ATORVASTATIN IN PULMONARY HYPERTENSION (APATH) STUDY

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Clinical trials

This trial was registered at ClinicalTrial.gov (NCT00615823).

Disclosures: None

Abstract

Statins have been shown to both prevent and attenuate pulmonary hypertension in animal models. This study investigates the potential therapeutic benefits of atorvastatin as an affordable treatment for pulmonary hypertension patients.

Two hundred and twenty patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) were randomised, double-blind, to receive atrovastatin 10 mg daily or matching placebo in addition to supportive care.

At 6 months, 6-minute walk distance decreased by 16.6m in the atorvastatin group and 14.1m in the placebo group. The mean placebo-corrected treatment effect was –2.5 m (95% confidence interval: -38 to 33; p=1.0), based on intention to treat. A small non-significant increase in pulmonary vascular resistance and fall in cardiac output was seen in both treatment groups. There was no significant difference in the proportion of patients who improved, remained stable or showed a deterioration in WHO functional class between atorvastatin and placebo treatments. Nine patients died in the atorvastatin group and 11 in the placebo group. Serum cholesterol levels fell significantly on atorvastatin treatment. Discontinuation rates were 23.2% and 26.9% on atorvastatin and placebo respectively.

Atorvastatin 10 mg daily has no beneficial effect on the natural history of PAH or CTEPH over 6 months.

Introduction

The treatment of pulmonary arterial hypertension (PAH) is a continuing challenge,
likewise the treatment of pulmonary hypertension secondary to inoperable chronic
thromboembolic disease[1]. Despite advances in treatment, mortality remains
unacceptably high[2-4]. In addition, the current therapeutic options - prostenoids,
endothelin receptor antagonists and phosphodiesterase-type 5 inhibitors - are expensive
and not widely available in developing countries. In China, only iloprost and bosentan
are licensed for PAH. Sildenafil is only licensed for erectile dysfunction. Many patients
in China have no access to approved PAH treatments. There is a need for more
effective, affordable drugs treatments.

The licensed treatments for pulmonary hypertension are drugs designed primarily to
reduce pulmonary vascular tone[5]. It is widely appreciated that the major pathology
contributing to the chronic increase in pulmonary vascular resistance is remodeling of
pulmonary resistance vessels. This has focused thoughts on strategies that target
directly the structural changes and the molecular mechanisms that underlie them.

It is in this context that statins have attracted interest. This drug class inhibits
3-Hydroxy-3-methylglutaryl (HMG) Co-A reductase, a key enzyme in cholesterol
synthesis but essential for the synthesis of isoprenoids (geranylgeranylpyrophosphate
and farnesylpyrophosphate), required for the post-translational isoprenylation of Rho
and Ras family GTPases[6]. This confers on statins pleotrophic properties, that include

antiproliferative, anti-inflammatory, anti-thrombotic and anti-oxidant effects. There is now a substantial body of data from animal models that show both attenuation in the development of and regression of established experimental pulmonary hypertension with statin treatment[7-18]. There is evidence that this is achieved through increased apoptosis as well as reduced proliferation of smooth muscle cells in obstructive vascular lesions.

Data from human studies are few. A series of case reports of patients treated with simvastatin suggested this drug was well-tolerated and may have beneficial effects in licenced doses[19]. The results of 2 small randomised clinical studies of simvastatin in human PAH involving have been disappointing, with no evidence of an improvement in 6 min walk distance[20, 21]. A study with rosuvastatin has reported a sustained reduction in P-selectin levels and a small (15m) improvement in 6 minute walk distance at 6 months in a small mixed cohort of patients with pulmonary hypertension of different aetiologies[22].

There are no data on the effect of statins on pulmonary haemodynamics in patients. To understand further the potential therapeutic benefits of statins as a treatment for pulmonary hypertension patients, we conducted a randomized, double-blind, placebo-controlled study of the effects of atorvastatin 10 mg daily for 6 months on exercise capacity and pulmonary haemodynamics.

Methods

Selection of Patients

This study included pulmonary hypertension patients 18 to 65 years of age with a diagnosis of Group 1 pulmonary arterial hypertension (specifically, idiopathic and hereditable pulmonary arterial hypertension, pulmonary arterial hypertension associated with connective tissue disease and pulmonary arterial hypertension associated with congenital heart disease) or inoperable chronic thromboembolic pulmonary hypertension. Patients with pulmonary arterial hypertension associated with congenital heart disease were enrolled if they had persistent pulmonary arterial hypertension at five years after surgical or interventional repair, or if they were not eligible for surgical or interventional treatment. Pulmonary arterial hypertension was defined as mean pulmonary artery pressure more than 25 mmHg, pulmonary capillary wedge pressure less than 15 mmHg, and pulmonary vascular resistance more than 3 Wood units.

The exclusion criteria were the following: (1) Groups 2, 3 and 5 pulmonary hypertension; (2) a forced expiratory volume in one second/forced vital capacity bellow 50% or a total lung capacity of less than 60 percent predicted value; (3) a 6-minute walk distance of less than 100 or more than 460 m; (4) a positive acute vasodilator response;(5) current treatment with calcium-channel blockers or PAH targeted therapy (endothelin receptor antagonist, phosphodiesterase-5 inhibitor, or prostacyclin); (6) inability to perform 6-minute walk test; (7) serum transaminase level three times above

the upper limit of normal; (8) creatinekinase level five times above the upper limit of normal; (9) previously diagnosed heart disease such as serious cardiac arrhythmias, unstable angina pectoris, myocardial infarction; (10) history of transient ischemia attack or stroke within three months; (11) bleeding disorder; (12) positive pregnancy test or breastfeeding practice; (13) history or suspicion of inability to cooperate.

This study was conducted according to the Declaration of Helsinki and in adherence to good clinical practice guidelines and was approved by the Institutional Review Boards of Fu Wai Hospital. All patients participated in the study on a voluntary basis after they had been fully informed of the therapy for PAH available to them. Written informed consent was obtained from all patients.

Study Design

This was a 24-week, randomized, double-blind and placebo-controlled trial, conducted in 26 centers in China between May 2007 and March 2010. Using a block randomization technique with block sizes of four, 220 patients were assigned to receive 10 mg of atorvastatin or matching placebo once daily for 24 weeks (supplied by JiaLin Pharmaceutical Co., Beijing, China). The randomization was not stratified for any factors. Randomization was performed using a randomization assignment program provided by SAS 9.1 (SAS Institute Inc., Cary, NC, USA). The dose was adjusted to 5 mg daily if serum transaminase levels increased by less than three times the upper limit of normal or creatinekinase levels increased to less than five times the upper limit of

normal. If serum transaminase and creatine kinase levels remained normal and

low-density lipoprotein level greater than 3.4mmol/L after 4 weeks of therapy, the dose

of atorvastatin was increased to 20 mg once daily. Blinding continued until all analyses

were completed.

Outcome measures

The primary end point of the study was the placebo-corrected change from baseline to

week 24 in 6-minute walk distance. The 6-minute walk testing was performed

according to the American Thoracic Society guidelines [23]. Secondary endpoints

included: time from randomization to clinical worsening (defined as death, the first

occurrence of hospitalization for pulmonary arterial hypertension, or initiation of PAH

targeted therapy decided by an independent panel of physicians) and change from

baseline to week 24 in World Health Organization (WHO) functional class (an

adaptation of the New York Heart Association classification [24]), Borg dyspnea score

(with 0 representing no dyspnea and 10 maximal dyspnea [23]), and hemodynamic

parameters (mean pulmonary artery pressure, right atrial pressure, cardiac output and

pulmonary vascular resistance) derived from right heart catheterization. Hemodynamic

parameters were measured as described previously [25]. Cardiac output was

determined using the thermodilution technique or calculated according to the Fick

method. Pulmonary vascular resistance was calculated as (mean pulmonary artery

pressure - pulmonary capillary wedge pressure)/pulmonary blood flow. 6-minute walk

test, evaluation of the Borg dyspnea score and right heart catheterization were

performed at baseline and at week 24. Physical examinations, assessment of WHO functional class and laboratory tests including a complete blood count and routine chemistry tests (creatinine, transaminases, creatine kinase and lipid profile) were performed at baseline and regular intervals. Investigators recorded adverse events throughout the study.

Statistical Analysis

One hundred and four patients in each of the two treatment groups (atorvastatin and placebo) were required to reject the null hypothesis if the means of the distributions, with equal standard deviations of 70m, differed by at least 35m, with a type 1 error of 0.05 (two-sided) and 95 percent power.

Analysis of efficacy end points was performed by intention-to-treat. Patients were excluded from the relevant efficacy analysis if they had a missing baseline value. Missing variables at 24-week for 6-minute walk distance, WHO functional class, Borg dyspnea score and hemodynamic parameters were replaced with the last available value carried forward unless clinical worsening or death occurred.

In the case of death, the value for 6-minute walk distance was imputed with "0" m, while in the case of clinical worsening, the valuewas replaced with "worst value". The worst value for a patient was defined as his or her baseline value adjusted for the worst percentage change from baseline observed during the study. If a patient discontinued

the study due to clinical worsening or death and did not have an assessment at the time of premature discontinuation, WHO functional class and Borg dyspnea scorewere replaced by the worst value observed in the present study.

Patients who had no hemodynamic parameters (mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance and mixed venous oxygen saturation) at the time of discontinuation due to clinical worsening or death were replaced using worst value defined as his or her baseline value corrected for the highest percentage of deterioration from baseline at the week 24 time point.

For low-density lipoprotein, missing values were replaced with expected variables calculated on the average percentage change between baseline and 24 weeks observed in the whole group. No imputation rule was applied to laboratory variables in patients who died during study period.

Comparison of the atorvastatin and placebo-treated groups for change in 6-minte walk distance, Borg dyspnea score, low-density lipoprotein level and hemodynamics parameters (mean right atrial pressure, mean pulmonary arterial pressure, cardiac index, pulmonary vascular resistance and mixed venous oxygen saturation) was made using the Wilcoxon rank sum test. The change in 6-minute walk distance was analyzed in subgroups defined by demographic, cause of disease and prognostic variables. Change from baseline in WHO functional class at week 24 was analyzed categorically

with a 3-point scale: less than 0 (improved), equal to 0 (no change), more than 0 (worsened).The proportions of patients with no clinical worsening were calculated using the Kaplan-Meier method. Time from randomization to the first occurrence of clinical worsening was compared with log-rank test. Subjects who completed the study or discontinued early without clinical worsening were considered censored at the time of study completion. Safety data were summarised descriptively. Analysis of PAH sub-groups was retrospective. Data are expressed as mean values ± SD or mean (95% confidence interval) or number of patients. Mean Change with 95% CI in hemodynamic variables are estimated by mean of differences of these variables from baseline to week 24 in treatment group minus that in placebo group. All reported p values are two-sided. All data analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline Patient Characteristics

A total of 220 patients were randomized to atorvastatin or placebo groups (Figure 1). Patient demographics and baseline characteristics were well matched between treatment groups, except for a higher proportion of PAH associated with congenital heart disease in the atorvastatin group (Table 1). The majority (44%) of patients had PAH associated with congenital heart disease. During the 24 weeks study period, 14 patients (11 patients in the atorvastatin group and 3 patients in the placebo group) reduced their dose of study medication from 10 mg to 5 mg daily. Sixteen patients (5

patients in the atorvastatin group and 11 patients in the placebo group) up-titrated their

dose of study medication from 10 mg to 20 mg daily after the initial 4 weeks of therapy.

Exercise Capacity

After 24 weeks of treatment, 6-minute walk distance decreased by 16.6m in the

atorvastatin group and 14.1m in the placebo group. The mean placebo-corrected

treatment effect at week 24 was –2.5 m (95% confidence interval: -38 to 33; p=1.0)

(Figure 2).

Borg Dyspnea Score

There was no significant change in Borg index from baseline in either the atorvastatin 3

(2, 4) to 3 (2, 5) or placebo 3 (2, 4) to 3 (2, 5) treated groups.

Hemodynamic Parameters

Changes in hemodynamic parametersare shown in Table 2. The patients treated with

atorvastatin showed an increase in right atrial pressure, mean pulmonary arterial

pressure, pulmonary vascular resistance from baseline, and a decrease in the cardiac

index and mixed venous oxygen saturation. These changes did not differ significantly

from those patients treated with placebo.

WHO functional class

In atorvastatin-treated patients, 14% improved WHO functional class and 19% deteriorated. In placebo-treated patients, 8% improved and 18% deteriorated. There was no significant difference between the two treatment groups in the proportion of patients who improved, remained stable or deterioratedin WHO functional class (p = 0.34) (Figure 3).

Clinical Worsening

There was no significant difference between the atorvastatin and placebo groups in time to clinical worsening (Figure 4). The proportion of each component of clinical worsening (death [p =0.6], hospitalizations for worsening of pulmonary hypertension [p =0.3] or initiation of PAH targeted therapy [p =1.0]) was similar between the atorvastatin group and the placebo group.

Laboratory Variables

Baseline low-density lipoprotein levels were 2.3±0.7mmol/L in the atorvastatin group and 2.3±0.8mmol/L in the placebo group, respectively (p = 0.7). At week 24 these were 1.8±0.6 and 2.2±0.8mmol/L, respectively. The mean placebo-corrected treatment effects at week 24 were -0.4mmol/L (95% confidence interval, -0.6 to -0.2, p <0.0001), indicating good compliance with atorvastatin treatment.

Response in Patient Subgroups

The primary efficacy measure and other variables were evaluated retrospectively in different subgroups of patients (Figure 5, Tables 4 and 5). With the exception of a reduction in plasma LDL levels, atorvastatin was not associated with any significant effect in any subgroup examined.

Safety

The most frequent adverse events in both groups are shown in table 3. The total number of adverse events was similar in the atorvastatin group and the placebo group. Fifty-one patients reported 79 adverse events. The common adverse events included indigestion, liver function abnormalities, irregular menstrual cycles, abdominal distention, abdominal pain, paresthesia, dizziness, myalgia and insomnia. Discontinuation rates were 23.2% and 26.9% in the two treatment groups: 26 patients receiving atorvastatin and 29 patients receiving placebo. Of the patients treated with atorvastatin, 17 discontinued because of clinical worsening (9 patients died during follow-up), 9 patients discontinued for other reasons (lost follow-up [n=2], poor compliance [n=3], adverse events [n=4]). Of the patients treated with placebo, 16 discontinued because of clinical worsening (11 patients died during follow-up), 13 patients discontinued for other reasons (lost follow-up [n=1], poor compliance [n=9], adverse events [n=3]). The adverse events leading to withdrawal included abnormal liver function (two in atorvastatin group and one in placebo group), indigestion (one in atorvastatin group and one in placebo group) and dizziness (one in atorvastatin group and one in placebo group). Twenty patients died during follow-up. Of these, 12 had IPAH, 4 had PAH

associated with congenital heart disease (CHD-PAH), 2 had PAH associated with connective tissue disorder (CTD-PAH) and 2 had CTEPH. Fourteen (70%) patients were in WHO functional class III. Of the nine non-survivors in the atorvastatin group, five patients died of right-sided heart failure, three patients died suddenly and one patient committed suicide. Of the 11 non-survivors in the placebo group, 10 patients died of right-sided heart failure, one patient who had PAH associated with connective tissue disease died of diffuse intravascular clotting. No death was considered to be related to the study treatment.

Discussion

This is the largest study to date evaluating the effect of statin treatment in patients with pulmonary hypertension and the only study with haemodynamic data. The underlying rationale, based on animal studies, was that atorvastatin would reduce pulmonary vascular resistance and so improve exercise capacity. Atorvastatin 10 mg daily was safe and reasonably well-tolerated in this study population and significantly reduced circulating cholesterol levels, but had no significant impact on 6-minute walk distance, cardio-pulmonary hemodynamics or survival at 6 months.

The findings are at variance with the conclusions of a number of studies using animal models. Treatment with statins, mostly simvastatin, has, with few exceptions, resulted in the prevention and reversal of pulmonary hypertension secondary to hypoxia and monocrotaline[8-14, 16]. One study showed that atorvastatin did not decrease pulmonary hypertension significantly in the monocrotaline model[13]. The findings are consistent with 2 recent studies with simvastatin in patients with pulmonary arterial hypertension, which reported no effect on 6-minute walk distance at 6 months[20, 21].

While statin treatment may enhance the effect of local and circulating vasorelaxant factors, for example by increasing the expression of endothelial nitric oxide synthase [9, 17], the main mechanism of action in animal models is thought to be through inhibiting cell proliferation and promoting apoptosis. Unlike changes in vasomotor tone, structural changes may take time to effect a measurable change in pulmonary

hemodynamics and exercise capacity. The predominant subgroup of patients included in this study (over 40%) had co-existing congenital heart disease. The natural history in this subgroup is one of gradual decline, compared to idiopathic pulmonary arterial hypertension[26]. Against a slow deterioration, a drug that acts to arrest rather than reverse pulmonary vascular modeling may need longer than 6 months to demonstrate any efficacy. But no benefit was detected in the combined subgroup of patients with idiopathic pulmonary arterial hypertension and PAH associated with connective tissue disease, a subgroup that typically exhibits a more rapid decline with time.

A strength of this study is that patients were receiving supportive medication, in the form of diuretics, digoxin and warfarin, but no PAH targeted therapy, allowing atorvastatin to be evaluated without the confounding effects of concomitant medication. Modern targeted therapy is expensive and sildenafil is not licensed for use in pulmonary hypertension in China. Accurate figures are difficult to obtain but it is estimated that only 20% of patients in China have access to modern therapies. Unfortunately, this study does not support the use of atorvastatin as a low-cost option for treating pulmonary hypertension.

There are several limitations to this study. One is the dose of atorvastatin used, which at 10 mg per day is at the lower end of the licensed dose for hypercholesterolaemia. The dose of atorvastatin selected was effective at reducing plasma cholesterol levels, a marker of the effect of the drug on isoprenoid synthesis. There was concern that higher

doses would produce unacceptably low cholesterol levels in this ethnic group and produce side effects, such as elevated liver transaminase levels[27] and gastrointestinal discomfort, which would limit the translation of any benefit into clinical practice. Statins may influence pulmonary vascular biology by mechanisms other than inhibition of HMG CoA reductase[28] and a higher dose of atorvastatin may have shown greater efficacy but the present signal from atorvastatin 10 mg is not encouraging.

Another limitation is that the study population comprised a mixture of IPAH, CHD-PAH, CTD-PAH and CTEPH. Nonetheless, while each may have a different pathobiology and natural history, histopathologic studies suggest a number of similarities in the vascular changes in CTEPH and CHD-PAH to those seen in IPAH[29, 30]. As in PAH, recent work also suggests a role for inflammation in the genesis of CTEPH [31].

It is also recognized that the majority of patients recruited to the study were in WHO functional class II. Approved treatments such as bosentan, which have benefits in advanced stage PAH, have not demonstrated an improvement in 6 minute walk distance in early stage disease[32].

The study also suffered from a relatively large drop out rate, equal in both arms, requiring imputation to address missing values. However, the results and conclusions were similar after per-protocol analysis (data not shown).

Rosuvastatin has been shown to reduce cardiovascular events in patients with normal cholesterol but elevated C-reactive protein (CRP) levels.[33] CRP have been reported to predict outcome in PAH and Quarck et al have reported that PAH patients normalizing their CRP levels on treatment (assigned as responders) showed a concomitant decrease in NYHA functional class and increase in cardiac index.[34] It might be anticipated that the effects of statins might be more pronounced in patients with higher CRP levels but this was not tested in our study.

In summary, there is no evidence that 6 months treatment with atorvastatin 10 mg daily targets directly pulmonary vascular disease in humans. It may be used safely in this patient population when clinically indicated to reduce cholesterol levels but should not be prescribed as a specific treatment for pulmonary hypertension.

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Jiangsu, China; **Tian-Lun Yang**, MD, **Zai-Xin Yu**, MD, **Qiong Liu**, MD, Xiangya

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Figure Legends

Figure 1. Numbers of patients enrolled in the 24-week study.
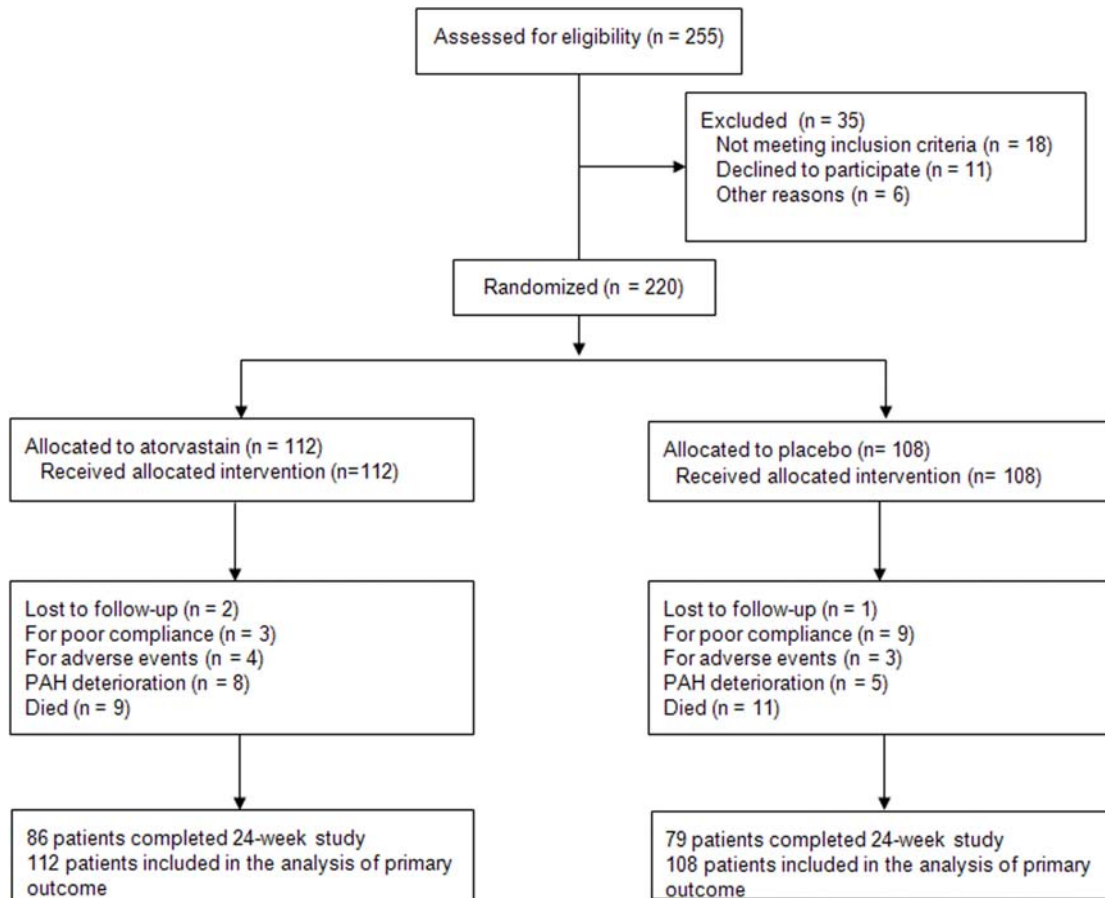
Figure 2. Changes from baseline of 6-minute walk distance in atorvastatin and placebo

groups. Values are expressed as means (standard error). TE= treatment effect.
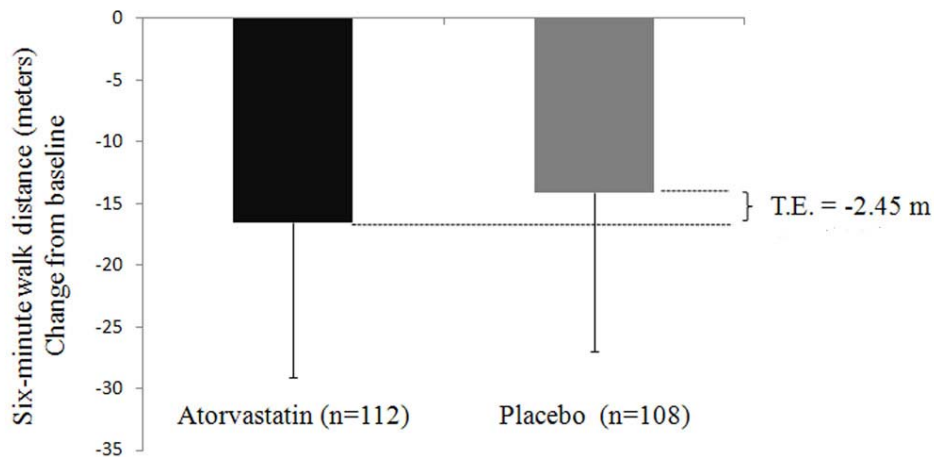
Figure 3. Change in WHO functional class from baseline to week 24 in the atorvastatin

and placebo groups. The treatment effect of atorvastatin on WHO functional class was

not statistically significant.

Figure4. Kaplan-Meier estimates of the proportion of patients without clinical

worsening.P = 0.98 for the comparison of atorvastatin with placebo.
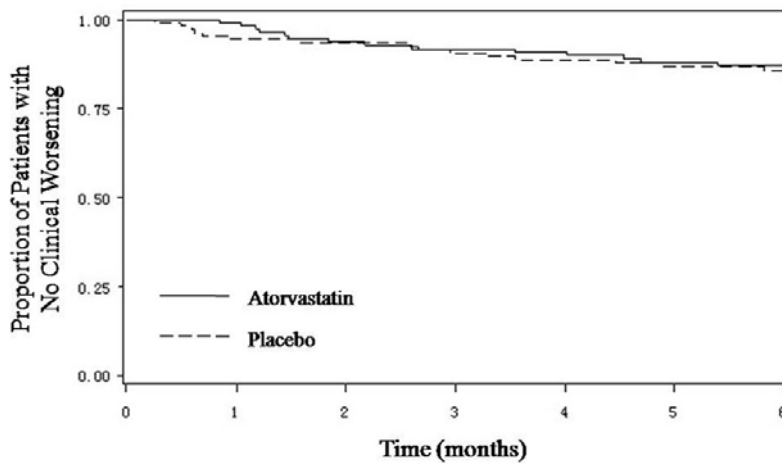
Figure 5. Effects of treatment on the 6-minute walk distance from baseline to week 24

in patient subgroups. Bars represent 95 percent confidence intervals. CHD = congenital

heart disease, CTD = connective tissue disease, CTEPH = chronic thromboembolic

pulmonary hypertension, WHO = World Health Organization, LDL = low-density

lipoprotein, PAP = pulmonary artery pressure.

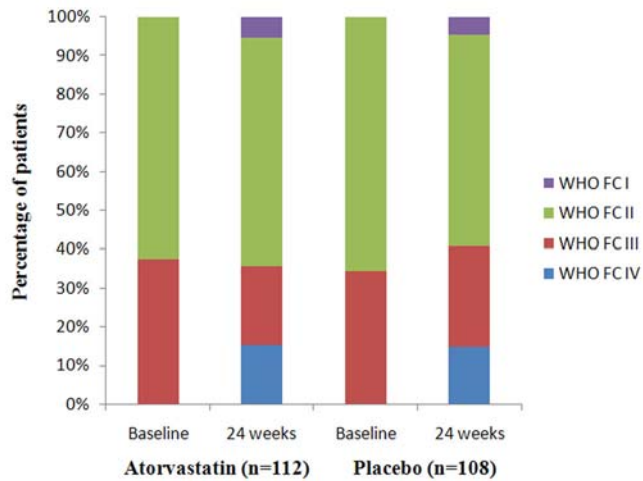|	Atorvastatin	Placebo
	(no. of patients)	
Age		
< Median	58	48
≥ Median	54	60
Sex		
Female	79	65
Male	33	43
Cause of PAH		
Idiopathic	30	34
CHD	59	38
CTD	8	13
CTEPH	15	23
Dosage		
5 mg	11	3
10 mg	96	94
20 mg	5	11
WHO functional class		
II	70	71
III	42	37
LDL		
< Median	52	47
≥ Median	50	53
Baseline walking distance		
< 350 m	48	48
≥ 350 m	64	60
Mean PAP		
< Median	48	61
≥ Median	64	46
Cardiac index		
< Median	58	48
≥ Median	52	58

-300 -250 -200 -150 -100 -50 0 50 100 150 200 250 300

Placebo-corrected change in 6-minute walk distance (m)

Table 1. Baseline Clinical, Functional, Laboratory, and Hemodynamic Characteristics of the Patients

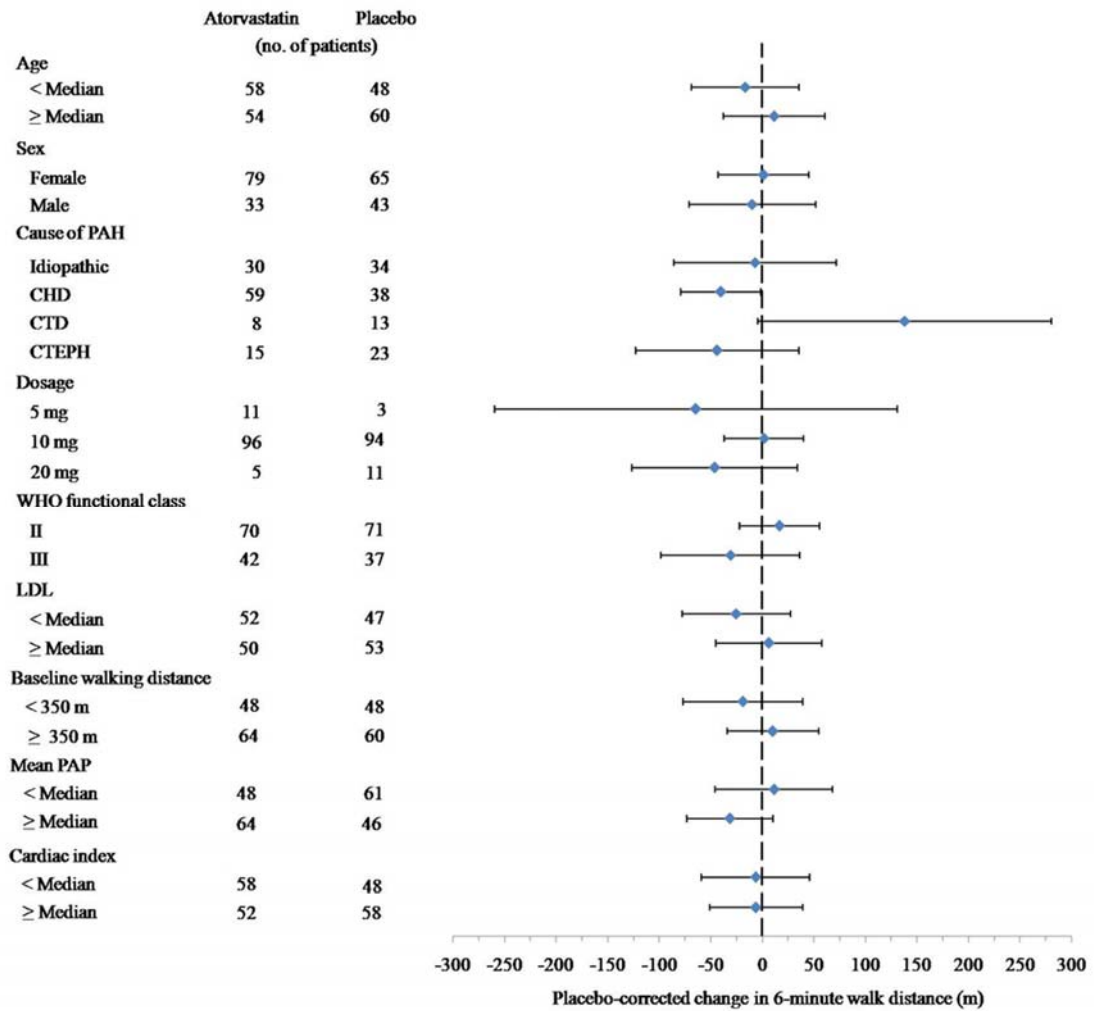| Characteristics	Atorvastatin (n=112)	Placebo (n=108)
Age, ys	35±13	37±13
Gender, n (%)		
Female	79 (71)	65 (60)
Male	33 (29)	43(40)
Weight, kg	54±12	57±11
Systolic blood pressure, mmHg	112±15	113±15
Diastolic blood pressure, mmHg	75±12	73±12
Heart rates, beats/minute	80±11.8	81±10.6
Cause of pulmonary hypertension (%)		
Idiopathic	30 (27)	34 (32)
Congenital heart disease	59 (53)	38 (35)
Atrialseptal defect	18	5
Ventricular septal defect	22	22
Patent ductus arteriosus	12	5
other	7	6
Connective-tissue disease	8 (7)	13 (12)
CTEPH	15 (13)	23 (21)
WHO functional class, n (%)		
II	70 (63)	71 (66)

III	42 (37)	37 (34)
Six-minute walk distance, m	355±74	346±84
Borg dyspnea index	3 (2, 4)	3 (2, 4)
Mixed venous oxygen saturation, %	65±8	66±8
Total cholesterol, mmol/L	4.0±0.9	4.2±1.0
Low-density lipoprotein, mmol/L	2.3±0.7	2.3±0.8
Hemodynamic parameters		
Right atrial pressure, mmHg	9±6	10±6
Mean pulmonary arterial pressure, mmHg	69±19	66±20
Pulmonary capillary wedge pressure, mmHg	9±4	10±4
Cardiac output, L/min	3.8±1.4	4.1±1.7
Cardiac indexes, L/min/m^2	2.4±0.8	2.6±1
Pulmonary vascular resistance, dyn·sec·cm^{-5}	1633±745	1456±699
Concomitant medication, n (%)		
Digoxin	67 (60)	58 (54)
Diuretics	87 (78)	84 (78)
Warfarin	64 (57)	60 (56)

Values are mean±SD, median (Q1, Q3)or n (%)when appropriate.

Table 2. Mean Change in Hemodynamic Variables from Baseline to Week 24.

Variables	Atorvastatin (N = 112)[*]	Placebo (N = 108) [*]	Mean Treatment Effect (95% CI)	p value (Wilcoxon Test)
Mean right atrial pressure, mmHg	3 (2 to 5)	3 (2 to 5)	0 (-2 to 3)	0.78
Mean pulmonary artery pressure, mmHg	4 (0 to 7)	3 (-1 to 6)	1 (-4 to 6)	0.94
Cardiac index, L/min/m^2	-0.1 (-0.2 to 0)	-0.2 (-0.3 to 0)	0.1 (-0.1 to 0.3)	0.19
Pulmonary vascular resistance, dyn·sec·cm^{-5}	203 (42 to 364)	287 (132 to 442)	-84 (-306 to 138)	0.15
Mixed venous oxygen saturation, %	-3 (-5 to -2)	-5 (-7 to -4)	2 (0 to 4)	0.06

Values are mean (95% CI)

CI = confidence intervals.

[*]The number of patients per treatment group varied slightly for each parameter because of missing assessments.

Table 3. Incidence of clinical worsening and adverse events.

Event	Atorvastatin (n=112)	Placebo (n=108)
Clinical worsening (%)		
Death (%)	9 (8)	11 (10)
Hospitalization or discontinuation	7 (6)	3 (3)
Initiation of PAH targeted therapy	3 (3)	2 (2)
Adverse event (%)		
Liver function abnormalities	6 (5)	4 (4)
Myalgia	2 (2)	3 (3)
Cramp	1 (1)	1 (1)
Constipation	2 (2)	2 (2)
Indigestion	8 (7)	10 (9)
Abdominal pain	3 (3)	1 (1)
Insomnia	2 (2)	1 (1)
Headache	1 (1)	2 (2)
Dizziness	2 (2)	4 (4)
Rash	0 (0)	5 (5)
Itching	0 (0)	5 (5)
Paresthesia	2 (2)	0 (0)
Abdominal distention	1 (1)	3 (3)
Irregular menstrual cycles	3 (3)	0 (0)

Data expressed as n (%)

Table 4. Change in 6MWD, Borg dyspnea index, WHO functional class, Hemodynamic Variables from Baseline to Week 24 in patients with IPAH and CTD-PAH.

Variables	Atorvastatin (N =38)[*]	Placebo (N =47) [*]	Mean Treatment Effect (95% CI)	p value
6-min walking distance, m	-52 (-103 to -1)	-79 (-126 to -33)	27 (-41 to 96)	0.34
Improved WHO functional class	5 (13)	2 (4)	-	0.26
Mean right atrial pressure, mmHg	6 (2 to 9)	5 (3 to 7)	1 (-4 to 5)	0.50
Mean pulmonary artery pressure, mmHg	11 (4 to 19)	10 (4 to 16)	1 (-9 to 9)	0.63
Cardiac index, L/min/m^2	-0.3 (-0.5 to 0)	-0.4 (-0.6 to -0.2)	0.1 (-0.2 to 0.4)	0.44
Pulmonary vascular resistance, dyn·sec·cm^{-5}	440 (119 to 762)	605 (313 to 897)	-165 (-592 to 262)	0.28
Mixed venous oxygen saturation, %	-5.0 (-9 to -1)	-8 (-11 to -5)	3 (-2 to 7)	0.16
Low-density lipoprotein, mmol/L	-0.5 (-0.7 to -0.3)	-0.3 (-0.5 to -0.1)	-0.2 (-0.5 to 0)	0.05

Data were expressed as mean (95% CI)or n (%)when appropriate.

Table 5. Change in 6-min walking distance, Borg dyspnea index, WHO functional class, Hemodynamic Variables from Baseline to Week 24 in patients CHD-PAH.

Variables	Atorvastatin (N =59)[*]	Placebo (N =38)[*]	Mean Treatment Effect (95% CI)	p value
6-min walking distance, m	10 (-19 to 39)	50 (31 to 69)	-40 (-79 to -1)	0.19
Improved WHO functional class, n (%)	10 (16.9)	2 (5.3)	-	0.16
Mean right atrial pressure, mmHg	3(1 to 5)	0 (-2 to 2)	3 (-1 to 6)	0.15
Mean pulmonary artery pressure, mmHg	0 (-5 to 4)	-5 (-10 to 0)	5(-2 to 12)	0.12
Cardiac index, L/min/m^2	0 (-0.1 to 0.2)	0 (-0.3 to 0.3)	0 (-0.3 to 0.4)	0.28
Pulmonary vascular resistance, dyn·sec·cm^{-5}	46 (-151 to 243)	8 (-150 to 165)	39 (-210 to 287)	0.39
Mixed venous oxygen saturation, %	-2 (-4 to 0)	-3 (-5 to -1)	1 (-2 to 4)	0.19
Low-density lipoprotein, mmol/L	-0.6 (-0.8 to -0.4)	0.05 (-0.2 to 0.3)	-0.6 (-0.9 to -0.3)	<0.001

Data were expressed as mean (95% CI), median (Q1, Q3)or n (%)when appropriate.

[*]The number of patients per treatment group varied slightly for each parameter because of missing assessments.

References

1.   Archer SL, Weir EK, Wilkins MR. Basic science of pulmonary arterial hypertension for clinicians: new concepts and experimental therapies. *Circulation* 2010; 121: 2045-2066.

2.   Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; 122: 164-172.

3.   Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156-163.

4.   Zhang R, Dai LZ, Xie WP, et al. Survival of Chinese patients with pulmonary arterial hypertension in the modern treatment era. *Chest* 2011; 140: 301-309.

5.   McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009; 53: 1573-1619.

6.   Wang CY, Liu PY, Liao JK. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol Med* 2008; 14: 37-44.

7.   Xie L, Lin P, Xie H, et al. Effects of atorvastatin and losartan on monocrotaline-induced pulmonary artery remodeling in rats. *Clin Exp Hypertens* 2010; 32: 547-554.

8.   Girgis RE, Li D, Zhan X, et al. Attenuation of chronic hypoxic pulmonary hypertension by simvastatin. *Am J Physiol Heart Circ Physiol* 2003; 285: H938-945.

9.   Guerard P, Rakotoniaina Z, Goirand F, et al. The HMG-CoA reductase inhibitor, pravastatin, prevents the development of monocrotaline-induced pulmonary hypertension in the rat through reduction of endothelial cell apoptosis and overexpression of eNOS. *Naunyn Schmiedebergs Arch Pharmacol* 2006; 373: 401-414.

10.   Laudi S, Trump S, Schmitz V, et al. Serotonin transporter protein in pulmonary hypertensive rats treated with atorvastatin. *Am J Physiol Lung Cell Mol Physiol* 2007; 293: L630-638.

11.   Murata T, Kinoshita K, Hori M, et al. Statin protects endothelial nitric oxide synthase activity in hypoxia-induced pulmonary hypertension. *Arterioscler Thromb Vasc Biol* 2005; 25: 2335-2342.

12.   Nishimura T, Faul JL, Berry GJ, et al. Simvastatin attenuates smooth muscle neointimal proliferation and pulmonary hypertension in rats. *Am J Respir Crit Care Med* 2002; 166: 1403-1408.

13.   Rakotoniaina Z, Guerard P, Lirussi F, et al. The protective effect of HMG-CoA reductase inhibitors against monocrotaline-induced pulmonary hypertension in the rat might not be a class effect: comparison of pravastatin and atorvastatin. *Naunyn Schmiedebergs Arch Pharmacol* 2006; 374: 195-206.

14.   Satoh K, Fukumoto Y, Nakano M, et al. Statin ameliorates hypoxia-induced pulmonary hypertension associated with down-regulated stromal cell-derived factor-1. *Cardiovasc Res* 2009; 81: 226-234.

15.   Nishimura T, Vaszar LT, Faul JL, et al. Simvastatin rescues rats from fatal pulmonary hypertension by inducing apoptosis of neointimal smooth muscle cells. *Circulation* 2003; 108: 1640-1645.

16. Girgis RE, Mozammel S, Champion HC, et al. Regression of chronic hypoxic pulmonary

hypertension by simvastatin. *Am J Physiol Lung Cell Mol Physiol* 2007; 292: L1105-1110.

17. Zhao L, Sebkhi A, Ali O, et al. Simvastatin and sildenafil combine to attenuate pulmonary

hypertension. *Eur Respir J* 2009; 34: 948-957.

18. Gao YF, Zhu XD, Shi DM, et al. The effects of atorvastatin on pulmonary arterial hypertension

and expression of p38, p27, and Jab1 in rats. *Int J Mol Med* 2010; 26: 541-547.

19. Kao PN. Simvastatin treatment of pulmonary hypertension: an observational case series. *Chest*

2005; 127: 1446-1452.

20. Wilkins MR, Ali O, Bradlow W, et al. Simvastatin as a treatment for pulmonary hypertension

trial. *Am J Respir Crit Care Med* 2010; 181: 1106-1113.

21. Kawut SM, Bagiella E, Lederer DJ, et al. Randomized clinical trial of aspirin and simvastatin

for pulmonary arterial hypertension: ASA-STAT. *Circulation* 2011; 123: 2985-2993.

22. Barreto AC, Maeda NY, Soares RP, et al. Rosuvastatin and vascular dysfunction markers in

pulmonary arterial hypertension: a placebo-controlled study. *Braz J Med Biol Res* 2008; 41:

657-663.

23. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166:

111-117.

24. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of

pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*

2004; 126: 14S-34S.

25. Jing ZC, Jiang X, Han ZY, et al. Iloprost for pulmonary vasodilator testing in idiopathic

pulmonary arterial hypertension. *Eur Respir J* 2009; 33: 1354-1360.

26. McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: 78S-92S.

27. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352: 1425-1435.

28. Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. *Nat Med* 2001; 7: 687-692.

29. Galie N, Kim NH. Pulmonary microvascular disease in chronic thromboembolic pulmonary hypertension. *Proc Am Thorac Soc* 2006; 3: 571-576.

30. Beghetti M, Tissot C. Pulmonary arterial hypertension in congenital heart diseases. *Semin Respir Crit Care Med* 2009; 30: 421-428.

31. Kimura H, Okada O, Tanabe N, et al. Plasma monocyte chemoattractant protein-1 and pulmonary vascular resistance in chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med* 2001; 164: 319-324.

32. Galie N, Rubin L, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 2093-2100.

33. Glynn RJ, Danielson E, Fonseca FA, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med* 2009; 360: 1851-1861.

34. Quarck R, Nawrot T, Meyns B, et al. C-reactive protein: a new predictor of adverse outcome in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 53: 1211-1218.