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The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study.

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Running head: Long term Bosentan in inoperable CTEPH

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Abstract:

Background: The treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH) is pulmonary endarterectomy (PEA). However, many patients develop a severe progressive small vessel pulmonary arteriopathy which is inaccessible to surgical intervention and is associated with poor survival. The purpose of the study was to evaluate the medium term efficacy and safety of the dual endothelin receptor antagonist, bosentan, in inoperable CTEPH.

Design: 47 patients with inoperable CTEPH (distal disease or persistent pulmonary hypertension following PEA) underwent evaluation after one year of bosentan therapy. Outcomes included assessment of six minute walk test (6MWT), haemodynamics and WHO functional classification. Monitoring of serious adverse effects and changes in therapy was undertaken.

Results: Patients showed sustaining improvements in 6MWT (49m +/- 8m), functional classification, cardiac index (+0.2 L/min/m2 ± 0.07) and total pulmonary resistance (-139 dyn.s.cm-5 ± 42). Those patients with persisting pulmonary hypertension following PEA showed the greatest improvement. One year survival was 96%, bosentan was well tolerated with only one patient developing derranged liver function.

Conclusion: Although all patients with CTEPH should be considered for PEA, bosentan provides an alternative medical therapy to improve function and delay the progression of this devastating disease in those in who surgery is not suitable.

Keywords: Bosentan, CTEPH, pulmonary hypertension, endothelin, thromboembolic.

Abstract word count: 200

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterised by obstruction of pulmonary arteries with organised fibrotic material, which results in a progressive increase in pulmonary vascular resistance, the development of right heart failure and markedly impaired survival.(1-3) The treatment of choice of this condition is that of surgical removal of this material from the central pulmonary arteries by means of Pulmonary Endarterectomy (PEA), a procedure which can be curative. (4-6)

The underlying aetiology is thought to be on the basis of unresolved pulmonary emboli, with up to 3.8% of patients developing evidence of CTEPH within the first two years following an acute embolus.(7) However, in many patients the distribution of this organised embolic material is confined to the sub-segmental and smaller branches of the pulmonary vascular bed, which are inaccessible to surgical removal (so called “Distal CTEPH”).(8)

Recurrent pulmonary embolism and thrombosis in situ contribute further to this vascular obstruction and it is imperative that patients receive long term anticoagulation. However, despite this intervention the obliteration of the pulmonary vascular bed may continue to progress due to the development a small vessel arteriopathy. The marked endothelial dysfunction and vascular remodelling seen in this process is similar to that seen in Pulmonary Arterial Hypertension (PAH) and appears to develop in unobstructed areas of the pulmonary vascular bed exposed to high pressure load and shear stress.(9) However, the pathophysiology of these conditions is different, with CTEPH patients showing less tendency to plexiform lesion formation and reduced vasoresponsiveness to acute vasodilator challenge testing. In addition, the strong familial tendency and association with genetic mutations of the bone morphogenic protein receptor type II (BMPR2) seen in idiopathic PAH has not been observed in the arteriopathy of CTEPH.

This process of small vessel arteriopathy not only occurs in patients with the more distal disease distribution, but can also develop in the setting of apparently surgically amenable central disease. This significantly increases the risk associated with PEA and explains the deterioration in function that some patients experience leading up to

their surgery, despite commencing anticoagulation and the insertion of inferior vena caval filter. This also increases the likelihood that the patient will be left with residual pulmonary hypertension following the procedure.

At present, there are no licensed medical therapies for inoperable CTEPH. Several small case series have reported long term improvements in markers of disease severity with the use of oral, inhaled and intravenous prostanoid therapies (10-15) and the phosphodiesterase 5 inhibitor, sildenafil.(16) One randomised clinical trial of inhaled Iloprost in pulmonary hypertension has included patients with CTEPH within the study population, although sample size has been small and subgroup analysis of these subjects has not been reported.(17)

Endothelin (ET)-1 is thought to play a key role in the small vessel remodelling that occurs in patients with CTEPH.(18) In animal models, circulating ET-1 levels correlate with disease severity and the ET receptor subtypes (ET_A and ET_B) seem unregulated in a similar fashion to that of PAH.(19, 20) The dual endothelin receptor antagonists, bosentan, has demonstrated significant clinical benefit in patients with PAH.(21-23) Whilst preliminary data of utilisation this agent in inoperable CTEPH has suggested benefit,(24-26) the longer term outcome from this approach is largely unknown.

The purpose of this study is to report the efficacy and safety of compassionate use of bosentan in patients with inoperable CTEPH after at least one year of therapy.

Patients and methods

Subject selection.

Patients with inoperable CTEPH commenced on bosentan between February 2002 and August 2004 at three European specialist centres routinely performing PEA were included. All patients had established pulmonary hypertension as confirmed by a mean pulmonary artery pressure of greater than 25mmHg, and wedge pressure of less than 15mmHg at rest during a right heart catheterisation. The diagnosis of CTEPH was based on multiple imaging modalities which included multi-slice CT, direct pulmonary angiography, ventilation perfusion scanning and MR angiography. Two groups of patients were included: those with "distal CTEPH" in whom the distribution of disease was considered unsuitable for PEA, and those who had persisting pulmonary hypertension following PEA (median duration since PEA 9 months, range 4 to 18). The investigations of all patients were reviewed by the multidisciplinary PEA assessment team, which included Surgeons, Cardiologists, Pulmonologists and Radiologists, and patients were deemed to be unsuitable for surgery on the basis of an unfavourable distribution of their disease on imaging.

This retrospective study was conducted in accordance with the Declaration of Helsinki 1975 and in adherence to local good clinical practice guidelines and legislative requirements. Compassionate use was sought and approved for each individual patient. All data was anonymised and held within a secure database. Specific written informed consent was only obtained for repeat right heart catheterisation in those centres where this procedure was not considered as part of routine clinical assessment. However, all patients were informed that they were receiving a novel drug for the management of their CTEPH, were fully advised of the potential adverse effects, and gave consent to be treated with bosentan.

Study design

All patients received anticoagulation therapy for at least three months prior to commencing bosentan. Routine evaluation to assess the severity of their pulmonary hypertension was performed on all patients within the month prior to commencing bosentan. This included right heart catheterisation, six minute walk test (6MWT), determination of WHO functional classification and appropriate imaging. In addition,

twenty six patients also underwent acute vasodilator testing with nitric oxide at baseline at two of the centres (Clarmart and Vienna). All of these studies showed absent responses to nitric oxide (fall in mean pulmonary artery pressure by at least 10mmHg from baseline to a level less than 40mmHg).

All subjects were then commenced on bosentan 62.5mg twice daily, which was subsequently increased to 125mg twice daily (if liver function remained within normal limits). Patients were reviewed clinically on a three to four monthly basis at the investigating centre. If clinical worsening of symptoms occurred, bosentan could be increased further to 250mg twice daily, or additional advanced therapy could be added. Liver function was monitored on a monthly basis and bosentan was reduced to 62.5mg twice daily or discontinued if significant liver function abnormalities occurred (sustained increase in transaminases greater than three times the upper limit of the normal reference range). Other significant adverse effect such as anaemia (fall in haemoglobin by greater than 2g/dL) were also recorded.

The primary outcomes were that of 6MWT and WHO functional classification following one year of therapy. Additionally, 28 patients underwent repeat right heart catheterisation for cardiac index (CI), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), and mean right atrial pressure (mRAP) at baseline and after 12 months.

Data was also analysed for the primary outcomes following at least four months of therapy to demonstrate the trend over time and rate of response to bosentan therapy. For 29 of the included patients this interim data has been published in previous reports (24, 26), and is included for completeness with the permission of the authors. However, only those patients who had been reassessed after completing 12 months of bosentan therapy at the time of this review have been included in this analysis.

Statistical Analysis

The baseline assessment was defined as the date of initiation of bosentan therapy. Patient characteristics and treatments are expressed as mean values +/- standard deviation (SD). Wilcoxon analysis was used to compare baseline, four month and twelve month continuous variables for all patients alive at one year, and are expressed

as mean values +/- standard error of the mean (SEM). All reported p values are paired two tailed. A p value of < 0.05 was considered statistically significant.
A survival estimate associated with longer term administration of bosentan was conducted by means of Kaplan Meier analysis.

The SPSS v12.0 statistical software package (SPSS Inc., Chicago, USA) was used for all analyses.

Results

Baseline

Forty seven subjects with inoperable CTEPH were commenced on bosentan during the study period. The baseline characteristics are presented in table 1. The majority of patients (80 percent) were WHO Class III or IV at baseline, with a significant proportion receiving chronic diuretic or oxygen (see table 1). One subject was anticoagulated with full dose low molecular weight heparin rather than oral anticoagulation due to a previous haemorrhagic pericardial effusion with tamponade. All other patients received long term oral coumadin-based anticoagulation.

Four month review

All patients remained on bosentan at the four month review (mean 4.4 ± 1.5 months). At this time the mean 6MWT had increased by 49 ± 8.4 m ($p < 0.001$) from baseline. Eight patients (17 percent) had improved by at least one WHO functional class, whilst one patient had deteriorated (see figure 1).

Review after one year

One year after commencing bosentan (mean 13.6 ± 2.1 months), two patients had died (one of progressive right heart failure, one of peritonitis), two had been commenced on alternative advanced therapy (one intravenous epoprostenol, one subcutaneous treprostinil) and in three patients the dose of bosentan had been increased to 250mg twice daily due to functional deterioration. In the 45 patients still alive who had been started on bosentan as first line therapy, the mean 6MWT had increased by 52 ±10 m ($p < 0.001$) from baseline. The improvement in 6MWT was most marked in the eight patients who had previously undergone PEA (102m vs 40m, p=0.001) (see figure 2). The WHO functional class had improved from baseline in 11 patients (24 percent), whilst in the remainder was stable (see figure 1).

Twenty eight subjects consented to repeat right heart catheterisation. There were significant improvements in CI, which increased by 0.2 ±0.07 l/min/m2 (p=0.004), and TPR, which fell by 138 ± 42 dyn.s.cm^{-5} (p=0.003). These improvements were more marked in the eight patients that had undergone PEA, where cardiac index rose by 0.4 ± 0.07 l/min/m2 (p=0.001) and TPR fell by 255 ± 57 dyn.s.cm^{-5} (p=0.003).

Two year efficacy and adverse effects

At the time of the analysis, eighteen patients had completed at least two years of therapy with bosentan. During this period, alternative advanced therapy had been required in three patients, whilst the remaining 15 subjects remained on bosentan monotherapy.

Bosentan was discontinued in one patient due to persistently deranged liver function (greater than three times the upper limit of the normal range) despite a dose reduction after 2.5 years of therapy. No other serious adverse effects, significant reduction in haemoglobin level or discontinuations occurred. Overall, the mean duration of exposure to bosentan was 20 months (range 7 to 41). During the course of this longer term follow-up three further patients died, all as a result of progressive right heart failure (figure 3). All five patients who died during the course of long term review had not undergone PEA.

Discussion:

The present study demonstrates sustained improvements in exercise capacity, WHO functional class and haemodynamic markers of disease severity after one year of bosentan therapy for inoperable CTEPH. One year survival was 96 percent with 43 patients (91 percent) remaining on Bosentan monotherapy. This is the first study to demonstrate the longer term efficacy of endothelin receptor antagonists in this difficult to treat patient group. The natural history of this condition is that of progressive increase in PVR, TPR and reduced right ventricular function resulting worsening exertional breathlessness and right heart failure.(1) The observed improvements in TPR and CI at one year are clinically significant, and are likely to reflect a partial reversal of the vascular remodelling of the small vessel pulmonary arteriopathy, rather than any effect on the fixed obstructive lesions. There appears to be a plateau in the improvement after four months of therapy, suggesting that the majority of this effect has occurred within this time period.

The improvement in 6MWT and WHO functional class noted after four months of therapy are in keeping with the results obtained from a recently published open label short term study.(25) These results are also of similar magnitude to those observed in clinical trials of bosentan in patients with pulmonary arterial hypertension.(21) Although there are some differences in the aetiology and pathophysiology of these conditions, it would appear that blockade of the deleterious effects of ET-1 is of similar importance in impeding disease progression. The effects of bosentan treatment seen after 4 months may be due to a variety of mechanisms: as endothelin receptor antagonists have an antiproliferative effect, they may act at least in part on pulmonary vascular remodelling. However, the observation that there was no further improvement after 12 months may either argue against this mechanism or indicate that initial antiremodelling effect with this agent is indeed incomplete, as is suggested in PAH therapy.(22) Other potential mechanisms such as a pulmonary vasodilator effect of bosentan may be of importance in the long term although it is well demonstrated that this subgroup of patients do not respond acutely to vasodilators such as nitric oxide or prostacyclin. Additional effects on cardiac function have also been considered previously.(27)

Despite similar baseline haemodynamic, exercise capacity and functional status, there is a suggestion of more marked improvements in those patients with persisting pulmonary hypertension following PEA. In this small sub-group, the 6MWT continued to improve throughout the first year of therapy with bosentan. This is not an unexpected result given that much of the sub-segmental obstruction will have been removed with the proximal fibrotic material during the endarterectomy. Any persisting resistance to flow is more likely to result from the potentially reversible small vessel arteriopathic component. All of these patients had been either stable or deteriorating prior to commencing bosentan, and in most cases bosentan was initiated many months after the PEA. It is therefore unlikely that the observed improvements in this group are due solely to delayed recovery or reconditioning following the surgery.(28) However, these results should be interpreted with caution given the small sample size of this sub group.

The limitation of this study is the lack of a control population. The majority of the patients included in this study had severe pulmonary hypertension, with rapid functional decline prior to commencing bosentan consistent with a very poor prognosis. Given the considerable evidence of benefit from bosentan in other forms of pulmonary hypertension, it was considered unethical to conduct a long term placebo controlled study. Historical data in this condition is limited but suggests that survival in this condition is directly related to the severity of haemodynamic markers at the time of diagnosis. In the study by Riedel et al which included all forms of CTEPH, including those with a proximal disease, a mPAP of greater than 50mmHg was associated with 40% survival at 1 year.(29) Given the severity of the haemodynamic compromise noted in the current population (mPAP 51mmHg), the observed survival of 96% at one year is likely to represent a significant improvement in outcome. However, the sample size is small, and it is necessary to confirm these findings in a larger study population. A multicentric randomised trial, which includes a 4 month placebo controlled phase, is currently being undertaken. By including both non-operated patients and those with persisting pulmonary hypertension following PEA, it is hoped that this larger study will be able to further explore any potential difference in response to bosentan between these subgroups as noted in the current report.

Bosentan was generally well tolerated in the study population, with only one patient having therapy withdrawn as a result of the hepatic dysfunction after 2.5 years of therapy. These data are in concordance with previous studies of bosentan in patients with PAH showing that doses up to 250mg twice daily can be safely administered under strict monitoring.(21, 22)

In conclusion, the results of this study suggest that therapy with the dual endothelin receptor antagonist, bosentan, was well tolerated and can result in sustained improvement in function, exercise capacity and markers of disease severity, and may improve survival in patients with inoperable CTEPH. Whilst all patients with CTEPH should receive long term anticoagulation and be assessed for suitability for a potentially curative PEA procedure, bosentan may offer an effective therapeutic option for those patients unsuitable for surgery.

Conflicts of interest:

RH has received consultation fees and travel grants from Actelion Pharmaceuticals.
XJ has received consultation fees and travel grants from Actelion Pharmaceuticals.
DB has received consultation fees and travel grants from Actelion Pharmaceuticals.
JS has received a travel grant from Actelion
MH has received consultation fees and travel grants from Actelion Pharmaceuticals, Pfizer Ltd, Schering and United Therapeutics.
IL has received consultation fees and travel grants from Actelion Pharmaceuticals.
GS has received consultation fees and travel grants from Actelion Pharmaceuticals, Pfizer Ltd, Schering, Encysive, GlaxoSmithKline and United Therapeutics.
JPZ has received consultation fees and travel grants from Actelion Pharmaceuticals Schering and Pfizer Ltd.

Author contributions:
All authors contributed to acquisition of patient data and clinical review. RH, XJ, DB and JS compiled the data for analysis. The manuscript was written by RH with contributions from all authors.

TABLE 1. Baseline demographic characteristics of patients included. Continuous variables are reported as mean ± SD.

CHARACTERISTIC	
Mean age (years)	59.5 (range 27 to 82)
Female / Male	27 / 20
Previous PTE	8 (17%)
WHO Class II / III / IV	10 / 32 / 5
6MWT (m)	291 ± 116
mPAP (mm Hg)	51 ± 11.3
TPR ($dyn.s.cm^{-5}$)	1122 ± 398
CI ($L.min^{-1}.m^{-2}$)	2.1 ± 0.5
Long term oxygen therapy	11 (23%)
Diuretic therapy	30 (64%)
Anticoagulation	47 (100%)

FIGURE 1. WHO classification at baseline, and following four months and one year (13.6 ± 2.1 months) of bosentan therapy.

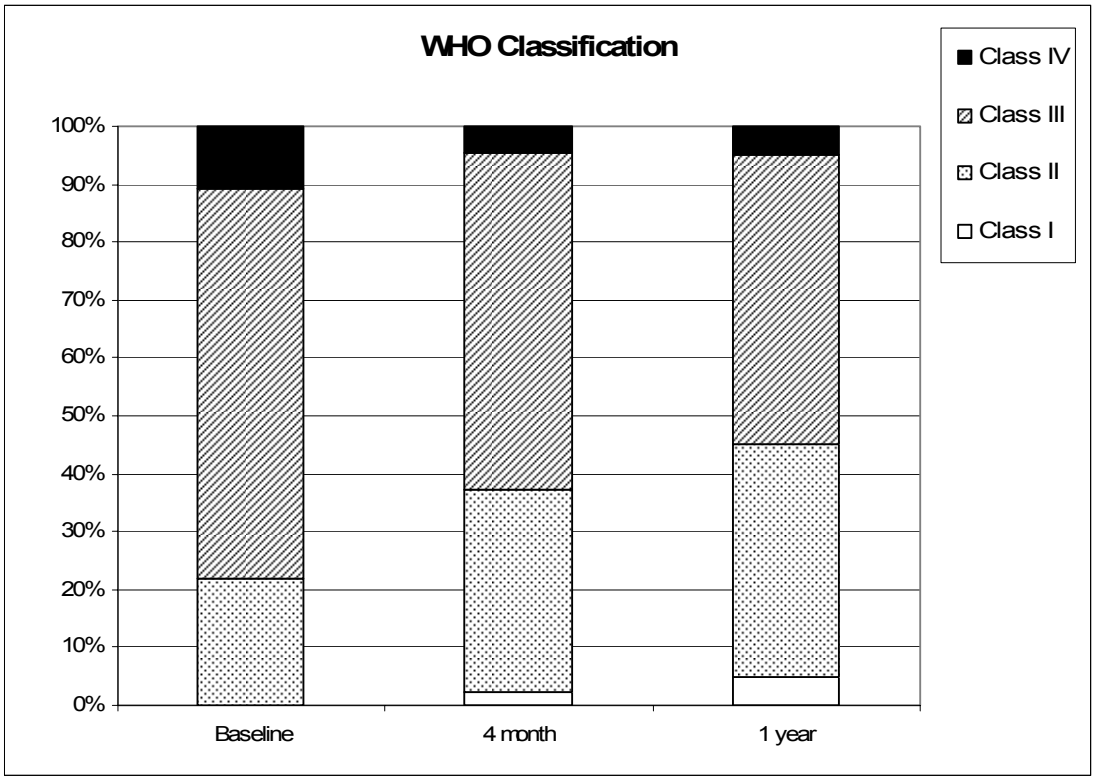


TABLE 2. Paired 6MWT (n=45) and haemodynamic data (n=28) following one year (13.6 ± 2.1 months) of Bosentan. Presented as mean ± SEM.

	Baseline ± SEM	**1 year ± SEM**	**p value**
6MWT (m)	312 ± 17	364 ± 18	**0.000**
Borg Score	3.9 ± 0.3	3.6 ± 0.3	0.24
mRAP (mmHg)	10 ± 1	8 ± 1	0.24
mPAP (mmHg)	50 ± 2	49 ± 2	0.45
CI ($L.min^{-1}.m^{-2}$)	2.1 ± 0.1	2.3 ± 0.1	**0.004**
TPR ($dyn.s.cm^{-5}$)	1107 ± 63	969 ± 62	**0.003**
PVR ($dyn.s.cm^{-5}$) **(n=18)**	916 ± 77	841 ± 81	0.171
SmVO2 (%)	60 ± 2	62 ± 1	0.147

FIGURE 2. Change in six minute walk distance following four months and one year (13.6 ± 2.1 months) of bosentan therapy (n=45). Presented as mean ± SEM.

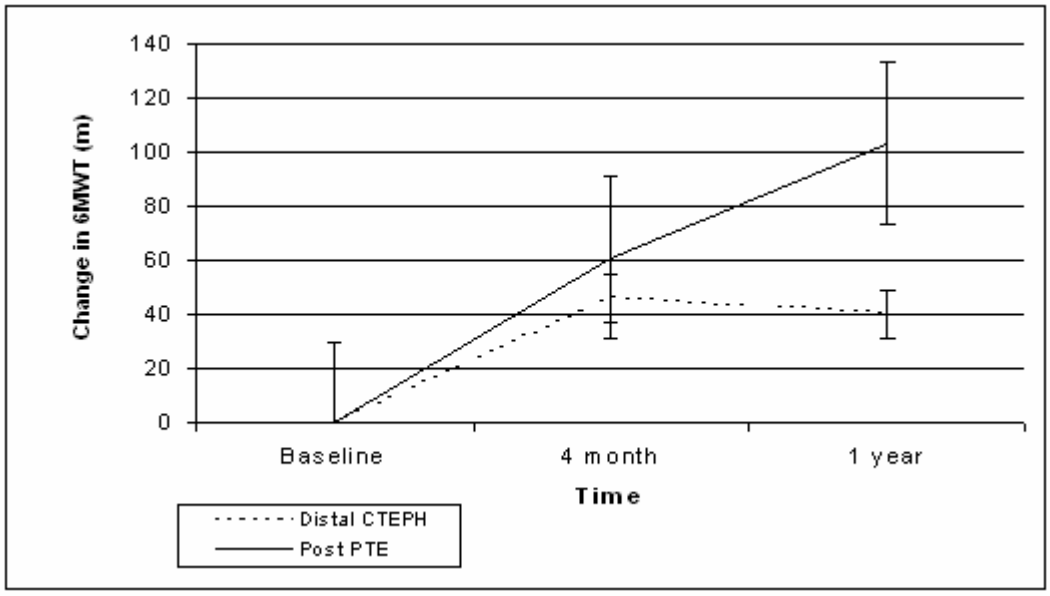
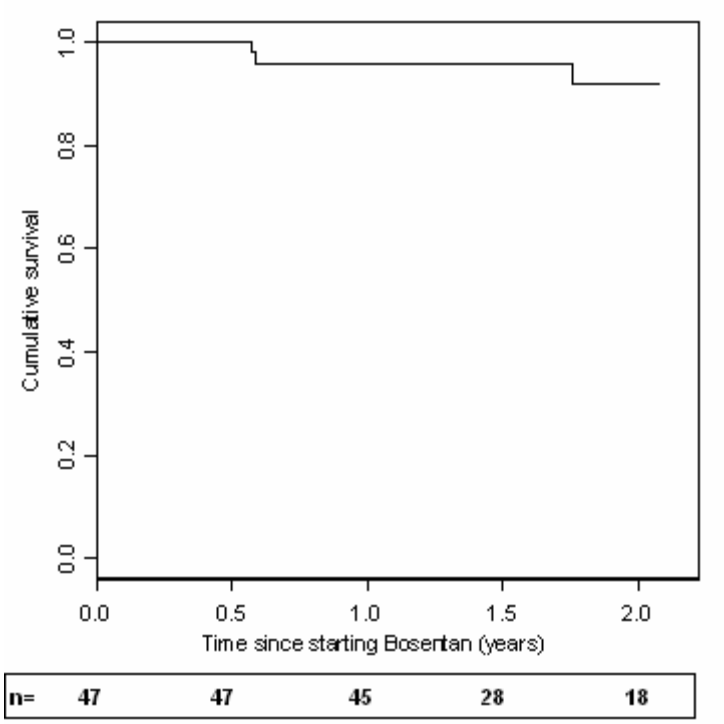


FIGURE 3. Long term survival for patients commenced on bosentan therapy as first line therapy for inoperable CTEPH.



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