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A Randomized Clinical Trial of Aspirin and Simvastatin for Pulmonary Arterial Hypertension: ASA-STAT

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Disclosures

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Abstract

Background—Pulmonary arterial hypertension (PAH) is a progressive disease which causes exercise limitation, heart failure, and death. We aimed to determine the safety and efficacy of aspirin and simvastatin in PAH.

Methods and Results—We performed a randomized, double-blind, placebo-controlled 2 × 2 factorial clinical trial of aspirin and simvastatin in patients with PAH receiving background therapy at four centers. A total of 92 patients with PAH were to be randomized to aspirin 81 mg or matching placebo and simvastatin 40 mg or matching placebo. The primary outcome was six-minute walk distance (6MWD) at six months. Sixty-five subjects were randomized when the trial was terminated by the DSMB after an interim analysis showed futility in reaching the primary end point for simvastatin. After adjustment for baseline 6MWD, there was no significant difference in the 6MWD at six months between aspirin (n = 32) and placebo (n = 33) [placebo-corrected difference = −0.5 m (95%CI, −28.4 – 27.4 m), p = 0.97] or between simvastatin (n = 32) and placebo (n = 33) [placebo-corrected difference = −27.6 m (95%CI, −59.6 – 4.3 m), p = 0.09]. There tended to be more major bleeding episodes with aspirin compared to placebo (4 events vs. 1 event, respectively, p = 0.17).

Conclusions—Neither aspirin nor simvastatin had a significant effect on the 6MWD, although patients randomized to simvastatin tended to have a lower 6MWD at six months. These results do not support the routine treatment of patients with PAH with these medications.

Keywords

pulmonary hypertension; clinical trial; anti-platelet agents; endothelial dysfunction

Pulmonary arterial hypertension (PAH) includes idiopathic (IPAH) and heritable forms, as well as PAH associated with connective tissue disease, portal hypertension, anorexigen use, HIV infection, congenital systemic-to-pulmonary shunts, and other conditions. In PAH, the small muscular pulmonary arteries show endothelial proliferation and smooth muscle hypertrophy, *in situ* thrombosis, and plexiform lesions. Right ventricular failure ensues, leading to exercise limitation and death.

Reduced prostacyclin (PGI_2) production, elevated endothelin-1 (ET-1) levels, and deficits in nitric oxide (NO) are seen in PAH and have guided therapeutic development. Platelet activation, endothelial nitric oxide synthase (eNOS) dysfunction, oxidative stress, and inflammation are also present, but these mechanisms have not been specifically targeted. Activated platelets produce thromboxane (Tx) A_2 which causes platelet aggregation, vasoconstriction, and vascular smooth muscle hypertrophy. Patients with PAH have increased TxA_2 (and TxB_2) production and decreased PGI_2 production resulting in an increased Tx:PGI_2 ratio, even with treatment.[1–5] Clinical trials of intravenous epoprostenol[6] and other prostacyclin analogs which are efficacious in PAH[7–9] were predicated on the inference that low endogenous PGI_2 (and increased Tx:PGI_2 ratio) is detrimental in PAH. Investigators have visualized circulating platelet aggregates in the blood of patients with PAH,[10] and increased platelet aggregation is associated with more severe PAH.[11] Soluble P-selectin is elevated in patients with PAH, and platelet-released CD40 ligand increases across the pulmonary vascular bed suggesting trans-pulmonary platelet activation.[12, 13] Thrombocytopenia due to platelet trapping in the lungs occurs during PAH "crises"[14, 15] and is associated with worse hemodynamics.[16] Aspirin lowers the Tx:PGI_2 ratio in PAH (even in patients chronically treated with PGI_2 analogues or other medications) and inhibits platelet activity,[2] offering a potential therapeutic approach. A recent study showed that aspirin decreased pulmonary artery pressure, reduced right ventricular hypertrophy, and improved survival in the monocrotaline animal model of pulmonary hypertension.[17]

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Reductions in NO production and eNOS activity and increases in oxidative stress contribute to endothelial dysfunction in patients with PAH.[18, 19] Statins inhibit proliferation, induce apoptosis, and cause vasorelaxation in vascular smooth muscle cells, enhance expression and activity of eNOS in endothelium, and reduce oxidative stress and inflammation.[20–24] Several studies have demonstrated the efficacy of statins in animal models of pulmonary hypertension.[25–32] Uncontrolled human studies of simvastatin have also suggested benefit in patients with PAH.[33, 34] One recently-published randomized clinical trial (RCT) showed that simvastatin decreased right ventricular mass and plasma N-terminus pro-brain natriuretic peptide (NT-proBNP), but had no effect on six-minute walk distance (6MWD) in patients with PAH.[35]

Aspirin and simvastatin have potential for the treatment of PAH by targeting platelet activation and endothelial dysfunction. We aimed to show the feasibility of studying these therapies and to get estimates of efficacy and safety in a Phase II RCT. We hypothesized that the 6MWD at six months would be greater in subjects with PAH assigned to aspirin or simvastatin than to the respective placebo after adjustment for baseline 6MWD.

Methods

Study Design

ASA-STAT was a four-center, randomized, double-blind, placebo-controlled 2 × 2 factorial study to determine the efficacy and safety of aspirin and simvastatin in patients with PAH. Details of the methods have been published elsewhere.[36] (See Supplemental Material.) The initial protocol called for the recruitment of 128 subjects with PAH (anticipating 100 completers) over approximately three years. The first patient was randomized in January 2007 and a total of 65 were randomized by September 2009, when the study was terminated (See below).

The trial protocol was approved by the institutional review board at each participating center and the Data Safety and Monitoring Board (DSMB). The trial was registered at clinicaltrials.gov before initiating recruitment (NCT00384865).

Study Participants

We included patients > 18 years of age with PAH without an indication for aspirin or statin therapy and without risk factors for adverse events from these medications (Table E1, Supplemental Material). Participants were recruited from four pulmonary vascular disease clinics (Columbia University College of Physicians and Surgeons, New York City, NY; Johns Hopkins University, Baltimore, MD; Tufts Medical Center, Boston, MA; University of Pennsylvania School of Medicine, Philadelphia, PA). All participants provided written informed consent.

Study Procedures

Patients were identified by medical staff. Subjects were randomly assigned in a 1:1:1:1 ratio by a Web-based computerized system to enteric coated aspirin 81 mg (Tiny Tablets, Bayer HealthCare LLC, Morristown, NJ) once daily/simvastatin 40 mg (Zocor, Merck & Co., Whitehouse Station, NJ) once daily, aspirin 81 mg once daily/simvastatin placebo once daily, aspirin placebo once daily/simvastatin 40 mg once daily, or aspirin placebo once daily/simvastatin placebo once daily. The randomization scheme was random permuted block, stratified by type of PAH (idiopathic/heritable vs. other) and center. All subjects and study personnel (other than the Data Coordinating Center (DCC) Chair and research pharmacy) were masked to treatment assignment and were not unmasked until the study was completed. Subjects were evaluated at baseline, six weeks, three months, and six months.[36]

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The primary outcome was the 6MWD at six months after randomization after adjustment for the baseline 6MWD. Secondary outcomes included 6MWD, measures of platelet activation (serum TxB_2, plasma β-thromboglobulin (β-TG), and soluble P-selectin levels) and endothelial function (brachial artery flow-mediated dilation (FMD) and plasma von Willebrand factor (vWF) levels), NT-proBNP levels, C-reactive protein (CRP) levels, oxidized low-density lipoprotein levels, WHO functional class, Borg dyspnea score, and Short Form-36 (SF-36) scores at six weeks, three months and six months after randomization. We assessed time to clinical worsening (defined by the addition of new PAH therapies or dose increases in previously stable PAH therapy, hospitalization for right-sided heart failure, lung transplantation, atrial septostomy, and cardiovascular and all-cause death). End point and bleeding definitions and details of end point assessments are provided in the Supplemental Material and have been published.[36]

Study Monitoring

Details of study monitoring are provided in the Supplemental Material.[36] The enrollment period lasted from January 2007 to September 2009. In July 2009, the DSMB requested a conditional power calculation by the DCC using the subjects enrolled to that point. This showed that the trial had a 4.9% chance of detecting a statistically significantly higher 6MWD for simvastatin vs. placebo. The DSMB determined that continuing the study with only the aspirin vs. placebo comparison would lead to a study with low scientific credibility and recommended study termination. The DSMB recommended that subjects currently active in the trial at that time (N = 16) should discontinue receiving all study drugs and should not be followed or undergo any additional study procedures. The DSMB reported that there were no significant safety concerns related to the recommendation for termination. The NHLBI accepted these recommendations, and active subjects stopped study medications and did not return to the Field Centers or have telephone follow-up after September 25, 2009.

Statistical Analysis

The primary end point of the trial was the 6MWD at six months after randomization after adjustment for the baseline 6MWD. Preliminary data suggested that a difference of > 50 m in 6MWD was associated with an improvement in symptoms and survival. A total of 100 subjects (25 in each of the four randomized groups, 50 in each active drug and placebo group) was necessary to detect a difference of 57 m with 80% power assuming no significant interaction between study drugs and without adjustment for the baseline 6MWD. With a significant interaction between study medications, we had 80% power to detect a difference of 80 m. Anticipating 20% attrition, we initially planned for the enrollment of 128 subjects. In May 2009, the DSMB requested revised sample size calculations (See Supplemental Material). The revised sample size of 92 was approved by the DSMB and NHLBI on June 4, 2009.

The primary analysis proceeded according to the intent-to-treat principle. Hypothesis testing for the primary and secondary end points was conducted using two-sided $\alpha = 0.05$. There was no observed clinically relevant statistical interaction between the study medications (See Protocol),[36] so all analyses proceeded “at the margins” by comparing patients assigned to aspirin to those who were assigned to aspirin placebo and comparing those assigned to simvastatin compared to those who were assigned to simvastatin placebo.

Continuous variables are presented as mean ± standard deviation or median (interquartile range (IQR)) and categorical variables as n (%). Skewed variables were natural log transformed before analysis. The analysis of the primary end point compared the absolute 6MWD at six month follow-up between active therapy and placebo groups while adjusting

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for the baseline 6MWD using linear regression models. Multiple imputation was performed for subjects without a six month 6MWD in the primary analysis (See Supplemental Material for details). Secondary analyses incorporated all of the available end point assessments (six weeks, three months, and six months) without imputation in linear mixed-effects models with adjustment for baseline values. There were no interim analyses or stopping rules planned *a priori* for the trial. Other analyses are described in the Supplemental Material.[36]

Results

We screened 712 PAH patients during the enrollment period from January 2007 to September 25, 2009. Of the adjusted target sample of 92, 65 were randomized and 49 had completed the six month assessment at study termination (3 died, 1 withdrew consent, and 12 were active in the trial and had not yet had their six month study visits) (Figure 1). One subject completed the study but was unable to perform the walk at the six month assessment. At study termination, 59 of the 65 randomized subjects had undergone at least one outcome assessment.

The mean age of the participants was 50.5 ± 13.9 yrs and 56 (86.1%) were female. Thirty-nine (60.0 %) were non-Hispanic white, 9 (13.9%) were Hispanic, 13 (20.0%) were black, and 3 (4.6%) were Asian. Thirty-three (51.6%) had idiopathic PAH, 3 (4.7%) had heritable PAH, 12 (18.8%) had PAH associated with systemic sclerosis, 9 (15.3%) had PAH associated with other connective tissue diseases, and 6 (9.2%) had congenital systemic-to-pulmonary shunts. Those enrolled were somewhat younger, but similar in terms of gender and race, to those screened and not enrolled (Table E2, Supplemental Material).

Aspirin vs placebo

Thirty-two subjects were randomized to aspirin and 33 were randomized to placebo (Table 1). The two groups were similar in terms of demographics. Subjects randomized to aspirin had a somewhat higher prevalence of idiopathic/heritable PAH than other forms, more frequent use of sildenafil, somewhat lower WHO functional class, and somewhat higher baseline 6MWD. Combination therapy was common, and most patients were treated with warfarin. Six subjects discontinued the aspirin study drug (2 aspirin, 4 placebo) (Figure 1). One participant was started on non-study aspirin after she was diagnosed with coronary artery disease. One patient stopped aspirin study drug for epigastric pain, one had a decrease in hemoglobin without clinical bleeding, one had a new gastic ulcer with bleeding, one had light-headedness, and one without providing a reason. Compliance with the study drug was > 95%.

There was no difference in 6MWD between aspirin and placebo groups at six months after adjustment for baseline 6MWD [least squares means, 438.0 m (95%CI, 415.9–460.1 m) vs. 438.5 m (95%CI, 419.2–457.8 m), respectively, p = 0.97] (n = 65). The placebo-corrected difference in 6MWD at six months was −0.5 m (95%CI, −28.4– 27.4 m). Median post-walk Borg dyspnea scores at six months were similar between the groups (aspirin, 3 (IQR, 2–4) vs placebo, 3 (IQR, 2–4), p = 0.39). Analyses including the 6MWD from all post-randomization visits without imputation after adjustment for baseline showed similar results (Figure 2A).

Aspirin reduced serum TxB_2 levels by 93% compared to placebo (Figure 2B), suggesting that the study drug had the expected effect on eicosanoid metabolism. However, there were no differences in soluble P-selectin, β-TG, or NT-proBNP levels between the groups (Figures E1A–C, Supplemental Material). There were no differences in any scales of the SF-36 (Table E3, Supplemental Material) or in WHO functional class (Data not shown).

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All clinical worsening events are shown in Table E4 in the Supplemental Material. Subjects receiving aspirin had two clinical worsening events and subjects receiving placebo had six events (p = 0.19) There was no difference in time to clinical worsening between the groups (p = 0.35) (Figure E2, Supplemental Material).

We performed prespecified subset analyses in patients with baseline 6MWD < 450 m (n = 32); there were no differences in the results from the full sample (Data not shown). In patients with idiopathic or heritable PAH, we found that aspirin may have lowered soluble P-selectin levels (p = 0.07), but did not impact on the 6MWD (Figure E3, Supplemental Material). Other results were similar to those from the main analysis (Data not shown).

Adverse events in the aspirin and placebo groups are shown in Table 2. There were no differences in the numbers of minor (p = 0.87) bleeding episodes between the groups, but there may have been an increase in major bleeding episodes in subjects treated with aspirin (p = 0.17). There were no differences in safety laboratory results between the groups (Data not shown).

Simvastatin vs placebo

Thirty-two subjects were randomized to simvastatin and 33 were randomized to placebo (Table 3). The two groups were similar in terms of demographics and type of PAH. Patients randomized to simvastatin had somewhat higher right ventricular systolic pressure by transthoracic echocardiography, but WHO functional class and 6MWD at baseline were similar between the groups. More than 60% of both groups were treated with sildenafil either as monotherapy or in combination therapy. Five subjects discontinued the simvastatin study drug (2 simvastatin, 3 placebo) (Figure 1). One participant was diagnosed with coronary artery disease and pravastatin was prescribed. Two patients discontinued for myalgias, one for headaches, and one without providing a reason. Compliance with the study drug was > 95%.

There was no difference in 6MWD between simvastatin and placebo groups at six months after adjustment for baseline 6MWD (least squares means, 425.0 m (95% CI, 400.2–449.9 m) vs 452.7 m (95% CI, 431.9 – 473.4 m), respectively, p = 0.09) (n = 65) with a placebo-corrected difference in 6MWD of −27.6 m (95%CI, −59.6–4.3 m), indicating that simvastatin may have reduced the 6MWD. Additionally, median post-walk Borg dyspnea scores at six months tended to be higher in the subjects assigned to simvastatin, suggesting greater breathlessness [simvastatin, 3 (IQR, 2–4) vs. placebo, 3 (IQR, 2–4) (p = 0.07)]. Analyses including the 6MWD from all post-randomization visits without imputation after adjustment for baseline 6MWD were also consistent with lower 6MWD in the group randomized to simvastatin (Figure 3A).

Simvastatin significantly decreased total cholesterol, low-density lipoprotein (LDL), and oxidized LDL levels (Figures 3B–D) compared to placebo, but did not affect triglycerides or high-density lipoprotein (HDL) levels (Figures E4A–B, Supplemental Material), consistent with the expected effects. However, there were no differences in levels of vWF, CRP, or NT-proBNP or FMD between the groups (Figures E5A–D, Supplemental Material). There were no differences in any scales of the SF-36 (Table E5, Supplemental Material) or in WHO functional class (Data not shown).

All clinical worsening events are shown in Table E6 in the Supplemental Material. Subjects receiving simvastatin and subjects receiving placebo each had four events (p = 0.33). There was no difference in time to clinical worsening between the groups (p = 0.80) (Figure E6, Supplemental Material).

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We performed prespecified subset analyses in patients with baseline 6MWD < 450 m (n = 32); there were no differences in the results from the full sample (Data not shown). In patients with idiopathic or heritable PAH, we found that simvastatin did not impact on the 6MWD (Figure E7, Supplemental Material). Other results were similar to those from the main analysis (Data not shown).

Adverse events in the simvastatin and simvastatin placebo groups are shown in Table 4. There was no difference in adverse events between the groups. There were no differences in safety laboratory results between the groups (Data not shown).

Discussion

This is the first RCT of traditional cardiovascular disease therapies targeting platelet and endothelial function and the first NIH-funded RCT in patients with PAH. Neither aspirin nor simvastatin had a significant effect on the primary end point of 6MWD at six months. If anything, 6MWD may have decreased and post-walk Borg dyspnea scores increased with simvastatin. While aspirin lowered serum TxB_2 levels, other traditional markers of platelet activation such as soluble P-selectin levels (except possibly in idiopathic/heritable PAH) and β-TG were not altered. There was a possible increased risk of major bleeding associated with aspirin use. While simvastatin lowered total cholesterol and LDL levels, there was no effect on other vascular or plasma markers of endothelial dysfunction or injury (FMD and vWF) or CRP. Simvastatin significantly lowered oxidized LDL levels, which reflect oxidative stress. Neither aspirin nor simvastatin affected NT-proBNP levels. The effects of aspirin and simvastatin on serum TxB_2 and lipid levels respectively provided evidence that subjects were compliant with the study medication and that the medications had their traditional effects in patients with PAH. Early termination of the trial for futility in detecting a positive effect of simvastatin on the 6MWD limited the power of some analyses. However, none of the point estimates for the end points suggested benefit, and the precision of the estimates of 6MWD was good, making it less likely that low power accounted for the results.

Aspirin reduced production of Tx both in the current study and in our previous study in idiopathic PAH, in which platelet aggregation was also significantly inhibited by low-dose aspirin.[2] Since Tx:PGI_2 ratio is elevated in PAH and platelet aggregation is thought to contribute to disease pathogenesis, it was hypothesized that platelet inhibition with aspirin would translate to clinical benefit in terms of exercise capacity. While aspirin suppressed production of TxB_2 by > 90%, there was no effect on 6MWD, NT-proBNP, or quality-of-life. This suggests that platelet Tx production does not contribute significantly to disease manifestations in PAH. One previous trial of a Tx synthase inhibitor was performed in PAH,[37] but it was terminated prematurely due to an excess of side effects (leg pain) and did not show a clinical benefit.

While aspirin did lower serum TxB_2, the effect was somewhat less than the 97–99% TxB_2 suppression usually seen with aspirin.[38] This suggests either aspirin resistance or another source of Tx unaffected by low dose aspirin (e.g., vascular endothelium). The lack of change of β-TG levels and borderline reductions in soluble P-selectin levels are also consistent with aspirin resistance. Ongoing vascular injury could also account for the smaller impact of aspirin on soluble P-selectin levels compared to that seen in normals.

There were no differences in health-related quality-of-life with aspirin. There tended to be fewer clinical worsening events in the aspirin group, but there was also a somewhat higher incidence of major bleeding events. We were unable to assess the interaction of aspirin with warfarin due to the small number of events.

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Simvastatin has a significant effect on pulmonary vascular disease and RV changes in a variety of animal models. We have shown that statins impact on pulmonary hypertension and vascular remodeling in the chronically hypoxic rat model.[25, 31, 39] Other studies have reproduced these findings in the monocrotaline animal model, but not universally.[26, 40, 41] There have been two previous small RCTs of statins in patients with PAH. One studied the effect of rosuvastatin in patients with PAH which was idiopathic or associated with congenital heart disease.[42] There were no statin-associated differences in 6MWD or other biomarkers. Wilkins et al. performed a placebo-controlled, double-blind RCT of simvastatin in 43 patients with PAH which was idiopathic, heritable, or associated with atrial septal defect or connective tissue disease.[35] Simvastatin significantly reduced right ventricular mass and plasma NT-proBNP at six months, changes which were not maintained at one year. Notably, there was no effect of simvastatin on 6MWD, other RV parameters, quality-of-life, or other biomarkers.

In the current study, simvastatin did not improve 6MWD, biomarkers of endothelial dysfunction and injury, or quality-of-life. If anything, there were trends toward decreased 6MWD and more dyspnea in patients randomized to simvastatin. These results suggest that simvastatin is not effective as “add-on” therapy in PAH. Systemic side effects, such as myalgia and arthralgia, could have impacted on the measured response to the study medication. However, an increasing Borg dyspnea score after the six-minute walk suggested respiratory limitation.

Studying PAH patients receiving background therapy makes it more difficult to conduct trials of new therapies focused on clinically meaningful end points within a reasonable period of time. Since patients in clinical trials much receive the “standard-of-care”, this is the only ethically justifiable approach to intermediate or long-term placebo-controlled trials in the era of available effective therapy.

Our study has several limitations. The primary end point which should be used in early-stage clinical trials in PAH is uncertain. We chose the 6MWD because it is the one upon which all PAH therapies have been approved; an effective treatment should show some signal in terms of this measure. Available therapies for PAH which increase the 6MWD often improve long-term clinical outcomes, although 6MWD has not been validated as a surrogate end point.[43] However, it remains possible that the active treatment had some favorable effect that went undetected. The development and validation of surrogate end points which change over a short period of time and reliably predict clinically meaningful outcomes is an unmet need in the field.

We did not include invasive hemodynamic end points. Measuring pulmonary hemodynamics as a secondary outcome would have been of interest, but for pragmatic reasons, could not be done. The requirement for multiple right heart catheterizations on otherwise stable, treated patients would have rendered the recruitment much more difficult and the study much more expensive, making the trial infeasible. While there is no specific biomarker “read-out” for pulmonary vascular function, the absence of any effect of the study drugs on NT-proBNP suggests that there was no impact on hemodynamics. Whether either agent had other long-term benefits beyond six months was not assessed.

This study was terminated due to a high likelihood of not rejecting the null hypothesis for the simvastatin arm even if fully recruited. Subjects were not followed or reassessed after study termination, leading to missing data for those active subjects in the trial at termination (n = 16). These missing data may have introduced bias, even though such data should be “missing completely at random”. The results and conclusions were similar whether we multiply imputed missing data or performed analyses with only the available data, making

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significant bias less likely. While even effective drugs may have reduced impact in the setting of background therapy in PAH, simvastatin was associated with a decrease in 6MWD and there was essentially no change in 6MWD with aspirin, making inadequate power an unlikely explanation for our results. Results from the subgroup with IPAH and heritable PAH did not differ from those of the main study; other disease subgroups were not large enough for meaningful analyses.

In summary, we have shown that while simvastatin 40 mg each day lowers total cholesterol, LDL, and oxidized LDL, there was no effect on 6MWD or biomarkers of endothelial dysfunction or injury in PAH. Similarly, while aspirin 81 mg each day reduced TxB_2 production and may have lowered soluble P-selectin levels (in IPAH), there was no effect on 6MWD and possibly increased the risk of major bleeding. Based on these findings, neither drug can be recommended for the treatment of PAH. These drugs should be used according to usual indications in PAH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Commentary

Pulmonary arterial hypertension (PAH) is a progressive disease which causes exercise limitation, heart failure, and death. Aspirin and simvastatin have powerful effects on atherosclerosis, but have not been studied in PAH. We performed a randomized, double-blind, placebo-controlled 2 × 2 factorial clinical trial of aspirin and simvastatin in patients with PAH receiving background therapy at four centers. Sixty-five subjects were randomized when the trial was terminated by the DSMB after an interim analysis showed futility in reaching the primary end point for simvastatin. After adjustment for baseline 6MWD, there was no significant difference in the 6MWD at six months between aspirin (n = 32) and placebo (n = 33) [placebo-corrected difference = −0.5 m (95%CI, −28.4 – 27.4 m), p = 0.97] or between simvastatin (n = 32) and placebo (n = 33) [placebo-corrected difference = −27.6 m (95%CI, −59.6 – 4.3 m), p = 0.09]. This trial did not show any clinical benefit with the use of aspirin or simvastatin in patients with PAH. Traditional indications for these drugs should guide their use in patients with PAH.

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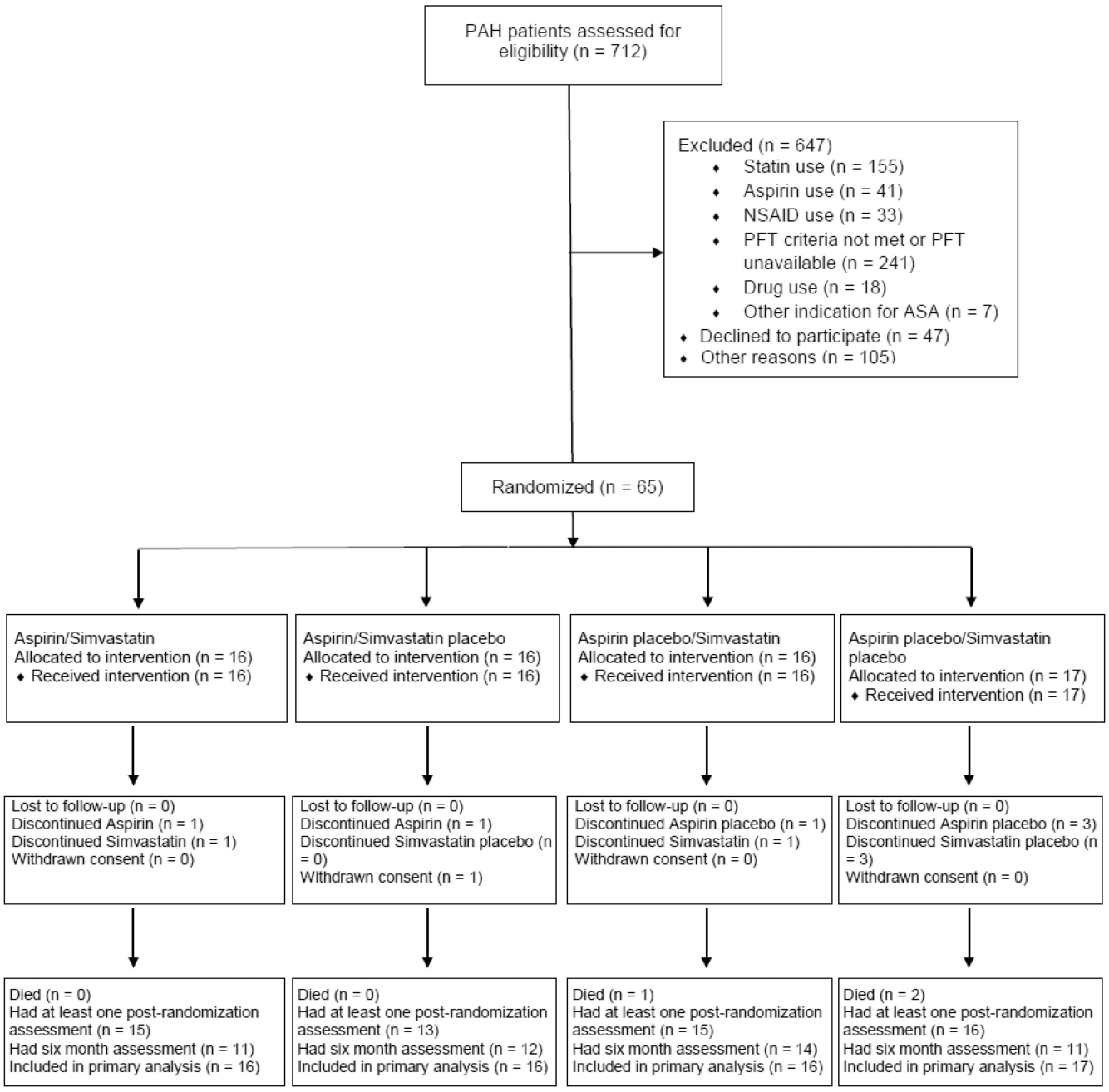

Figure 1.
Flow diagram

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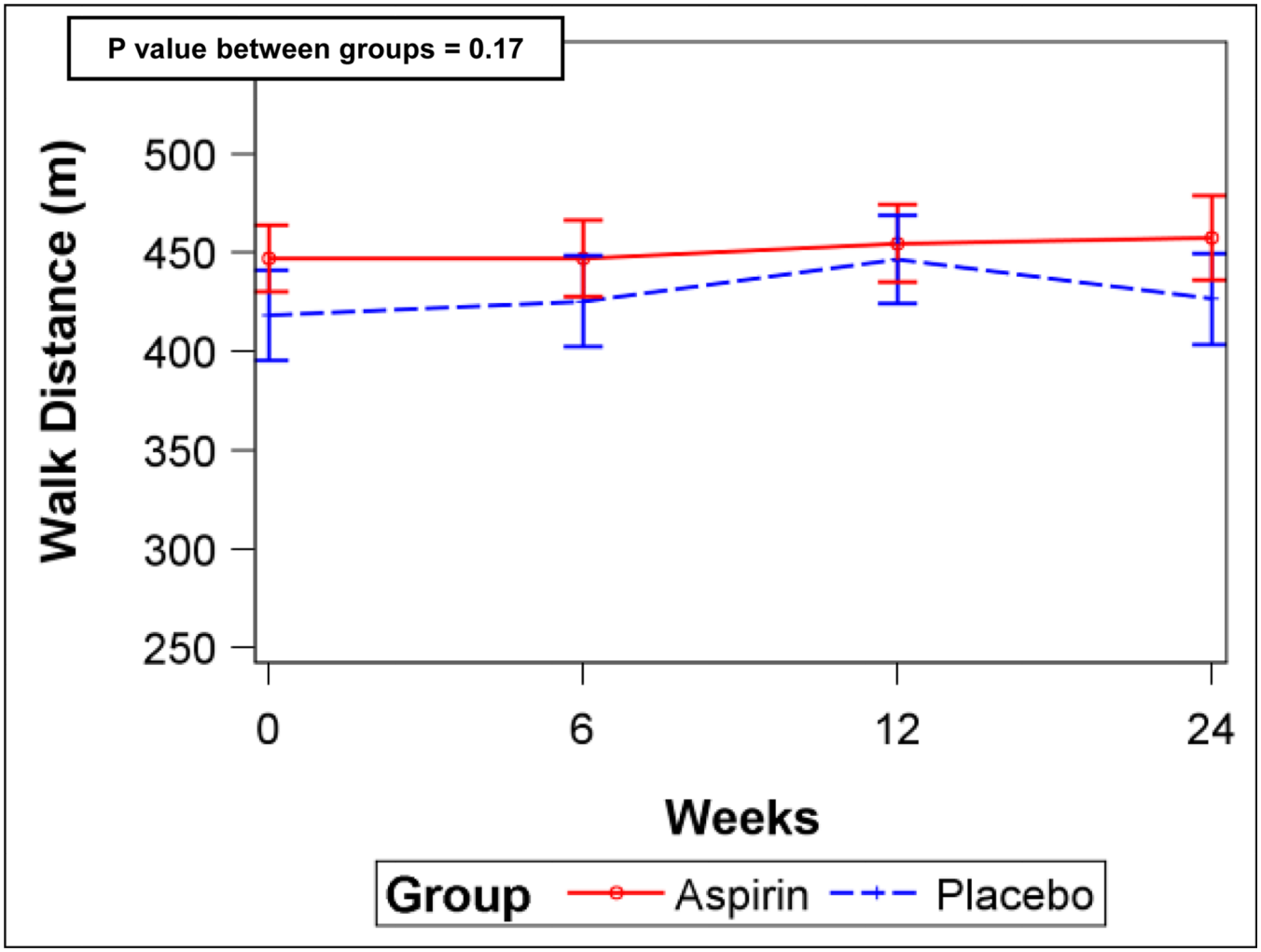

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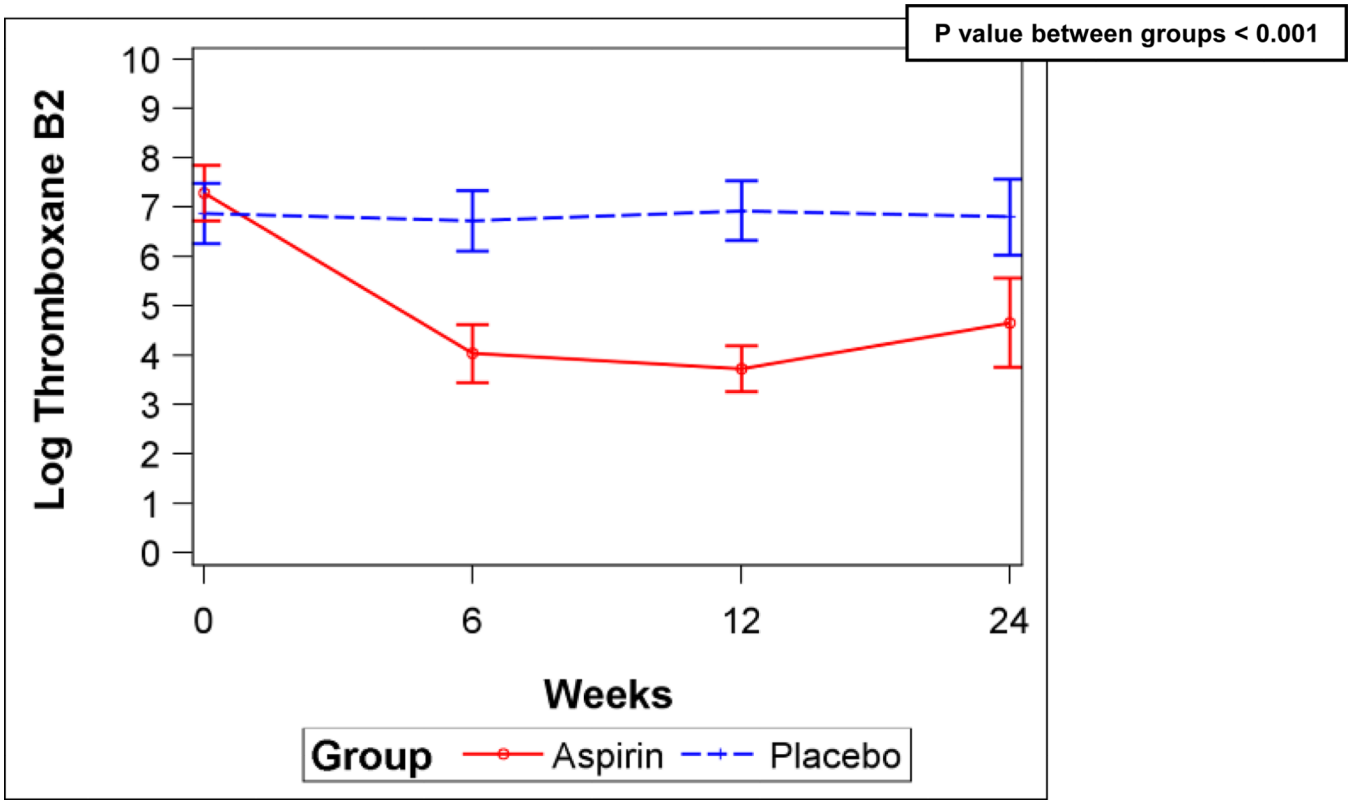

Figure 2.

A) Six-minute walk distance for aspirin and placebo (error bars are 95% confidence intervals). B) Serum ln (TxB_2) levels for aspirin and placebo. P values from linear mixed-effects models.

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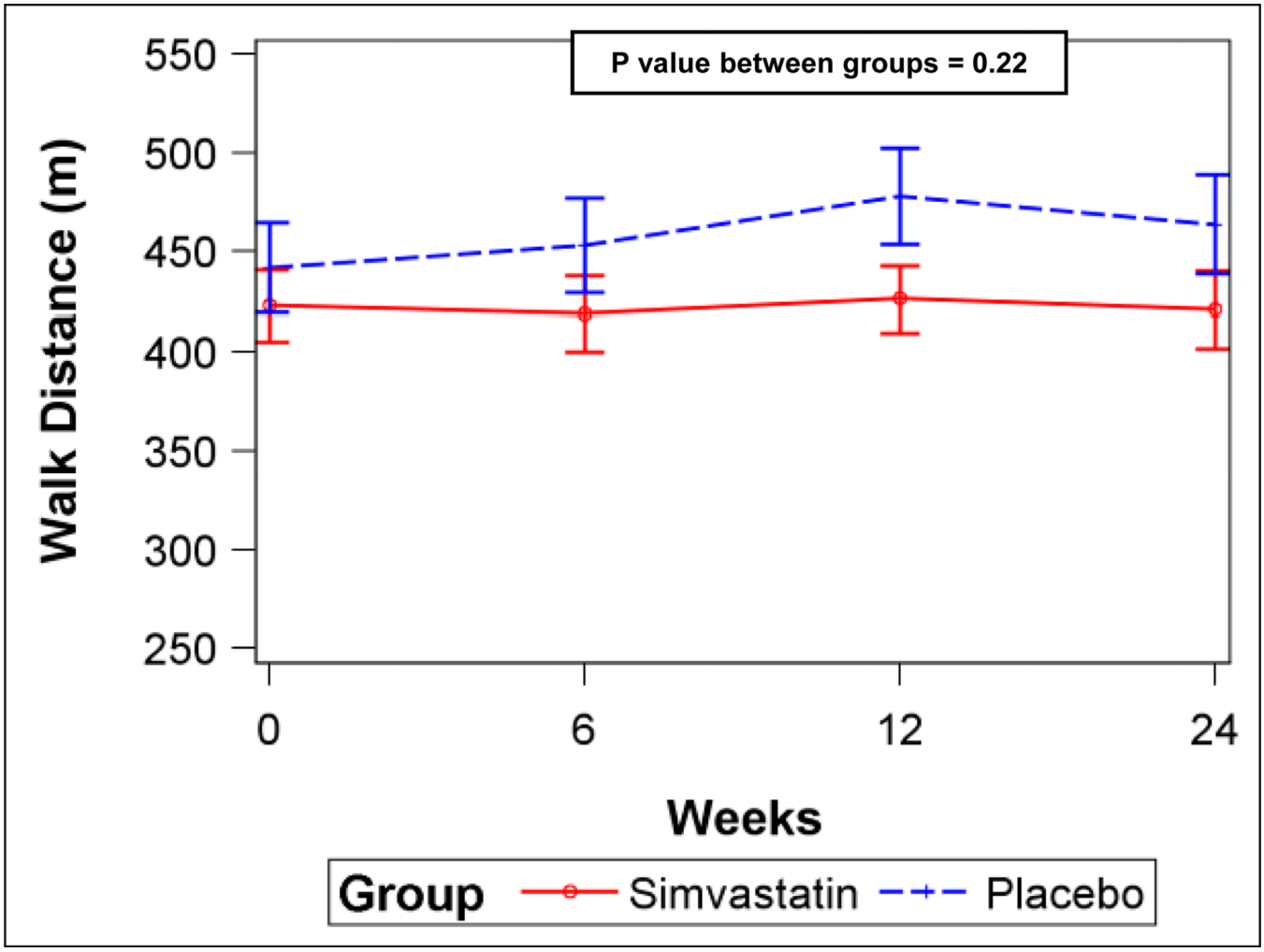

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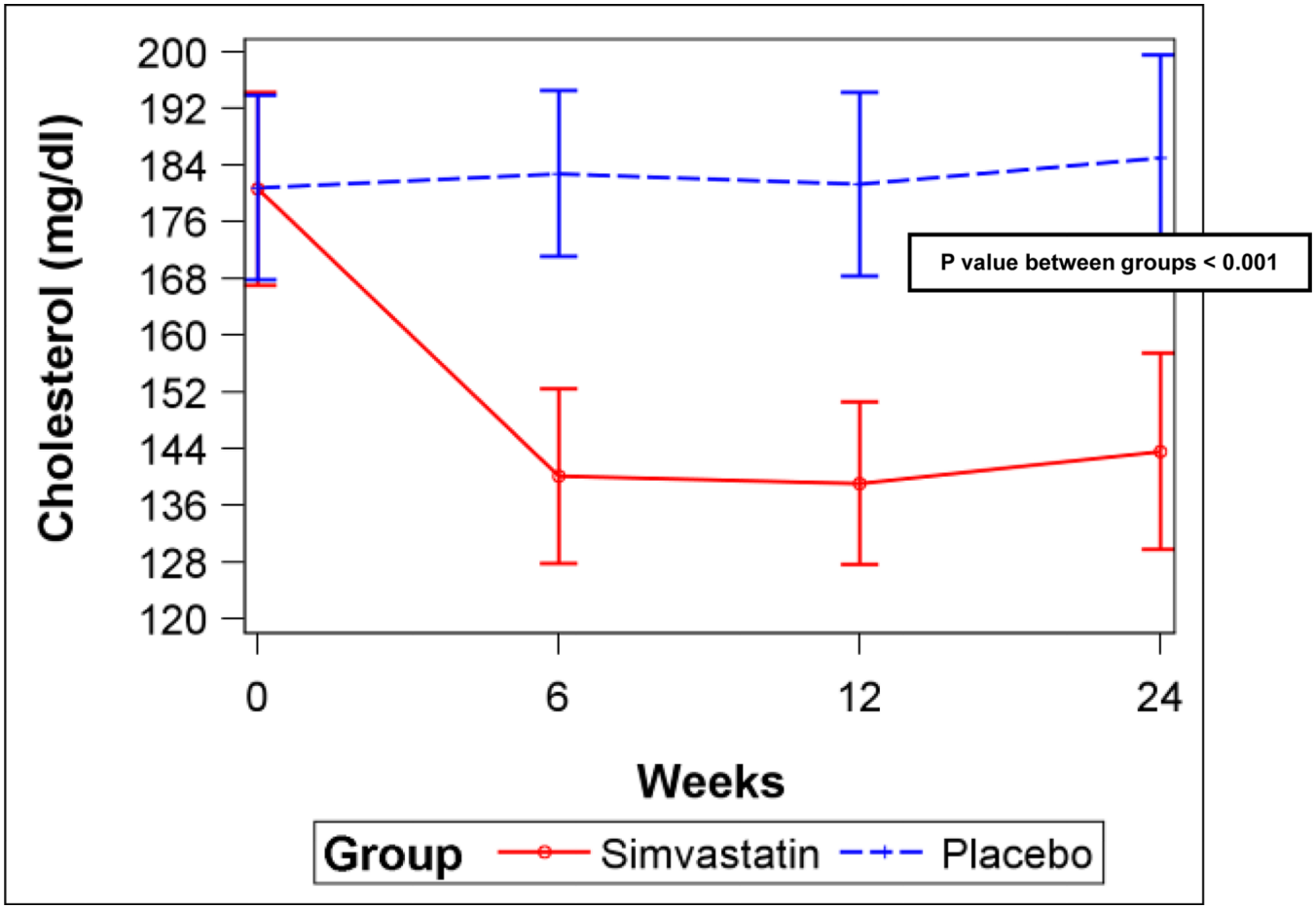

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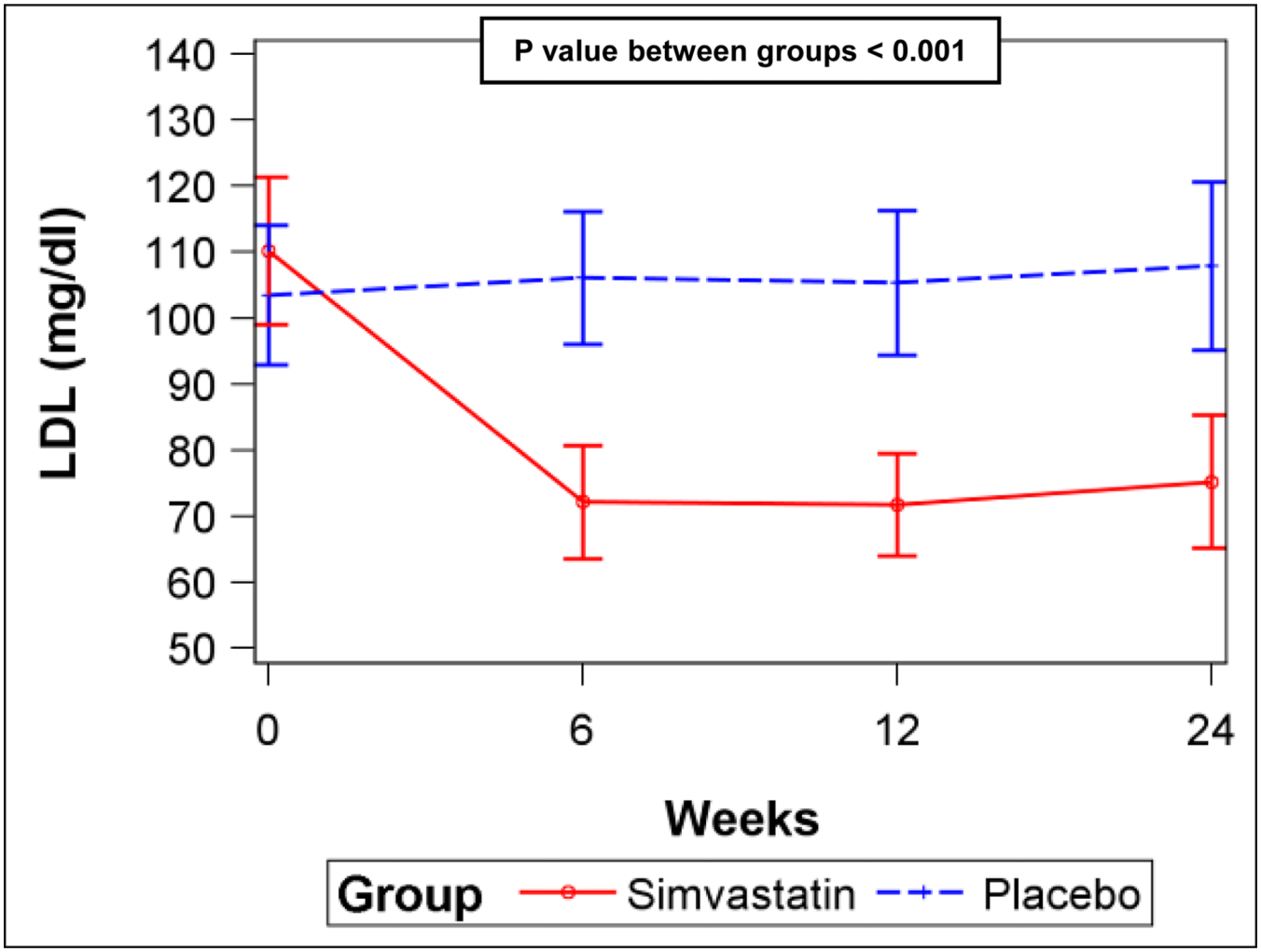

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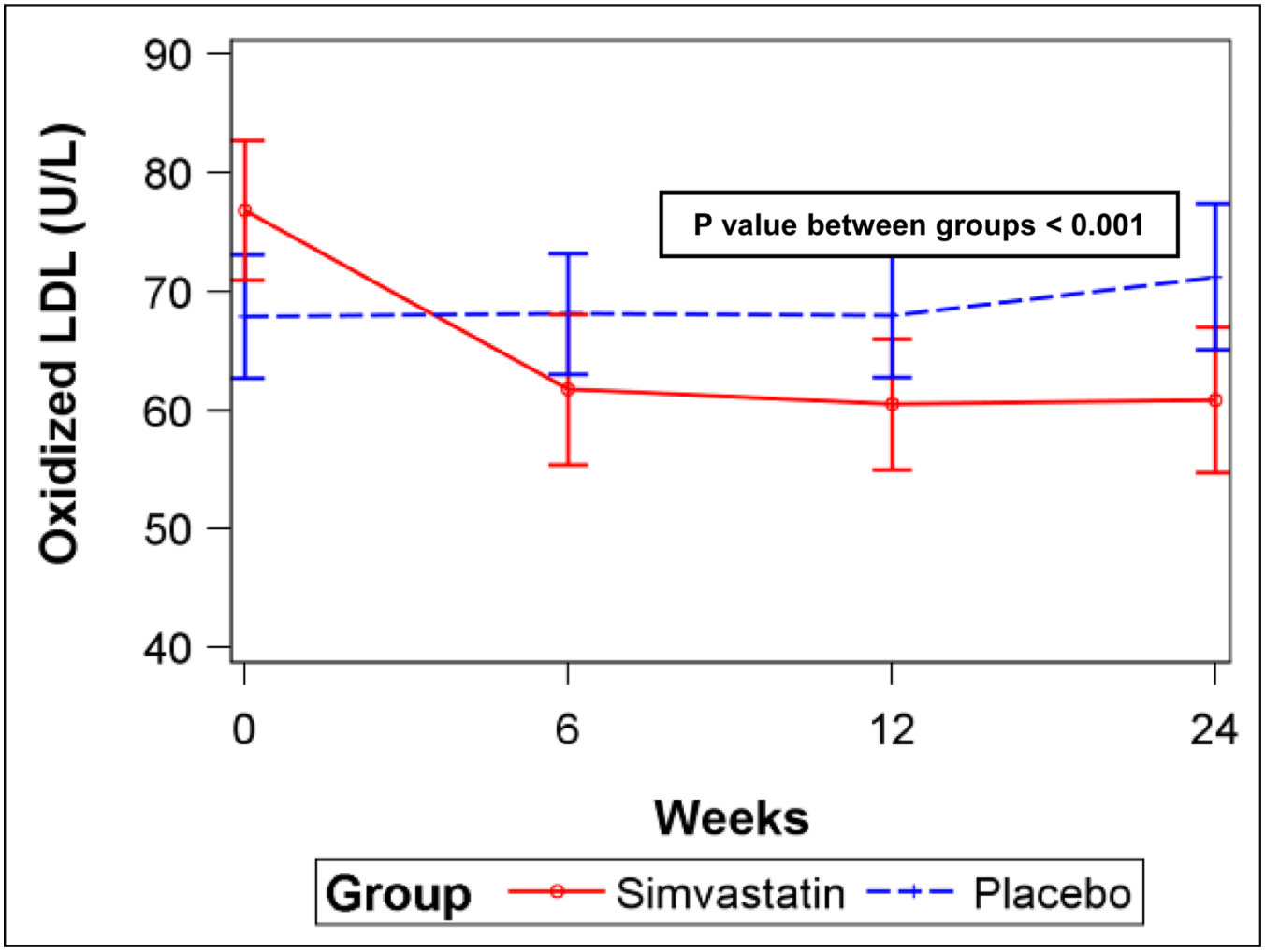

Figure 3.
A) Six-minute walk distance for simvastatin and placebo (error bars are 95% confidence intervals). B) Serum total cholesterol levels for simvastatin and placebo. C) Serum low-density lipoprotein (LDL) levels for simvastatin and placebo. D) Plasma oxidized low-density lipoprotein (LDL) levels for simvastatin and placebo. P values from linear mixed-effects models.

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Table 1

Baseline characteristics of subjects randomized to aspirin and placebo

		Placebo (n = 33)	Aspirin (n = 32)
Age,yrs		51.7 ± 13.0	49.2 ± 14.7
Gender, Female		30 (90.9)	26 (81.2)
Body mass index, kg/m^2		28.6 ± 7.8	27.4 ± 6.2
Race/ethnicity			
	White (Non-Hispanic)	17 (51.5)	22 (68.8)
	Hispanic or Latino	6 (18.2)	3 (9.4)
	Black	8 (24.2)	5 (15.6)
	Asian	2 (6.1)	1 (3.1)
	Other	0	1 (3.1)
PAH diagnosis			
	Idiopathic	14 (42.4)	19 (61.3)
	Heritable	2 (6.1)	1 (6.2)
	Congenital systemic-to-pulmonary shunt	4 (12.1)	2 (6.3)
	Systemic sclerosis	8 (24.2)	4 (12.9)
	Other connective tissue disease	5 (15.1)	4 (12.5)
	Drugs/toxins	0	2 (6.5)
Right ventricular systolic pressure by echocardiography	(n=57)	69.5 (53–91)	70.0 (56–87)
Concomitant medications			
	Ambrisentan	8 (24.2)	10 (31.3)
	Bosentan	12 (36.4)	6 (18.8)
	Epoprostenol	8 (24.2)	7 (21.9)
	Iloprost (inhaled)	4 (12.1)	5 (15.6)
	Sildenafil	16 (48.5)	26 (81.3)
	Treprostinil (intravenous)	3 (9.1)	2 (6.3)
	Combination therapy	17 (51.5)	23 (71.9)
	Warfarin	28 (84.8)	23 (71.9)
WHO functional class			
	Class I	4 (12.1)	1 (3.1)
	Class II	17 (51.5)	24 (75)
	Class III	12 (36.4)	7 (21.9)
Six minute walk distance, m		418.3 ± 131.7	447.3 ± 96.1
Post-test Borg dyspnea score		3 (2–3)	3 (2–3)

Data shown as mean ± standard deviation, median (interquartile range), or n (%).

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Table 2

Frequency of adverse events of subjects randomized to aspirin and placebo

	Placebo (n = 33)	Aspirin (n = 32)
Upper respiratory infection	11 (33.3)	10 (31.3)
Bruising	8 (24.2)	8 (25.0)
Myalgia	5 (15.2)	3 (9.4)
Headache	3 (9.1)	5 (15.6)
Other infections	4 (12.1)	4 (12.5)
Diarrhea	4 (12.1)	3 (9.4)
Dyspnea	4 (12.1)	2 (6.3)
Rash	3 (9.1)	3 (9.4)
Arthralgia	3 (9.1)	3 (9.4)
Chest pain	3 (9.1)	1 (3.1)
Increased transaminases	3 (9.1)	1 (3.1)
Insomnia	2 (6.1)	1 (3.1)
Number of bleeding episodes		
Minor	12	11
Major	1	4

Data shown as n (%).

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Table 3

Baseline characteristics of subjects randomized to simvastatin and placebo

		Placebo (n = 33)	Simvastatin (n = 32)
Age,yrs		51.0 ± 13.6	50.0 ± 14.3
Gender, Female		30 (90.9)	26 (81.2)
Body mass index, kg/m^2		27.8 ± 6.5	28.1 ± 7.7
Race/ethnicity			
	White (Non-Hispanic)	20 (60.6)	19 (59.4)
	Hispanic or Latino	2 (6.1)	7 (21.9)
	Black	8 (24.2)	5 (15.6)
	Asian	3 (9.1)	0
	Other	0	1 (3.1)
PAH diagnosis			
	Idiopathic	17 (53.1)	16 (50)
	Heritable	1 (3.1)	2 (6.3)
	Congenital systemic-to-pulmonary shunt	1 (3)	5 (15.6)
	Systemic sclerosis	7 (21.2)	5 (15.6)
	Other connective tissue disease	5 (15.2)	4 (12.5)
	Drugs/toxins	2 (6.3)	0
Right ventricular systolic pressure by echocardiography, mm Hg	(n=57)	63.5 (50–81)	82.0 (59–100)
Concomitant medications			
	Ambrisentan	10 (30.3)	8 (25.0)
	Bosentan	9 (27.3)	9 (28.1)
	Epoprostenol	6 (18.9)	9 (28.1)
	Iloprost (inhaled)	5 (15.2)	4 (12.5)
	Sildenafil	21 (63.6)	21 (65.6)
	Treprostinil (intravenous)	3 (9.1)	2 (6.3)
	Combination therapy	22 (66.7)	18 (56.3)
	Warfarin	23 (69.7)	28 (87.5)
WHO functional classification			
	Class I	5 (15.2)	0
	Class II	18 (54.6)	23 (71.9)
	Class III	10 (30.3)	9 (28.1)
Six minute walk distance, m		442.0 ± 128.8	422.9 ± 101.4
Post-test Borg Dyspnea Score		3 (2–3)	3 (2–3)

Data shown as mean ± standard deviation, median (interquartile range), or n (%).

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Table 4

Frequency of adverse events of subjects randomized to simvastatin and placebo

	Placebo (n = 33)	Simvastatin (n = 32)
Bleeding	13 (39.4)	14 (43.8)
Upper respiratory infection	9 (27.3)	12 (37.5)
Bruising	6 (18.2)	10 (31.3)
Myalgia	5 (15.2)	3 (9.4)
Headache	3 (9.1)	5 (15.6)
Other infections	4 (12.1)	4 (12.5)
Diarrhea	4 (12.1)	3 (9.4)
Dyspnea	3 (9.1)	3 (9.4)
Rash	2 (6.1)	4 (12.5)
Arthralgia	2 (6.1)	4 (12.5)
Chest pain	3 (9.1)	1 (3.1)
Increased transaminases	2 (6.1)	2 (6.3)
Insomnia	2 (6.1)	1 (3.1)

Data shown as n (%).