The role of per cent predicted 6-min walk distance in pulmonary arterial hypertension

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ABSTRACT: **Absolute 6-min walk distance (6MWD) predicts mortality in pulmonary arterial hypertension (PAH), but varies greatly between normal individuals due to physiological factors such as age, sex, height and weight. The % predicted 6MWD adjusts for these factors and may predict mortality more reliably. The aim of the study was to compare the strength of mortality prediction by absolute and % predicted 6MWD in PAH at baseline and on treatment.**

% predicted 6MWD was calculated using four different reference equations in 137 PAH patients (idiopathic and connective tissue disease associated) diagnosed between November 2000 and November 2009. Cox proportional hazards and receiver-operating characteristic (ROC) analyses were used to compare the prognostic strength of absolute and % predicted 6MWD.

% predicted 6MWD was predictive of all-cause mortality at baseline (hazard ratio 0.74–0.83 per 10% increase; $p < 0.05$) and on treatment (0.67–0.75 per 10% increase; $p < 0.01$), but each respective area under the ROC curve was not different from that of absolute 6MWD for predicting 2-yr mortality at baseline (absolute *versus* % predicted: 0.74 *versus* 0.71–0.75) or on treatment (0.77 *versus* 0.72–0.78).

In conclusion, % predicted 6MWD may help clinicians interpret the 6-min walk test, but its prognostic value is not superior to that of absolute 6MWD.

KEYWORDS: 6-min walk distance, mortality, pulmonary hypertension

Absolute 6-min walk distance (6MWD) has been established as the principal clinical outcome measure in pulmonary arterial hypertension (PAH) and has been used as the primary end-point in most clinical trials of new PAH therapies [1]. As a measure of submaximal exercise capacity, it correlates with variables of maximal cardiopulmonary exercise testing, such as peak oxygen uptake and oxygen pulse [2, 3], and metabolic equivalent measured at exercise treadmill testing [4]. In addition, it correlates with markers of disease severity in PAH, such as World Health Organization functional class (WHO FC) and pulmonary haemodynamics [3]. Most importantly, the ability of baseline 6MWD to predict mortality has been demonstrated in a 12-week randomised controlled trial of intravenous epoprostenol therapy in idiopathic pulmonary arterial hypertension (IPAH) [5], the only clinical trial showing a survival benefit of PAH-specific therapies. This was confirmed by subsequent observational studies on the long-term impact of PAH-specific therapies [6–9]. However, there is ongoing debate as to whether % predicted 6MWD should be used instead of absolute 6MWD as it gives a more accurate reflection of the functional impact of disease on an individual.

As with other measurements of physical function, such as lung function and cardiopulmonary exercise capacity, 6MWD varies greatly between individuals due to physiological factors such as age, sex, height and weight, and pathological factors such as cardiopulmonary and musculoskeletal diseases. Adjusting for physiological variation should help clinicians interpret the result of the 6-min walk test (6MWT) and estimate the degree of exercise impairment due to disease in an individual. Several reference equations already exist to calculate % predicted 6MWD based on an individual's age, sex, height and weight [10–13]. They have been derived from healthy adults sampled from populations in North America and Europe. What is not known is whether % predicted 6MWD is superior to absolute 6MWD at predicting mortality in PAH. The aim of this study was, therefore, to compare the relative strength of mortality prediction by absolute and % predicted 6MWD in PAH

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measured at baseline and on treatment, respectively, using four different published reference equations.

METHODS

Study population

The study cohort was derived by a retrospective case note review of patients treated in the Scottish Pulmonary Vascular Unit, which provides the tertiary pulmonary hypertension service for the whole population in Scotland, UK. All consecutive incident cases of IPAH and connective tissue disease-associated pulmonary hypertension (CTDPH) treated with PAH-specific therapy between November 2000 and November 2009 were identified. The diagnosis of PAH was based on right heart catheterisation carried out by the pulmonary vascular team in our institution. PAH was defined as mean pulmonary artery pressure ($\bar{P}$pa) >25 mmHg at rest or >30 mmHg on exercise, with pulmonary capillary wedge pressure (Ppcw) $\leqslant$15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units [14]. For patients diagnosed after August 2009, PAH was defined as $\bar{P}$pa $\geqslant$25 mmHg at rest with Ppcw $\leqslant$15 mmHg, and normal or reduced cardiac output [1]. Patients with recorded 6MWD at diagnosis or within 12 months of starting treatment were included in this study. Patients with significant lung disease as defined by forced expiratory volume in 1 s <60% pred or forced vital capacity <60% pred or total lung capacity <60% pred (based on European Coal and Steel Community reference values) were excluded [15]. Ethical review was considered unnecessary by the West Glasgow research ethics committee.

Treatment and follow-up

All patients received conventional therapies, such as supplemental oxygen, diuretics and warfarin. PAH-specific monotherapies (prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase-5 inhibitors) were initiated after confirmation of diagnosis at right heart catheterisation. Treatment response was assessed after a period of 3–6 months by means of clinical assessment, WHO FC and 6MWD. Patients were subsequently followed up at 3–6 month intervals in outpatient clinics. Right heart catheterisation was not routinely repeated during follow-up. Baseline data including age, height, weight, lung function, 6MWD, WHO FC, mean right atrial pressure ($\bar{P}$ra), $\bar{P}$pa, PVR, cardiac index (CI) and mixed venous

oxygen saturation (Sv,O$_2$), and follow-up data including 6MWD, WHO FC and all-cause mortality were collected.

6MWT protocol

6MWT was performed by a trained respiratory physiologist on a 20-m corridor with no prior practice walks. Patients were instructed to walk to cover as much ground as possible in 6 min. After 2003, standardised encouragement at 1-min intervals was given as described in the American Thoracic Society guidelines and, before that, 6MWT was performed without encouragement [16]. Predicted 6MWD in each patient was calculated based on their age, sex, height and weight using each of four reference equations (table 1). Absolute 6MWD was expressed as a percentage of the predicted 6MWD.

Statistical analysis

Statistical analysis was performed using Statview version 5.0.1 (SAS Institute, Cary, NC, USA) and Graphpad Prism version 5.00 (Graphpad Software, La Jolla, CA, USA). Quantitative data were tested for normality using D'Agostino and Pearson omnibus normality test. Parametric data were described by the mean and standard deviation, and compared using paired or unpaired t-test. Nonparametric data were described by the median and interquartile range and compared using Mann–Whitney U-test. Qualitative data were described by number (%) and compared by Chi-squared test. The relationship between 6MWD (absolute and each expression of % predicted 6MWD) and other clinical markers of disease severity was determined by Spearman correlation coefficients. A two-tailed p-value <0.05 was defined as significant.

Survival time was defined as time from the date of right heart catheterisation to death or data cut-off on November 30, 2009. Patients who received lung transplantation or who were lost to follow-up were censored at the time of procedure or last clinical contact (clinic visit, telephone contact or renewal of drug prescription). Univariate Cox proportional hazards analysis was carried out to determine the association between all-cause mortality and age, sex, aetiology, lung function, haemodynamics, WHO FC, absolute 6MWD and each expression of % predicted 6MWD at baseline, and WHO FC, absolute 6MWD and each expression of % predicted 6MWD on treatment. Multiple bivariate Cox models, one for absolute 6MWD and one for each expression of % predicted 6MWD at

TABLE 1	Previously published reference equations for predicting 6-min walk distance in healthy adults based on an individual's age, sex, height and weight			
First author [Ref.]	**Publication year**	**Study populations**	**Reference equations**	**R^2**
ENRIGHT [11]	1998	USA; 117 males, 173 females; age 40–80 yrs	Males: (7.57 × Ht)-(5.02 × age)-(1.76 × Wt)-309 Females: (2.11 × Ht)-(5.78 × age)-(2.29 × Wt)+667	0.40
TROOSTERS [13]	1999	Belgium; 29 males, 22 females; age 50–85 yrs	218+(5.14 × Ht)-(5.32 × age)-(1.8 × Wt)+(51.31 × sex) Male=1, female=0	0.66
GIBBONS [12]	2001	Canada; 41 males, 38 females; age 20–80 yrs	868.8-(age × 2.99)-(sex × 74.7) Male=0, female=1	0.41
CHETTA [10]	2006	Italy; 48 males, 54 females; age 20–50 yrs	518.853+(1.25 × Ht)-(2.816 × age)-(39.07 × sex) Male=0, female=1	0.42

Ht: height in cm; Wt: weight in kg. R^2 indicates the degree of inter-subject variance explained by the equation.

baseline, were derived by including variables with p<0.2 in the univariate analysis to adjust for the effect of confounding. Correlation between candidate variables and the predictor of primary interest (absolute or % predicted 6MWD) was checked to limit collinearity. The variables would not be considered for inclusion if r>0.70. The same variables were included to adjust 6MWD in each model to facilitate comparison. The bivariate Cox analysis was repeated for absolute 6MWD and each expression of % predicted 6MWD on treatment. Date of follow-up 6MWD was used as the index date for determining survival time for the analysis on treatment.

To compare the relative prognostic strength among expressions of 6MWD against each other at baseline and on treatment respectively, and each corresponding expression of 6MWD at baseline *versus* on treatment, receiver-operating characteristic (ROC) analysis was used to determine their respective area under the ROC curves (AUC) for predicting 2-yr mortality. The significance of differences in AUC was assessed using a paired z-test [17]. Optimal thresholds were identified by selecting the data point closest to the coordinate $x=0$ (1-specificity) and $y=1$ (sensitivity) on the ROC curves.

TABLE 2	Baseline characteristics of all patients and subgroups according to the aetiology of pulmonary arterial hypertension			
	All patients	**Aetiology**		**p-value**[#]
		IPAH	**CTDPH**	
Patients n	137	86	51	
Age[¶] yrs	60 (22)	60 (29)	62 (13)	0.18
Females	95 (69)	54 (63)	41 (80)	<0.05
Lung function[¶] % pred				
FEV1	87 (22)	88 (19)	85 (24)	0.84
FVC	99 (23)	101 (22)	98 (32)	0.48
$D_{L,CO}$	43 (32)	45 (38)	41 (18)	0.22
WHO FC				
I and II	22 (16)	17 (20)	5 (10)	<0.05
III	104 (76)	59 (69)	45 (88)	
IV	11 (8)	10 (12)	1 (2)	
Haemodynamics				
$\bar{P}_{ra}$[¶] mmHg	6 (7)	6 (7)	7 (8)	0.40
$\bar{P}_{pa}$[¶] mmHg	48 (19)	50 (18)	42 (19)	<0.01
CI[¶] L·min⁻¹·m⁻²	2.1 (0.9)	2.2 (0.9)	2.0 (0.9)	0.92
PVR[¶] Wood units	10.5 (8.4)	10.6 (7.8)	9.7 (9.9)	0.36
S_{V,O_2} %	63±8	64±8	63±9	0.60
6MWD[+]				
Absolute 6MWD m	264±111	271±117	251±102	0.33
6MWD % pred				
ENRIGHT [11]	50±19	50±20	50±19	0.95
TROOSTERS [13]	41±16	41±16	42±15	0.84
GIBBONS [12]	41±16	41±16	40±15	0.81
CHETTA [10]	49±19	49±20	49±18	0.92

Data are expressed as mean±SD or n (%), unless otherwise stated; [¶]: median (interquartile range). IPAH: idiopathic pulmonary arterial hypertension; CTDPH: connective tissue disease-associated pulmonary hypertension; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; WHO FC: World Health Organization functional class; $\bar{P}_{ra}$: mean right atrial pressure; $\bar{P}_{pa}$: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance; S_{V,O_2}: mixed venous oxygen saturation; 6MWD: 6-min walk distance. [#]: comparing IPAH *versus* CTDPH patients; [+]: n=130.

TABLE 3	Univariate Cox proportional hazards analysis	
	HR (95% CI)	**p-value**
Age at diagnosis (per decade increase)	1.43 (1.11–1.86)	<0.005
Sex		
Female	0.61 (0.32–1.19)	0.14
Male (reference)		
Lung function at baseline		
FEV1 (per 10% pred increase)	1.09 (0.91–1.31)	0.36
FVC (per 10% pred increase)	1.07 (0.91–1.26)	0.42
$D_{L,CO}$ (per 10% pred increase)	0.75 (0.63–0.90)	<0.005
WHO FC at baseline		
I/II	0.60 (0.18–2.02)	0.41
III	0.63 (0.24–1.67)	0.34
IV (reference)		
WHO FC on treatment		
I/II	0.13 (0.04–0.43)	<0.001
III	0.28 (0.09–0.89)	<0.05
IV (reference)		
Aetiology		
CTDPH	1.63 (0.87–3.06)	0.12
IPAH (reference)		
Haemodynamics at baseline		
$\bar{P}_{ra}$ (per 5 mmHg increase)	1.19 (0.90–1.58)	0.21
$\bar{P}_{pa}$ (per 5 mmHg increase)	1.01 (0.91–1.12)	0.81
CI (per 1 L·min⁻¹·m⁻² increase)	0.83 (0.49–1.39)	0.47
PVR (per 1 Wood unit increase)	1.01 (0.96–1.06)	0.68
S_{V,O_2} (per 5% increase)	0.93 (0.73–1.19)	0.56
6MWD at baseline[#]		
Absolute 6MWD (per 50 m increase)	0.78 (0.67–0.95)	<0.005
6MWD % pred (per 10% increase)		
ENRIGHT [11]	0.83 (0.69–0.99)	<0.05
TROOSTERS [13]	0.77 (0.62–0.96)	<0.05
GIBBONS [12]	0.74 (0.61–0.90)	<0.005
CHETTA [10]	0.79 (0.66–0.94)	<0.01
6MWD on treatment[¶]		
Absolute 6MWD (per 50 m increase)	0.74 (0.64–0.90)	<0.005
6MWD % pred (per 10% increase)		
ENRIGHT [11]	0.75 (0.61–0.93)	<0.01
TROOSTERS [13]	0.68 (0.53–0.89)	<0.005
GIBBONS [12]	0.67 (0.53–0.85)	<0.005
CHETTA [10]	0.72 (0.59–0.88)	<0.005

HR: hazard ratio; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; WHO FC: World Health Organization functional class; CTDPH: connective tissue disease-associated pulmonary hypertension; IPAH: idiopathic pulmonary arterial hypertension; $\bar{P}_{ra}$: mean right atrial pressure; $\bar{P}_{pa}$: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance; S_{V,O_2}; mixed venous saturation; 6MWD: 6-min walk distance. [#]: n=130; [¶]: n=110.

a) Absolute 6MWD

	HR (95% CI)	p-value
Unadjusted	0.78 (0.67–0.90)	<0.005
Variable adjusted for		
$D_{L,CO}$ at baseline	0.90 (0.74–1.05)	0.23
$\bar{P}_{ra}$ at baseline	0.82 (0.70–0.95)	<0.05
Sex	0.78 (0.67–0.90)	<0.005
Aetiology	0.78 (0.67–0.90)	<0.005
Age	0.82 (0.70–1.00)	<0.05

HR (per 50 m increase)

b) ENRIGHT and SHERRILL [11] % predicted 6MWD

	HR (95% CI)	p-value
Unadjusted	0.83 (0.69–0.99)	<0.05
Variable adjusted for		
$D_{L,CO}$ at baseline	0.96 (0.77–1.20)	0.72
$\bar{P}_{ra}$ at baseline	0.87 (0.70–1.04)	0.15
Sex	0.83 (0.69–0.99)	<0.05
Aetiology	0.82 (0.68–0.98)	<0.05
Age	0.84 (0.70–1.00)	<0.05

HR (per 10% increase)

c) TROOSTERS et al. [13] % predicted 6MWD

	HR (95% CI)	p-value
Unadjusted	0.77 (0.63–0.95)	<0.05
Variable adjusted for		
$D_{L,CO}$ at baseline	0.91 (0.70–1.19)	0.51
$\bar{P}_{ra}$ at baseline	0.83 (0.66–1.03)	0.09
Sex	0.78 (0.63–0.97)	<0.05
Aetiology	0.76 (0.61–0.99)	<0.05
Age	0.79 (0.65–0.97)	<0.05

HR (per 10% increase)

d) GIBBONS et al. [12] % predicted 6MWD

	HR (95% CI)	p-value
Unadjusted	0.74 (0.61–0.91)	<0.005
Variable adjusted for		
$D_{L,CO}$ at baseline	0.86 (0.66–1.12)	0.26
$\bar{P}_{ra}$ at baseline	0.78 (0.63–0.97)	<0.05
Sex	0.74 (0.61–0.90)	<0.005
Aetiology	0.73 (0.58–0.90)	<0.005
Age	0.78 (0.63–0.97)	<0.05

HR (per 10% increase)

e) CHETTA et al. [10] % predicted 6MWD

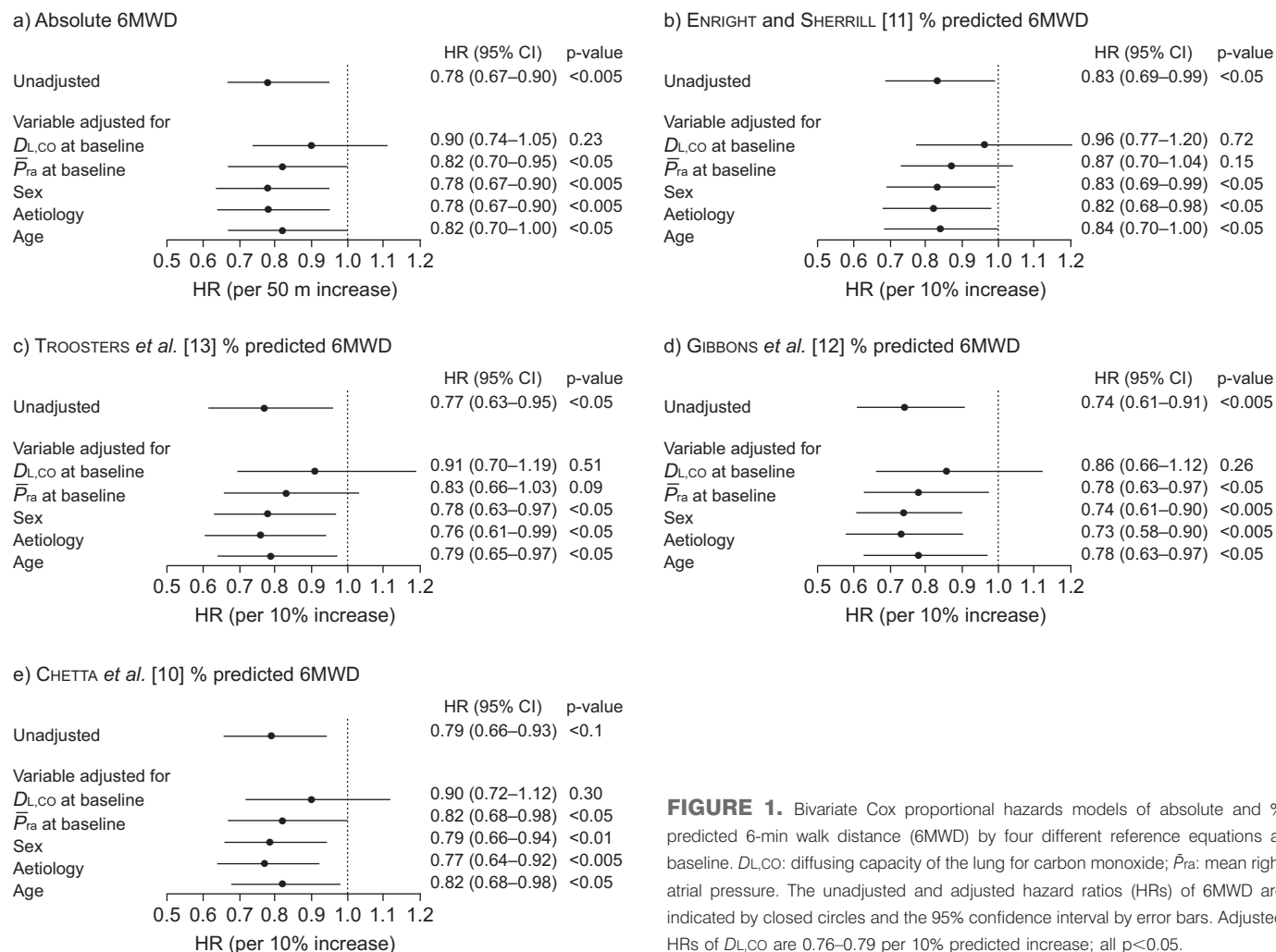|	HR (95% CI)	p-value
Unadjusted	0.79 (0.66–0.93)	<0.1
Variable adjusted for		
$D_{L,CO}$ at baseline	0.90 (0.72–1.12)	0.30
$\bar{P}_{ra}$ at baseline	0.82 (0.68–0.98)	<0.05
Sex	0.79 (0.66–0.94)	<0.01
Aetiology	0.77 (0.64–0.92)	<0.005
Age	0.82 (0.68–0.98)	<0.05

HR (per 10% increase)

FIGURE 1. Bivariate Cox proportional hazards models of absolute and % predicted 6-min walk distance (6MWD) by four different reference equations at baseline. $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; $\bar{P}_{ra}$: mean right atrial pressure. The unadjusted and adjusted hazard ratios (HRs) of 6MWD are indicated by closed circles and the 95% confidence interval by error bars. Adjusted HRs of $D_{L,CO}$ are 0.76–0.79 per 10% predicted increase; all p<0.05.

RESULTS

Patient characteristics

137 patients were included in the cohort (IPAH 86, CTDPH 51). The baseline characteristics of the study patients are outlined in table 2. During follow-up (median 2 yrs; range 1.2 months to 8.8 yrs), 41 patients died from all causes (IPAH 20, CTDPH 21), two patients were lost to follow-up and two patients received lung transplantation. After receiving PAH-specific monotherapy (7% prostacyclin analogues, 46% endothelin receptor antagonists and 47% phosphodiesterase-5 inhibitors) for 4.1 ± 1.8 months (median 3.5 months; range 2.2–11 months), absolute 6MWD and each expression of % predicted 6MWD were 311 ± 111 m, $59\pm18\%$ (ENRIGHT and SHERRILL [11]), $48\pm15\%$ (TROOSTERS et al. [13]), $48\pm16\%$ (GIBBONS et al. [12]) and $58\pm19\%$ (CHETTA et al. [10]) respectively (n=110, all p<0.0001 versus baseline). The distribution of absolute 6MWD at baseline, on treatment and the distance changed are shown in figure 1 in the online supplementary material. On treatment, 41% of patients were in WHO FC II, 54% in III and 4% in IV (n=123; p<0.005 versus baseline). At the time of death or censoring, 69% of patients remained on monotherapy and 31% were on combination therapy.
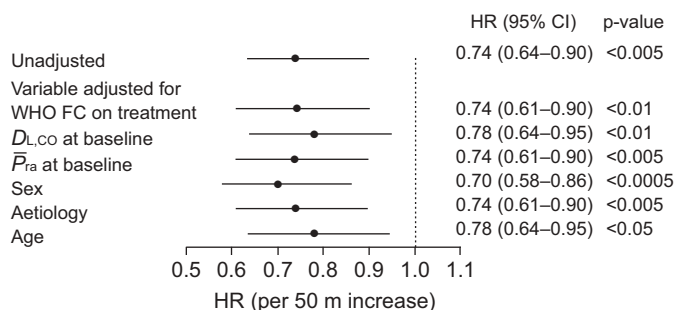
Correlation with other markers of disease severity at baseline

Baseline absolute and % predicted 6MWD correlated weakly with $\bar{P}_{ra}$ (absolute 6MWD r= -0.23; p<0.01 versus % predicted 6MWD by all equations r= -0.23 to -0.25; p<0.01), CI (r=0.24; p<0.01 versus r=0.21 to 0.22; p<0.05), Sv,O_2 (r=0.21; p<0.05 versus r=0.19 to 0.21; p<0.05) and WHO FC (r= -0.33; p<0.0005 versus r= -0.32 to -0.34; p<0.005). Only 6MWD % predicted by ENRIGHT and SHERRILL [11] and TROOSTERS et al. [13] equations correlated weakly with PVR (r= -0.23 and r= -0.19; both p<0.05). Neither absolute 6MWD nor % predicted 6MWD correlated with $\bar{P}_{pa}$.

Independent effect on mortality

Age and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) at baseline, absolute and % predicted 6MWD at baseline and on treatment, and WHO FC on treatment predicted all-cause mortality in univariate Cox proportional hazards analysis (table 3). The predictive value of absolute and % predicted 6MWD at baseline remained significant after adjusting for age, sex and aetiology of PAH but not $D_{L,CO}$ in bivariate Cox proportional hazards analysis (fig. 1). Absolute 6MWD, and 6MWD % predicted by GIBBONS et al. [12] and
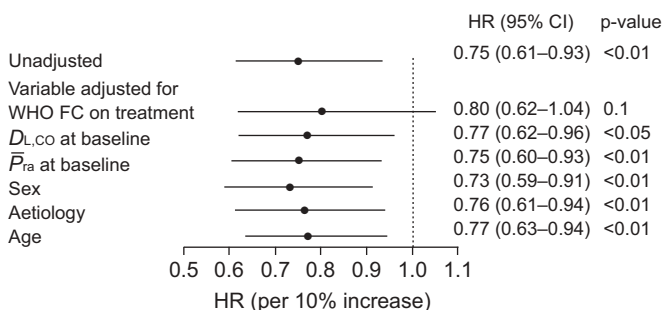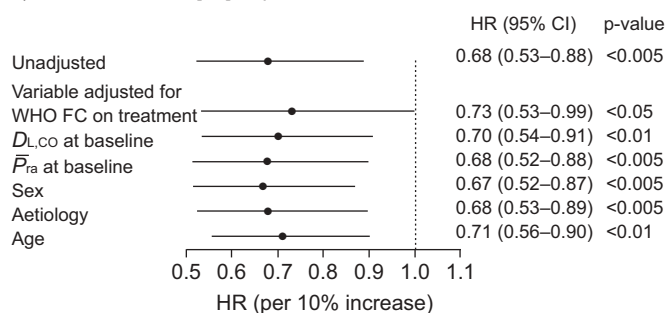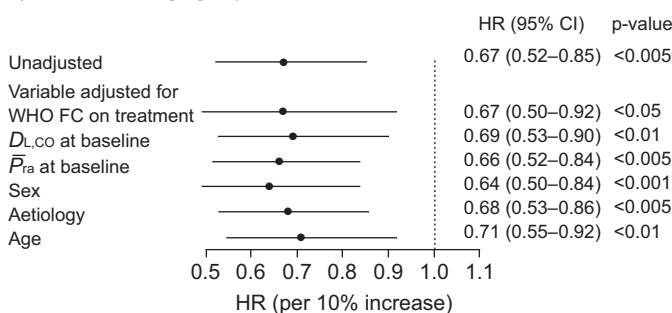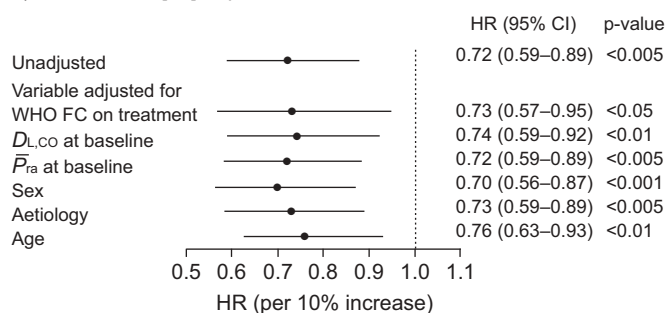
FIGURE 2. Bivariate Cox proportional hazards models of absolute and % predicted 6-min walk distance (6MWD) by four different reference equations on treatment. WHO FC: World Health Organization functional class; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; $\bar{P}_{ra}$: mean right atrial pressure. The unadjusted and adjusted hazard ratios (HRs) of 6MWD are indicated by closed circles and the 95% confidence interval by error bars.

CHETTA et al. [10] predicted mortality after adjusting for $\bar{P}_{ra}$ but 6MWD % predicted by ENRIGHT and SHERRILL [11] or TROOSTERS et al. [13] did not. On treatment, absolute and % predicted 6MWD was predictive of mortality independently of WHO FC (except ENRIGHT and SHERRILL [11] equation), age, sex, aetiology, baseline $D_{L,CO}$ and $\bar{P}_{ra}$ (fig. 2). When combined with absolute or % predicted 6MWD on treatment, $D_{L,CO}$ at baseline no longer predicted mortality.

Relative strength of mortality prediction

ROC curves of absolute 6MWD and % predicted 6MWD by each of four reference equations at baseline and on treatment are shown in figure 3. There were no significant differences in AUC of absolute versus each expression of % predicted 6MWD for predicting 2-yr mortality at baseline or on treatment (table 4). In addition, there were no significant differences in AUC among % predicted 6MWD by the four reference equations. The optimal thresholds of absolute 6MWD and each expression of % predicted 6MWD at baseline and on treatment for predicting 2-yr mortality had modest sensitivity and specificity. The thresholds of absolute 6MWD and 6MWD

% predicted by equations from TROOSTERS et al. [13], GIBBONS et al. [12] and CHETTA et al. [10] on treatment had slightly higher sensitivity and specificity than those at baseline, but the respective differences in AUC between baseline and treatment did not reach statistical significance. This analysis was repeated including only patients diagnosed from 2003 onwards as the 6MWT protocol changed at that point and the results were similar (table 1 and fig. 2 in the online supplementary material).

DISCUSSION

This study addresses an important clinical issue regarding the role of % predicted 6MWD in the management of PAH. The data analysis showed that % predicted 6MWD at baseline derived from currently available reference equations predicts all-cause mortality but its prognostic ability is not superior to that of absolute 6MWD despite adjusting for physiological inter-subject variance. In addition, there is no difference in the prognostic ability between each of the four studied reference equations. Assuming that the long-term prognosis of patients improves with PAH-specific therapy, 6MWD on treatment
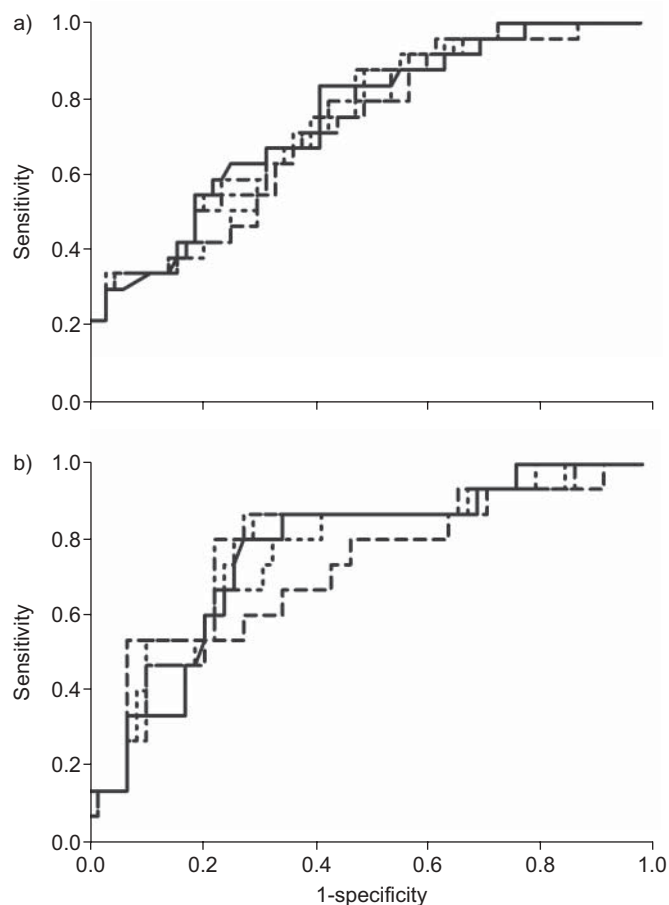
FIGURE 3. Receiver-operating characteristic curves of absolute and % predicted 6-min walk distance (6MWD) by four different reference equations in predicting 2-yr mortality a) at baseline and b) on treatment. ———: absolute 6MWD; – – – –: ENRIGHT and SHERRILL [11] % predicted 6MWD; - - - - -: TROOSTERS *et al*. [13] % predicted 6MWD; - - - - -: GIBBONS *et al*. [12] % predicted 6MWD; - - - - -: CHETTA *et al*. [10] % predicted 6MWD. All p>0.05 when area under the receiver-operating characteristic curves is compared among expressions of 6MWD at baseline and on treatment, respectively, by a paired z-test.

may be a stronger predictor of mortality than that at baseline, and hence the difference in the relative prognostic strength between absolute and % predicted 6MWD may be more apparent on treatment. However, this is not supported by the results of this analysis. % predicted 6MWD was not more predictive of mortality than absolute 6MWD on treatment.

% predicted 6MWD calculated from the equations of TROOSTERS *et al*. [13] and GIBBONS *et al*. [12] was slightly lower than that from ENRIGHT and SHERRILL [11] and CHETTA *et al*. [10] equations. This disparity is due to differences in the 6MWT protocol used in the studies, such as the length of corridor, type and frequency of encouragement and the number of practice walks. A 50-m corridor was used by TROOSTERS *et al*. [13] and the best of four walks by GIBBONS *et al*. [12], which resulted in higher predicted absolute 6MWD. The equations were also derived from healthy adults in different age groups. Patients younger than 40 yrs of age were included by CHETTA *et al*. [10] and GIBBONS *et al*. [12] only. This highlights the

importance of giving consideration to the characteristics of the study population and the 6MWT protocol used in deriving the reference equation when applying predicted values. The American Thoracic Society guidelines on 6MWT recognise that % predicted 6MWD is under-utilised due to a lack of optimal reference equations [16]. Only 40–66% of physiological inter-subject variance of 6MWD is explained by the currently available equations. Therefore, there are other factors influencing the performance at the 6MWT that have not been identified or accounted for. This may partly explain the failure to demonstrate the superiority of % predicted 6MWD by any of the four reference equations to absolute 6MWD in predicting mortality.

There are other potential explanations for the negative findings in this study. It might be possible for patients with low or high 6MWD to dominate the analysis, thereby obscuring any prognostic difference between absolute and % predicted 6MWD. However, this was not the case as the 6MWD data were normally distributed with few patients at either end of the range. The use of all-cause mortality rather than disease-specific mortality may also be relevant as this could shift the comparison of prognostic strength in favour of absolute 6MWD. For example, consider the case of a 40-yr-old male with severe PAH (height 186 cm, weight 90 kg) and an 80-yr-old female with mild PAH (height 157 cm, weight 60 kg) both of whom walk the same 6MWD of 300 m and survive for 5 yrs. This walk distance corresponds to 40% and 75% pred, respectively, using the ENRIGHT and SHERRILL [11] equation, reflecting more severe disease in the male. The 40-yr-old male is more likely to die from PAH, whereas the 80-yr-old female is more likely to die from other causes, as she approaches the natural limit of life expectancy. In this scenario, absolute 6MWD is the better predictor of all-cause mortality as it has automatically incorporated the influence of age on mortality, with age being the most important physiological determinant of 6MWD. Conversely, % predicted 6MWD would be expected to perform better at predicting disease-specific mortality. All-cause mortality was used in this study to avoid the subjectivity associated with disease-specific mortality.

The fact that there is a considerable amount of unexplained physiological variance in 6MWD raises concerns about its reliability as an outcome measure in PAH. Some clinicians propose that 6MWD should be used instead to set a treatment goal in individual patients based on their starting parameters, where inter-subject variance is not as relevant. To set an appropriate goal, the knowledge of predicted 6MWD in an individual is essential. Therefore, despite having no added prognostic information, % predicted 6MWD would help clinicians to ascertain the degree of improvement achievable should a goal-oriented treatment strategy be adopted. There is also a suggestion that 6MWD should be replaced altogether by alternative outcome measures that are more directly linked to right heart function or pulmonary haemodynamics, such as cardiac magnetic resonance or noninvasive cardiac output measurements. There is no doubt that more robust exercise outcome measures than 6MWD are needed in PAH, but until they are developed and validated, 6MWD on balance remains the best available option in the appropriate setting given its proven prognostic value and simplicity.

TABLE 4	Receiver-operating characteristic (ROC) analysis comparing the ability of absolute and % predicted 6-min walk distance (6MWD) to predict 2-yr mortality			
	ROC curve area (95% CI)	Optimal threshold	Sensitivity/specificity	p-value
At baseline				
Absolute 6MWD	0.74 (0.63–0.86)	<295 m	0.83/0.59	<0.0005
6MWD % pred				
ENRIGHT [11]	0.71 (0.59–0.83)	<51%	0.75/0.56	<0.005
TROOSTERS [13]	0.73 (0.62–0.85)	<43%	0.79/0.57	<0.001
GIBBONS [12]	0.75 (0.64–0.85)	<43%	0.75/0.60	<0.0005
CHETTA [10]	0.74 (0.63–0.85)	<53%	0.75/0.57	<0.001
On treatment				
Absolute 6MWD	0.77 (0.64–0.90)	<296 m	0.87/0.66	<0.005
6MWD % pred				
ENRIGHT [11]	0.72 (0.56–0.87)	<53%	0.67/0.66	<0.01
TROOSTERS [13]	0.76 (0.63–0.90)	<45%	0.80/0.67	<0.005
GIBBONS [12]	0.78 (0.64–0.91)	<44%	0.87/0.72	<0.005
CHETTA [10]	0.78 (0.65–0.91)	<53%	0.87/0.71	<0.005

The prognostic value of $D_{L,CO}$ in PAH has been explored in a large retrospective study that showed that $D_{L,CO}$ at baseline predicted mortality after adjusting for age, CTDPH aetiology, WHO FC, haemodynamics and lung abnormalities on computed tomography [18]. However, the finding of $D_{L,CO}$ predicting mortality more strongly than 6MWD at baseline in this analysis is of interest and to our knowledge has not been reported before. It would be interesting to explore the predictive value of $D_{L,CO}$ on treatment but such data were not available in this study cohort.

The study has a number of limitations. First, selection bias cannot be excluded as this is a retrospective study and gaps due to missing data are unavoidable. 14 (10%) patients with no 6MWD data at baseline or within 12 months of starting treatment were excluded from the analysis. This is unlikely to have affected the main outcome of the analysis, namely the comparison between absolute and % predicted 6MWD. Secondly, patients were recruited over a relatively long period of time during which treatment approaches had evolved. This may have led to differences in prognosis of patients diagnosed in the earlier years compared to those diagnosed more recently. While this cannot be excluded, it is worth pointing out that there is as yet no conclusive evidence to support improved prognosis with the widespread use of oral agents in the past few years compared to the epoprostenol era. Thirdly, the 6MWT protocol changed during the study period and encouragement may have significantly influenced 6MWD. However, the results were similar with patients diagnosed after 2003 only. Finally, the reference equations were derived from healthy populations with differing age groups and hence no single equation was perfectly applicable to the study patients.

In conclusion, % predicted 6MWD may help clinicians quantify the functional impact of disease on an individual, but its prognostic ability is not superior to that of absolute 6MWD. In addition, the prognostic ability of currently available reference equations is similar. To explore the role of % predicted 6MWD in the management of PAH further, efforts should be made to develop more robust reference equations using a standardised 6MWT protocol and sampling healthy adults from more representative populations, particularly in relation to age.

REFERENCES
1 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30: 2493–2537.
2 Oudiz RJ, Barst RJ, Hansen JE, *et al.* Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. *Am J Cardiol* 2006; 97: 123–126.
3 Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161: 487–492.
4 Gomberg-Maitland M, Huo D, Benza RL, *et al.* Creation of a model comparing 6-minute walk test to metabolic equivalent in evaluating treatment effects in pulmonary arterial hypertension. *J Heart Lung Transplant* 2007; 26: 732–738.
5 Barst RJ, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996; 334: 296–302.
6 Hoeper MM, Gall H, Seyfarth HJ, *et al.* Long-term outcome with intravenous iloprost in pulmonary arterial hypertension. *Eur Respir J* 2009; 34: 132–137.
7 McLaughlin VV, Sitbon O, Badesch DB, *et al.* Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005; 25: 244–249.

8 Provencher S, Sitbon O, Humbert M, *et al.* Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2006; 27: 589–595.

9 Sitbon O, Humbert M, Nunes H, *et al.* Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780–788.

10 Chetta A, Zanini A, Pisi G, *et al.* Reference values for the 6-min walk test in healthy subjects 20–50 years old. *Respir Med* 2006; 100: 1573–1578.

11 Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998; 158: 1384–1387.

12 Gibbons WJ, Fruchter N, Sloan S, *et al.* Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. *J Cardiopulm Rehabil* 2001; 21: 87–93.

13 Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; 14: 270–274.

14 Galie N, Torbicki A, Barst R, *et al.* 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: 2243–2278.

15 Quanjer PH, Tammeling GJ, Cotes JE, *et al.* [Lung volumes and forced ventilatory flows. Work Group on Standardization of Respiratory Function Tests. European Community for Coal and Steel. Official position of the European Respiratory Society]. *Rev Mal Respir* 1994; 11: Suppl. 3, 5–40.

16 Brooks D, Solway S, Gibbons WJ. ATS statement on six-minute walk test. *Am J Respir Crit Care Med* 2003; 167: 1287.

17 Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983; 148: 839–843.

18 Chandra S, Shah SJ, Thenappan T, *et al.* Carbon monoxide diffusing capacity and mortality in pulmonary arterial hypertension. *J Heart Lung Transplant* 2010; 29: 181–187.