Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for congenital heart defects

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Aims	We aimed to assess the contemporary outcome of Eisenmenger syndrome (ES), delineate the use of disease targeting therapies (DTT) in these patients and to investigate the effect of treatment on outcome in the community.
Methods and results	Patients with ES were systematically identified from the German National Register for Congenital Heart Defects. Data on underlying diagnosis, medical therapy, and survival were collected. The impact of DTT on survival was assessed using time-dependant Cox analysis. Overall, 153 ES patients were included (mean age 34.0 ± 13.3 years, 46% females). Of these, 88 (57.5%) were treated with at least one DTT (76.1% Bosentan, 20.5% Sildenafil) while 17.6% were on dual DTT. In addition, 24.8% of patients received digoxin, 10.5% angiotensin-converting enzyme-inhibitors/angiotensin receptor blockers, and 17.6% β-blockers. Moreover, 17.6% of patients were treated with oral anticoagulants, while 23.5% of patients received Aspirin. The survival rate at 1, 5, and 10 years of follow-up was only 92, 75, and 57% in the entire cohort, and was even worse in treatment naive ES patients (survival rate 86, 60, and 34% at 1, 5, and 10 years). Use of DTT was independently associated with a better survival (hazard ratio 0.42, P = 0.015).
Conclusion	This study illustrates the alarmingly poor survival prospects of Eisenmenger patients by community-based data even in the current era with advanced DTT and in a country with a wealthy health system. Treatment naive ES patients had especially high mortality rates approaching 60−70% at 10 years of follow-up. Treatment with DTT was associated with better survival.
Keywords	Adult congenital heart disease • Eisenmenger syndrome • Advanced therapy • Registry

Introduction

Eisenmenger syndrome (ES) is a multisystem disorder characterized by severely elevated pulmonary arterial pressures and right-to-left shunting with cyanosis.[1−4] It is a common complication in patients with large, unrestrictive and unrepaired shunt lesions, especially at arterial or ventricular level. The exact prevalence of the condition in the community is unknown but it has been reported to account for ∼4% of adult patients seen at large tertiary centres for congenital heart disease.[5] With increasing availability of timely surgical or interventional repair over the last few decades the number of ES

patients in developed countries is likely to decrease. Nevertheless, the condition will continue to occur in patients, unsuitable for early repair, and individuals immigrating from regions with reduced access to high-quality paediatric cardiology and cardiothoracic surgery.

Data on symptoms and survival prospects of ES patients have been published previously based on single, tertiary centre cohorts or consortia of such centers.[6−8] Nevertheless, conflicting data exist on the outcome of the condition.[9,10] The assumed relatively benign outcome compared with idiopathic pulmonary hypertension has recently been questioned.[9,11] In addition, it remains unclear whether the available data, mainly based on cohorts of patients treated at

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specialized expert centres, is subject to referral bias (favouring patients with more advanced disease) and whether outcomes and treatment regimes are similar in ES patients in the community. Furthermore, only limited data exist on the use of vasoactive disease targeting therapies (DTT) at large and on the effect of this type of medical treatment on survival.[12,13] The rather unique data set of the German National Register for Congenital Heart Defects allows to address these questions. Specifically, we aimed to assess the outcome of ES patients in the current era, delineate the use of DTT in this cohort, and investigate the effect of treatment on outcome in the community.

Patients and methods

The German National Register for Congenital Heart Defects provides a nation-wide data base with a uniquely large population of patients with congenital heart disease not primarily gathered by tertiary referral centres but rather representing the community-based population. By now, the register comprises 46 628 patients. All patients included in the Register were screened for the diagnosis of pulmonary arterial hypertension and ES syndrome. Initially, an electronic database search was performed based on the International Paediatric and Congenital Cardiac Code published by the International Society for Nomenclature of Paediatric and Congenital Heart Disease (http://www.ipccc.net).[14] The search included the following codes: 10.13.01—PH = pulmonary hypertension; 10.13.02—PH, pulmonary hypertension, primary; 10.13.20—PH, pulmonary hypertension, secondary; 10.13.21—PH, pulmonary hypertension, associated with left-to-right shunts; 10.13.06—PH, pulmonary vascular disease; 10.13.08—PH, irreversible pulmonary vascular disease (Eisenmenger). Subsequently, all electronically identified patients were screened manually to ensure that they had ES syndrome in accordance to current recommendations and as published previously.[5]

Eisenmenger syndrome was defined as pulmonary hypertension in the presence of a large non-restrictive intracardiac or extracardiac communication. Patients who previously underwent corrective surgery or interventions and did not present with an unrestrictive residual shunt were excluded. In addition, patients with Glenn-type physiology and those with segmental pulmonary hypertension (e.g. pulmonary atresia with ventricular septal defects) were excluded. The diagnosis of congenital heart disease was based on echocardiography, cardiovascular magnetic resonance, or cardiac catheterization data in all patients. Cardiac defects were classified into two categories according to complexity, as simple and complex defects. Simple defects comprised atrial or ventricular septal defects and persistent arterial duct, while complex defects represent combinations of congenital defects as well as atrioventricular septal defects, transposition of the great arteries, and patients with functionally univentricular hearts. Data on age, gender, cardiac and extracardiac diagnosis, NYHA functional class, resting oxygen saturation (SpO_2), pulmonary hypertension specific medication, heart failure medication, oral anticoagulation, aspirin, and 6-min walk test (6-MWT) results were extracted from the medical reports. For the scope of the study, follow-up at a larger centre of care was defined as being followed at one of the top four contributing centres to the register.

This was a retrospective study. The starting point for analysis was the time of inclusion in the register for all patients. Survival status and time of death were ascertained from medical records and through inquiries at the local registration office for all patients. Approval by the appropriate Ethics Committee was obtained.

Statistical analysis

Data are presented as numbers (percentage) for categorical variables or mean ± standard deviation or median (25th to 75th percentile) for continuous variables, as appropriate. The relation between parameters and all-cause mortality was assessed with the use of uni- and multivariable time-dependent Cox proportional hazards regression analysis, with the date of inclusion in the register or start/escalation date of therapy used as start date. The proportional hazards assumption was verified for each time-dependent variable using generalized linear regression analysis, thus testing for a non-zero slope of the scaled Schoenfeld residuals on functions of time in addition to visual inspections of the graphs of the regression. Relevant clinical parameters were tested for significance on univariable analysis. Parameters significantly predicting prognosis on univariable analysis were subsequently included in multivariable time-dependent models. Interaction terms were used to explore the association between DTT and outcome with respect to centre size. For all analyses, a two-tailed *P*-value of <0.05 was used as the criterion for statistical significance. Analyses were performed with the use of R version 3.1.0 (R Foundation for Statistical Computing).

Results

Overall, 153 ES patients were identified and included in the current analysis. Of these, 83 (54%) presented with simple lesions (five of them with atrial septal defects) and 70 had complex congenital heart lesions. The included patients were under follow-up at one of 21 different institutions in Germany. The included patients per institution ranged from 1 to 68 patients. As illustrated in *Table 1*, patients with complex defects were significantly younger and had lower resting oxygen saturations compared with patients with simple defects. There were no significant differences with regard to height, weight, functional capacity, and medication between the groups.

In total, 10.5% of patients were treated with angiotensin-converting enzyme (ACE)-inhibitors or angiotensin receptor blockers (ARBs). Especially in ES patients with complex defects, a considerable proportion (16%) of patients received these drugs. In addition, 25% of patients were treated with digoxin and 18% with β-blockers. Oral anticoagulation was administered in 18% of patients and aspirin in 23%.

As illustrated in *Figure 1*, 57.5% of patients were treated with at least one DTT, while 17.6% of patients were treated with a combination of two drugs. The majority of them were on Bosentan (76.1% of patients on monotherapy). In addition, this drug was used as a second line medication in 44.4% of patients treated primarily with Sildenafil. The median time to escalation of therapy was 2.6 years (interquartile range, IQR, 0.9–5.2 years). A greater proportion of patients without Down syndrome was treated with DTT compared with those with Down syndrome (62 vs. 48%); however, this difference did not reach significance (*P* = 0.14).

Over a median follow-up period of 5.0 years (IQR 1.4–9.3 years), 47 patients (30%) died. Survival rates at 1, 5, and 10 years of follow-up were 92.1% [95% confidence interval, CI, 87.8–96.7%], 74.9% [95% CI 67.6–83.1%], and 57.2% [95% CI 47.6–68.8%], respectively (*Figure 2*). The leading causes of death were heart failure, sudden cardiac death, malignant disease, perioperative mortality, and infections as illustrated in Supplementary material online, *Figure SA1*. No difference in survival was observed between males and females (log-rank *P* = 0.92), between patients with or without Down syndrome (*P* = 0.31) or patients with simple or complex underlying heart defects (*P* = 0.48). *Table 2* shows the results of

Table 1 Baseline characteristics, diagnoses, and therapy of the included patients

Parameter	All	Simple defects	Complex defects	P-value
n	153	83	70	
Age	34.0 ± 13.3	36.6 ± 14.2	30.9 ± 11.4	0.007
Gender (female, %)	45.8	60.2	55.7	0.69
Down syndrome	50 (32.7%)	22 (26.5%)	28 (40.0%)	0.11
Diagnoses				
ASD	5	5		
VSD	66	66		
PDA	12	12		
AVSD	35		35	
APW/TAC	11		11	
TGA	1		1	
Univentricular physiology	23		23	
Weight (kg)	57.0 ± 14.5	57.5 ± 15.2	56.4 ± 13.9	0.68
Height (cm)	159.5 ± 16.7	159.4 ± 15.4	159.5 ± 18.2	0.98
Resting SpO$_2$ (%)	81.2 ± 8.9	83.8 ± 8.6	78.3 ± 8.3	<0.0001
NYHA class (I/II/III/IV)	0/66/77/10	0/41/39/3	0/25/38/7	0.11
6-MWT distance (m)	380.1 ± 108.3	395.8 ± 122.8	360.5 ± 85.2	0.24
DTT (%)	57.5	60.2	54.3	0.56
Diuretics (%)	35.3	28.9	42.9	0.10
Digoxin (%)	24.8	21.7	28.6	0.43
ACE-i/ARBs (%)	10.5	6.0	15.7	0.09
β-Blocker (%)	17.6	15.7	20.0	0.63
Oral anticoagulation (%)	17.6	20.5	14.3	0.43
Aspirin (%)	23.5	25.3	21.4	0.71

P-values compare patients with simple defects with those having complex underlying heart conditions.

the Cox proportional hazards analysis. On univariable Cox analysis, resting oxygen saturation, follow-up at a larger centre and use of DTT emerged as the only significant predictors of mortality. On stepwise multivariable analysis, only oxygen saturation (hazard ratio, HR, 0.952 [95% CI 0.922−0.983], P = 0.0024) and use of DTT (HR 0.436 [95% CI 0.198−0.959], P = 0.04), were independently related to outcome. In fact, ES patients at larger centres were more likely to be treated with DTT (62.7 vs. 47.1% on DTT, P = 0.08) and there was a statistically significant interaction between centre size and use of DTT on Cox analysis (P = 0.0004).

Survival at 5 years of follow-up was 60.3% [95% CI 48.2−75.5%] in treatment naive patients and 83.0% [95% CI 72.6−94.9%] in those with DTT. This is illustrated in Figure 3, based on the results of the Cox proportional-hazard analysis. In addition, Supplementary material online, Figure SA2 illustrates the association between DTT and outcome using patient age as a time scale variable. No difference could be found between survival in patients on mono- vs. dual therapy on time-dependant Cox analysis (Figure 4). No significant association between conventional medical treatment (Diuretics, Digoxin, ACE-inhibitors/ARBs, etc.) and outcome could be established, although a trend between β-blocker therapy and better survival was observed on this analysis. Similarly, oral anticoagulation or aspirin use was not significantly related to outcome (see Supplementary material online, Figure SA3; Table 2).

Discussion

The data from the German National Register for Congenital Heart Defects highlights poor survival prospects of ES patients, worse than in previous reports.[6−8,10] In addition, our results suggest that patients at larger centres and especially those treated with DTT fared better compared with the remaining patients. This is in agreement with a recent report suggesting improved survival of adult congenital heart disease patients, in general, after the establishment of large tertiary centres in Canada, but is a new finding specifically for ES patients.[15] Interestingly, the association between centre size and outcome appears to be mainly mediated via the more frequent use of DTT at these larger centres. This observation is consistent with a recent report showing no clear indication that survival prospects of treatment naive ES patients have improved since the 1960s.

The relatively poor survival prospects of Eisenmenger patients observed in the current study are of particular relevance when considering that the study comprises a relatively contemporary cohort of patients treated in a well-developed, wealthy health system with universal access to paediatric and adult cardiology services. Unlike, previous studies, the current report is not based on data from a single tertiary institution or groups of expert centres specialized in adult congenital heart defects but rather reflects the treatment reality and fate of ES patients at large.[6−8] We have recently reviewed the
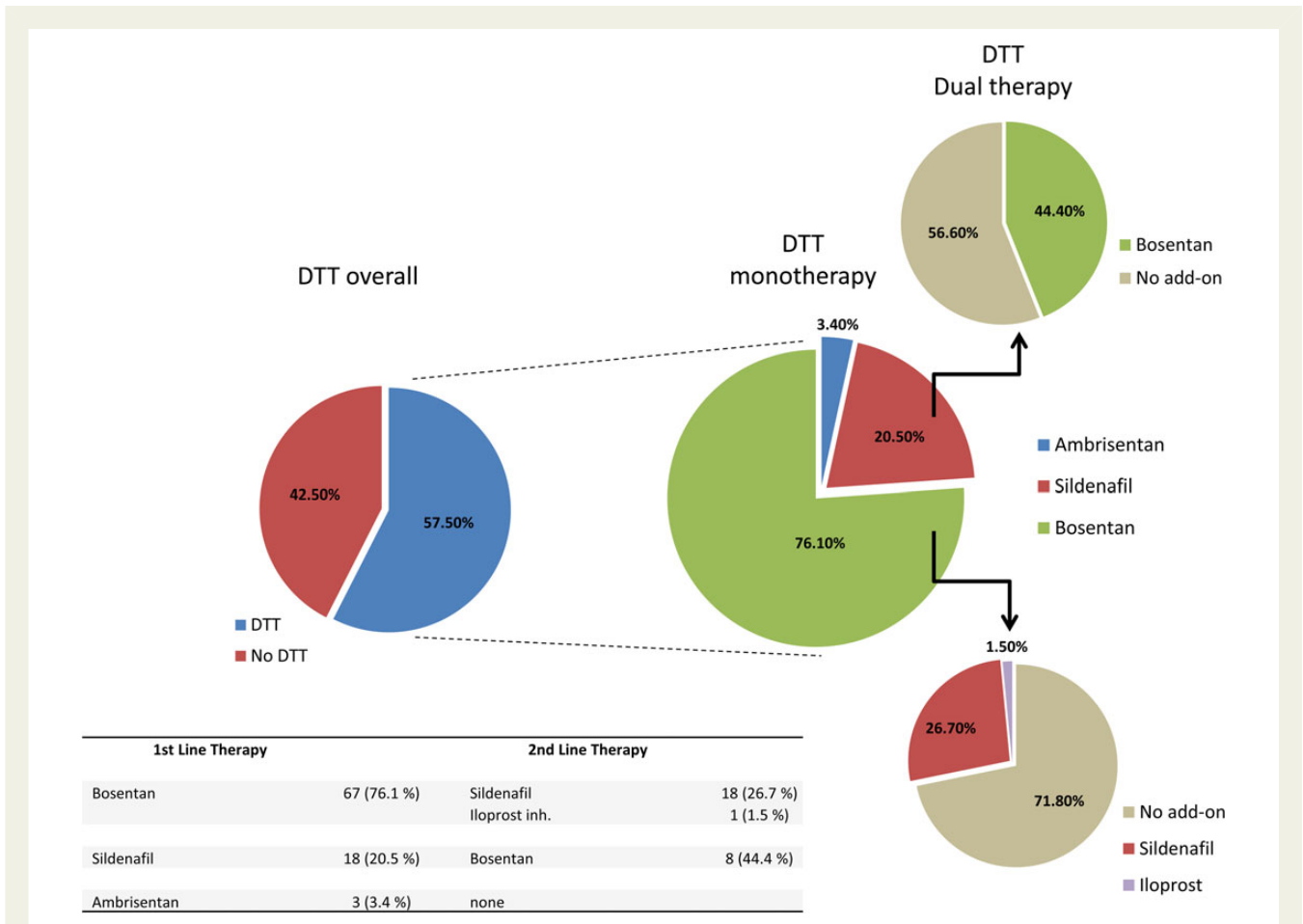
Figure 1 Distribution of therapy. The Figure illustrates that overall 57.5% of patients were treated with at least one disease targeting therapy drug. Of those patients treated with disease targeting therapies, over 95% of patients were on Bosentan or Sildenafil.
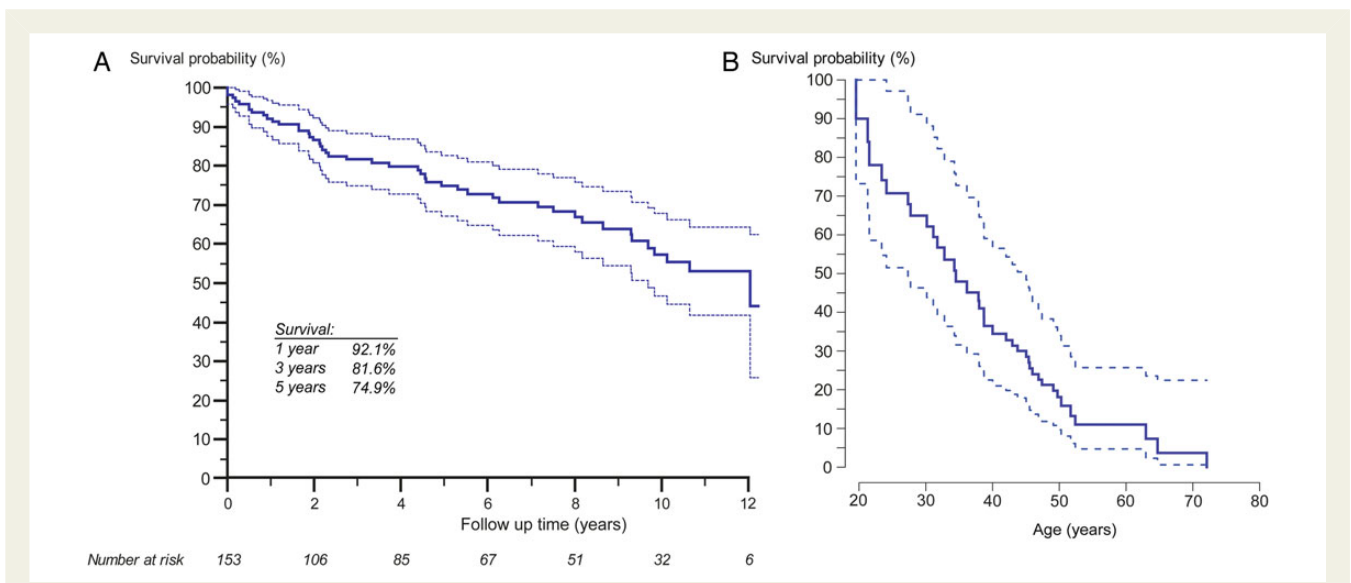

Figure 2 Kaplan–Meier survival function of all Eisenmenger patients included in the current study. (*A*) Time scale based on follow-up time in the National Register. (*B*) Time scale based on patients' age.

Table 2 Results of the univariate Cox analysis

Parameter	HR (95% CI)	*P*-value
Age (years)	0.99 (0.97–1.02)	0.54
Female gender	0.97 (0.54–1.74)	0.92
Complex lesion	0.81 (0.46–1.44)	0.48
Down syndrome	0.72 (0.39–1.35)	0.31
Weight (kg)	0.98 (0.96–1.01)	0.23
Height (cm)	0.98 (0.96–1.00)	0.054
Resting SpO$_2$ (%)	0.95 (0.92–0.98)	0.0015
NYHA Class > II	0.75 (0.42–1.33)	0.33
6-MWT distance (m)	1.00 (0.99–1.00)	0.14
Larger centre of care[a]	0.53 (0.30–0.97)	0.04
DTT	0.30 (0.17–0.54)	0.0001
Diuretics	1.01 (0.55–1.85)	0.97
Digoxin	1.59 (0.85–2.98)	0.14
ACE-i/ARBs	1.30 (0.52–3.29)	0.58
β-Blocker	0.35 (0.13–1.00)	0.051
Oral anticoagulation	1.07 (0.52–2.22)	0.86
Aspirin	0.93 (0.47–1.82)	0.83

DTT, disease targeting therapies.
[a]Larger centre of care was defined as the top four contributors of patients to the register.
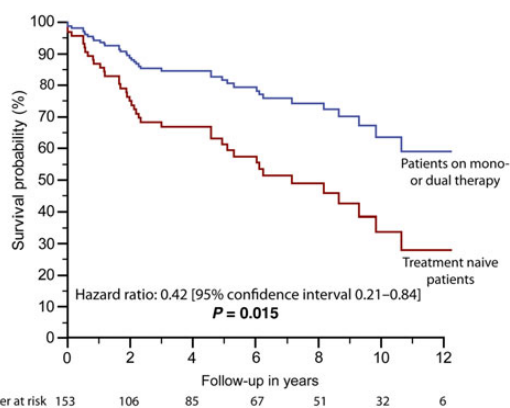

Figure 3 Survival of treatment naïve patients compared with those treated with at least one disease targeting drug modelled based on the results of time-dependant Cox analysis.

Figure 4 Survival of patients on disease targeting monotherapy compared with those treated with dual therapy modelled based on the results of time-dependant Cox analysis.

literature on survival prospects of ES patients and found that, after accounting for confounding statistical effects, the 10-year mortality rate is ∼30–40% in treatment naive individuals.[9] In contrast, the current study—using a broader cohort of patients, not all of whom were attending specialized centres—revealed a 10-year mortality rate approaching 60–70%. The reasons for this discrepancy are unclear, especially given that this still represents a selected cohort of patients registered in a National database for congenital heart disease. Although, enrolment in the Register is patient driven, it is generally prompt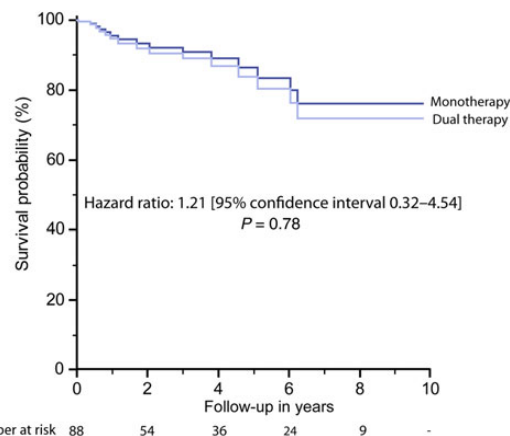ed by an according recommendation of the treating physician. In addition, ours is a relatively contemporary cohort (registration date between 2001 and 2012) and, thus, should supposedly not fare worse compared with published historical cohorts.

Our analysis illustrates that despite absent scientific data and guideline recommendations many ES patients are still treated with Digoxin, standard heart failure medication, and subjected to oral anticoagulation or aspirin treatment. The use of Digoxin is concerning as it has been demonstrated in other cardiovascular settings to increase mortality[10,16–18] and a similar tendency was seen in this study (HR 1.6, *P* = 0.14). Other standard heart failure drugs, namely ACE-inhibitors and ARBs may not share the problem of increasing mortality in their own right, but they have a hypotensive effect and may preclude the use of DTT in adequate doses and especially combination therapy. Therefore, we believe that the use of these drugs should be very restrictive in the absence of guideline recommendations and positive scientific data. The issue of anticoagulation remains controversial. While a recent study found no evidence of a specific survival benefit in congenital pulmonary hypertension patients[19] and current guidelines discourage the routine use of oral anticoagulation in ES patients in the absence of additional indications,[20] selected patients with large pulmonary thrombi may benefit from this therapy.[21] It is likely, however, that a proportion of patients are given oral anticoagulation based on recommendations extrapolated from—but specifically intended for—patients with idiopathic pulmonary hypertension.[22] Furthermore, no data on the beneficial effects of aspirin are available—to our knowledge—and the use of this drug is likely to represent the pragmatism of some colleagues who aim to offer some protection against thrombosis, while fearing the potential complications of anticoagulation.

While anticoagulation, aspirin treatment, and heart failure medication were not related to outcome, we found a pronounced association between DTT and all-cause mortality. This is in agreement with a previous study by Dimopoulos et al. reporting an association between use of DTT and lower mortality in ES patients.[12] Comparing the current study with this previous report reveals some

interesting findings. Firstly, the proportion of ES patients treated with DTT was 57% in the current analysis compared with only 30% in the former study. This likely reflects the increasing uptake of DTT in the setting of ES syndrome by the medical profession. Of those patients treated, a similar percentage was treated with endothelin receptor antagonists (79.5% in our study vs. 73.5% in the study by Dimopoulos). Comparing the two studies also reveals a higher proportion of patients on dual therapy in the current study (27/153 vs. 6/299), likely also related to a more proactive use of DTT driven by an increased experience with the medication and also supported by the positive results of previous studies.

We found a hazard ratio of 0.42 for mortality in treated patients compared with treatment naive individuals as opposed to lower values reported by Dimopoulos et al. (0.21 and 0.16 based on unadjusted and adjusted Cox analyses). This suggests the impact of DTT on survival may be lower in a community setting compared with the results that can be achieved at tertiary institutions but still is substantial as it indicated that the hazard of death is 2.4-times higher (i.e. 1/0.42) in untreated compared with treated ES patients.

Despite the use of a monotherapy-first approach, with escalation of therapy after a median of 2.6 years, we found no evidence of worse survival of patients on dual therapy. As the general approach is to start ES patients on DTT monotherapy and to only escalate therapy when patients deteriorate or fail to achieve a pre-specified therapy goal or an acceptable clinical status, patients on dual therapy represent a sicker patient population with more advance symptoms. The lack of a difference in survival between patients on mono and those on dual DTT should therefore not be interpreted as an argument against escalation of therapy. Rather, we contend that this finding suggests that beyond the recognized impact on symptoms and exercise capacity,[23–26] escalation of therapy may be associated with clinical stabilization and may aid to preserve the positive impact of DTT on survival over time. This observation is consistent with findings reporting haemodynamic improvements with dual therapy in ES patients,[27] which may provide the pathophysiologic rationale for the observed clinical stabilization.

The borderline association between β-blocker therapy and improved outcome of ES patients in the current study deserves future attention. A potential role for β-blocker therapy to protect right ventricular function has been advocated by some,[28,29] and these drugs are currently undergoing clinical trials, albeit in the setting of idiopathic pulmonary hypertension.[30]

Study limitations

We accept that this study has limitations related to the nature of the data employed. Unlike previous single centre studies, we did not have access to an entire hospital medical database but had to rely on information available from medical reports and clinic letters. We cannot, therefore, exclude the possibility that the association between DTT and outcome was mediated by unobserved variables. However, even after adjusting for other significant determinants of outcome we found that DTT use was associated with better survival compared with treatment naive patients. We believe that this, together with the observation that none of the other conventional drugs showed an effect similar to DTT, suggests that DTT may be genuinely associated with reduced mortality in the setting of ES. One hundred and two (67%) of the included patients were under follow-up at the four largest contributors of patients to the current study. Therefore, it is likely that the patients included here represent a mixture of Eisenmenger patients in the community and those followed at specialized centres, with the latter cohort potentially dominating numerically. Nevertheless, it appears that the superior outcome of patients at larger centres was chiefly mediated by a more frequent use of DTT there, thus supporting the main results of the study. Furthermore, patients with learning difficulties or disabilities may be underrepresented in the study and although the percentage of patients with Down syndrome was comparable with previous Eisenmenger studies,[12] the true prevalence of Eisenmenger patients with learning difficulties in the community remains unknown. While the association between use of DTT and outcome presented here and in a previous study[12] are impressive, the cost of DTT is considerable and further studies focusing on cost utility and cost benefit analyses are desirable. Due to the limited sample size, the possibility of type II errors (i.e. the failure to detect an actual effect) should be considered especially as hazard ratios for some parameters are in the range of clinical relevance.

Conclusions

The current study illustrates the alarmingly poor survival prospects of Eisenmenger patients even in the current era with the option of DTT and in a wealthy health system. Treatment naive ES patients had especially high mortality rates approaching 60–70% at 10 years of follow-up. Consistent with a previous report, treatment with DTT was associated with better survival in the current study. In addition, a strategy of escalation of therapy was associated with similar survival benefits of dual therapy compared with DTT monotherapy. The results of this study imply that ES patients should be linked to tertiary specialist centres and a proactive approach of treatment with DTT should be considered for all eligible patients, based on the dismal natural prognosis and the potentially substantial prognostic benefit of therapy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

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