Eisenmenger syndrome in adults: ventricular septal defect, truncus arteriosus, univentricular heart. *J Am Coll Cardiol* 1999; **34**: 223-32.
18. Perloff JK. Systemic complications of cyanosis in adults with congenital heart disease. Hematologic derangements, renal function, and urate metabolism. *Cardiol Clin* 1993; **11**: 689-99.
19. Tempe DK, Virmani S. Coagulation abnormalities in patients with cyanotic congenital heart disease. *J Cardiothorac Vasc Anesth* 2002; **16**: 752-65.
20. Broberg C, Ujita M, Babu-Narayan S, Rubens M, Prasad SK, Gibbs JS, Gatzoulis MA. Massive pulmonary artery thrombosis with haemoptysis in adults with Eisenmenger's syndrome: a clinical dilemma. *Heart* 2004; **90**: e63.
21. Perloff JK, Rosove MH, Child JS, Wright GB: Adults with cyanotic congenital heart disease: hematologic management. *Ann Intern Med* 1988; **109**: 406-13.
22. Broberg CS, Ujita M, Prasad S, Li W, Rubens M, Bax BE, Davidson SJ, Bouzas B, Gibbs JS, Burman J, Gatzoulis MA. Pulmonary arterial thrombosis in Eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. *J Am Coll Cardiol* 2007; **50**: 634-42.
23. Galie N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, Chiossi E, Landzberg M. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006; **114**: 48-54.
24. Gatzoulis MA, Beghetti M, Galie N, Granton J, Berger RM, Lauer A, Chiossi E, Landzberg M: Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study. *Int J Cardiol* 2008; **127**: 27-32.
25. Adriaenssens T, Delcroix M, Van Deyk K, Budts W. Advanced therapy may delay the need for transplantation in patients with the Eisenmenger syndrome. *Eur Heart J* 2006; **27**: 1472-7.
26. Apostolopoulou SC, Manginas A, Cokkinos DV, Rammos S. Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital

heart disease: a 2-year study. *Heart* 2007; **93**: 350-4.
27. van Loon RL, Hoendermis ES, Duffels MG, Vonk-Noordegraaf A, Mulder BJ, Hillege HL, Berger RM. Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: does the beneficial effect persist? *Am Heart J* 2007; **154**: 776-82.
28. Duffels MG, Vis JC, van Loon RL, Nieuwkerk PT, van Dijk AP, Hoendermis ES, de Bruin-Bon RH, Bouma BJ, Bresser P, Berger RM, Mulder BJ. Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without Down's syndrome. *Am J Cardiol* 2009; **103**: 1309-15.
29. Duffels MG, Vis JC, van Loon RL, Berger RM, Hoendermis ES, van Dijk AP, Bouma BJ, Mulder BJ. Down patients with Eisenmenger syndrome: is bosentan treatment an option? *Int J Cardiol* 2009; **134**: 378-83.
30. Kermeen FD, Franks C, O'Brien K, Seale H, Hall K, McNeil K, Radford D. Endothelin receptor antagonists are an effective long term treatment option in pulmonary arterial hypertension associated with congenital heart disease with or without trisomy 21. *Heart Lung Circ* 2010; **19**: 595-600.