Effect of fluticasone propionate/salmeterol on arterial stiffness in patients with COPD

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KEYWORDS
Augmentation index; Computed tomography scanning; Emphysema; Aortic pulse wave velocity

Summary
Background: COPD is associated with increased arterial stiffness which may in part explain the cardiovascular morbidity observed in the disease. A causal relationship between arterial stiffness and cardiovascular events has not been established, though their strong association raises the possibility that therapies that reduce arterial stiffness may improve cardiovascular outcomes. Prior studies suggest that fluticasone propionate/salmeterol (FSC) may improve cardiovascular outcomes in COPD and we hypothesized that FSC would reduce arterial stiffness in these patients.

Methods: This multicenter, randomized, double-blind, placebo-controlled study compared the effects of FSC 250/50 μg twice-daily and placebo on aortic pulse wave velocity (aPWV) as determined by ECG-gated carotid and femoral artery waveforms. The primary endpoint was aPWV change from baseline at 12-weeks (last measure for each patient).

Results: 249 patients were randomized; the mean FEV1 in each group was similar (55% predicted) and 60% of patients reported a cardiovascular disorder. At 12-weeks, aPWV between FSC and placebo was -0.42 m/s (95%CI -0.88, 0.03; p = 0.065). A statistically significant reduction in aPWV between FSC and placebo was observed in those who remained on study.

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Introduction

Although the past decade has witnessed a significant improvement in the symptomatic treatment of COPD, mortality in patients with the disease remains high. Cardiovascular (CV) disease is a major cause of death and morbidity in COPD and a growing body of epidemiological evidence demonstrates an association between these events and impaired lung function that is independent of smoking. The underlying explanation for this phenomenon remains unclear though possible mechanisms include endothelial dysfunction, elastin degradation and increased sympathetic tone that occur in both the systemic vasculature and the emphysematous lung. These pathologic processes lead to abnormal vascular function and increased arterial stiffness. The latter has recently emerged as an important independent risk factor for CV disease in a number of population-based studies.

Aortic pulse wave velocity (aPWV) is the gold standard for assessing arterial stiffness in research studies and clinical practice, and has been shown to be predictive of CV outcomes. Increased aPWV has been demonstrated in patients with chronic lung disease including those with COPD (in whom it correlates with emphysema severity) and cystic fibrosis. It was recently demonstrated that there is an inverse association between both forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) and aPWV in 800 men from the Caerphilly Prospective study. This finding is supported by another population-based study demonstrating a significant association between pulse pressure, a surrogate for arterial stiffness, and lung function in 13,090 patients enrolled in the NHANES III study.

This evidence suggests that increased arterial stiffness may mediate part of the increased CV risk associated with impaired lung function. Though a causal link between arterial stiffness and CV events has not been established, these data raise the possibility that therapies that decrease arterial stiffness may improve CV outcomes in COPD. Indeed several prior reports have suggested that inhaled steroids (ICS) and the inhaled steroid, long-acting beta agonist combination fluticasone propionate/salmeterol (FSC) may reduce CV events and death in patients with COPD though the underlying mechanism is unclear. Beta-agonists have been shown to increase endothelium derived nitric oxide production and therefore may reduce arterial stiffness in patients with COPD. Studies in other chronic inflammatory conditions have demonstrated increased arterial stiffness and endothelial dysfunction and that both can be mitigated with anti-inflammatory therapy. Inhaled corticosteroids are known to have anti-inflammatory effects and as a result may also have benefits on arterial stiffness. We hypothesized that FSC would reduce arterial stiffness compared with placebo in a group of well characterized COPD patients.

Materials and methods

Study design

This was a multicenter, randomized, double-blind, placebo-controlled study (NCT00857766) conducted in the United States. In order to qualify for the study, patients could not be taking ICS or ICS/LABA combination products 30 days prior to the run-in period. Patients completed a 1–14 day run-in on short acting beta-agonists followed by a 12-week double-blind treatment period. Patients were randomized to fluticasone propionate/salmeterol 250/50 µg twice-daily via DISKUS (FSC; Advair, Seretide, GlaxoSmithKline, Research Triangle Park, NC, USA) or placebo DISKUS twice-daily. After the 12-week treatment period, patients in both treatment arms received open label tiotropium bromide Handihaler 18 µg QD (Boehringer Ingelheim GmbH and Co. KG, Ingelheim, Germany) for 4 weeks in addition to blinded study drug.

Study patients

The study was approved by each institutional review board or ethics committee. All patients provided written informed consent. Patients at least 50 years of age, with a diagnosis of COPD, and a cigarette smoking history of ≥10 pack-years were eligible for the study. In addition, patients were required to have a post-albuterol FEV1 <80% predicted and a FEV1/FVC ratio <0.70. Patients were excluded from the study unless classes and dosing of medicines used for cardiovascular disorders, diabetes, and hyperlipidemia were stable for 3 months prior to enrollment. If a patient started medications for cardiovascular disorders, diabetes or hyperlipidemia at anytime during the conduct of the study they were withdrawn.

Clinical assessments

Aortic PWV (aPWV) was measured at baseline, and weeks 4, 8, 12 and 16 using the SphygmoCor™ system (AtCorMedical, Sydney, Australia) by sequentially recording ECG-gated carotid and femoral artery waveforms and dividing the distance between the two recording sites by the wave transit time. Augmentation Index (Alx) was assessed by radial artery tonometry using the same device.

Patients underwent a multidetector-row CT scan of the chest (minimum 16-slice scanner) between randomization and week 8 for quantitative assessment of emphysema. The lungs were scanned at full inspiration (120 kVp, 100 mAs, slice thickness 1 or 1.25-mm for 16-slice scanners and 0.65 or 0.5-mm for 64 slice scanners). The image reconstruction used a low spatial frequency algorithm (GE standard,

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This evidence suggests that increased arterial stiffness may mediate part of the increased CV risk associated with impaired lung function. Though a causal link between arterial stiffness and CV events has not been established, these data raise the possibility that therapies that decrease arterial stiffness may improve CV outcomes in COPD. Indeed several prior reports have suggested that inhaled steroids (ICS) and the inhaled steroid, long-acting beta agonist combination fluticasone propionate/salmeterol (FSC) may reduce CV events and death in patients with COPD though the underlying mechanism is unclear. Beta-agonists have been shown to increase endothelium derived nitric oxide production and therefore may reduce arterial stiffness in patients with COPD. Studies in other chronic inflammatory conditions have demonstrated increased arterial stiffness and endothelial dysfunction and that both can be mitigated with anti-inflammatory therapy. Inhaled corticosteroids are known to have anti-inflammatory effects and as a result may also have benefits on arterial stiffness. We hypothesized that FSC would reduce arterial stiffness compared with placebo in a group of well characterized COPD patients.
Siemens — b35f). The extent of emphysema was assessed quantitatively as the percent low attenuation areas (LAA%) at −950 HU using the Pulmonary Workstation 2.0 Software (VIDA Diagnostics, Iowa City Iowa).

Statistical analysis

We powered the study to detect a 1.5 m/s difference in aPWV between treatment groups based on previous pilot data. Assuming this difference and a standard deviation of 3 m/s, 86 patients per treatment group were needed to achieve 90% power with a 2-sided significance level of 0.05. The primary efficacy measure, aPWV change from baseline at the 12-week endpoint (defined as the last measurement of aPWV during the 12-week double-blind treatment period), was compared between treatment groups using ANCOVA with terms for treatment group, investigator, sex, smoking status, age, BMI, waist circumference, and baseline value. Secondary efficacy analyses of changes in aPWV in those who remained on study drug throughout the 12-week periods as well as of AIx were conducted in the same manner. Linear regression modeling was used to investigate the relationship between aPWV and study assessments of interest. Univariate analyses were performed with the independent variable aPWV and each explanatory variable to identify candidate independent predictors. A stepwise multiple linear regression analysis, including all explanatory variables (p < 0.10) from the univariate analyses, was then performed and covariates with statistically significant p-values (p < 0.05) were retained. Statistical programming was performed using SAS.

Results

Of the 370 patients screened, 249 were randomized and comprised the intent-to-treat population. The details of patient disposition are shown in Fig. 1 and the baseline characteristics are shown in Table 1. Patients were predominantly male and Caucasian though a significant number of women were enrolled. Approximately half the patients were active smokers. Sixty percent (60%) of patients reported having any CV disorder with the highest prevalence being hypertension (54% in the FSC group; 43% in the placebo group).

A summary of baseline serum markers of CV risk is provided in Table 2. There were no differences in these measures between the placebo and FSC groups.

Baseline data for blood pressure, aPWV, and AIx are provided in Table 3; no differences between treatment groups were observed. We found significant univariate correlations between baseline aPWV and age (r = 0.26; p < 0.001), pack-years of smoking (r = 0.18; p = 0.006), systolic (r = 0.30; p < 0.001) and central systolic (r = 0.27; p < 0.001) blood pressure, pulse pressure (r = 0.30; p < 0.001), mean arterial pressure (r = 0.21; p = 0.001),...
log hsCRP (r = 0.13; p = 0.040), log BNP (r = 0.14; p = 0.035), FEV1/FVC ratio (r = −0.16; p = 0.014) and square root CT emphysema (r = 0.15; p = 0.046). No correlation was found between aPWV and FEV1 or BMI. In multivariate analysis, age, pack-years, and systolic blood pressure continued to be associated with aPWV.

Aortic pulse wave velocity (aPWV)

Data on aPWV at endpoint was available for 113 patients in the FSC group and 110 patients in the placebo group. The mean (SE) aPWV for the FSC group decreased from 10.06 (0.26) m/s at baseline to 9.83 (0.24) m/s at endpoint. For the placebo group the aPWV mean (SE) was 9.87 (0.25) m/s at baseline and 9.95 (0.26) m/s at endpoint. The least squares mean difference (SE) between FSC and placebo was 0.42 (0.23) m/s (95% CI −0.88, 0.03; p = 0.065) (Fig. 2). These results were unchanged when adjusted for changes in mean arterial pressure during the study, which were minimal (−0.2 in the FSC group and −0.6 in the placebo group). We also examined the least squares mean difference between the study groups in patients who remained on treatment throughout the 12-week study and found that FSC (n = 96) reduced aPWV vs. placebo (n = 96) by 0.49 (0.24) m/s (95% CI 0.98, −0.01; p = 0.045).

Augmentation index (AIx)

Data on AIx at endpoint was available for 114 patients in the FSC group and 111 patients in the placebo group. No changes in AIx were observed over the treatment period in either the FSC group [27.9 (0.83)% at baseline and 27.2 (0.82)% at endpoint] or the placebo group [27.8 (0.83)% at baseline and 27.6 (0.82)% at endpoint].

### Table 1 Patient characteristics at baseline.

<table>
<thead>
<tr>
<th></th>
<th>FSC (N = 123)</th>
<th>Placebo (N = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>63.6 ± 8.9</td>
<td>63.5 ± 7.9</td>
</tr>
<tr>
<td>Male, %</td>
<td>55</td>
<td>59</td>
</tr>
<tr>
<td>White Caucasian, %</td>
<td>93</td>
<td>90</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>51</td>
<td>47</td>
</tr>
<tr>
<td>Pack-years</td>
<td>55.8 ± 27.1</td>
<td>54.1 ± 26.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.7 ± 4.8</td>
<td>26.6 ± 4.2</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>95.5 ± 13.7</td>
<td>97.3 ± 11.3</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.64 ± 0.58</td>
<td>1.65 ± 0.60</td>
</tr>
<tr>
<td>FEV1/% predicted</td>
<td>56.0 ± 14.9</td>
<td>55.0 ± 15.2</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>0.54 ± 0.11</td>
<td>0.54 ± 0.11</td>
</tr>
<tr>
<td>% Non-reversible</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>LAA, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.76 ± 12.24</td>
<td>9.27 ± 10.47</td>
</tr>
<tr>
<td>Any CV disease, %</td>
<td>80 (65)</td>
<td>70 (56)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>67 (54)</td>
<td>54 (43)</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>6 (5)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>31 (25)</td>
<td>24 (19)</td>
</tr>
<tr>
<td>Beta-blockers, %</td>
<td>26 (21)</td>
<td>23 (18)</td>
</tr>
<tr>
<td>Calcium channel blockers, %</td>
<td>16 (13)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>ACE Inhibitors, %</td>
<td>33 (27)</td>
<td>27 (21)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers, %</td>
<td>7 (6)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Statins, %</td>
<td>44 (36)</td>
<td>39 (31)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or %. FEV1 values are post-bronchodilator. CAD includes past history of myocardial infarction. No statistically significant differences between groups.

<sup>a</sup> LAA (%) = low attenuation area median (IQR) values for FSC = 4.86 (1.15–11.24) and placebo = 5.40 (1.74–11.77).

### Table 2 Lab measures at baseline.

<table>
<thead>
<tr>
<th></th>
<th>FSC (N = 123)</th>
<th>Placebo (N = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mg/dL</td>
<td>185.8 ± 40.9</td>
<td>195.6 ± 44.0</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>56.1 ± 16.6</td>
<td>58.5 ± 22.6</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>102.3 ± 37.2</td>
<td>107.3 ± 39.3</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>139.1 ± 86.1</td>
<td>153.6 ± 178.1</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>3.3 (1.3–5.5)</td>
<td>2.5 (1.2–4.9)</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>2.96 (2.48–3.46)</td>
<td>2.88 (2.40–3.52)</td>
</tr>
<tr>
<td>BNP, ng/L</td>
<td>28 (14–50)</td>
<td>22 (12–45)</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>101.1 ± 22.0</td>
<td>103.2 ± 23.6</td>
</tr>
</tbody>
</table>

Values for hsCRP, BNP and fibrinogen are median (interquartile range). All others are mean ± SD. All assessments are from fasting patients. No statistically significant differences between groups.
Add on open label tiotropium to the FSC and placebo group at week 12

No significant changes in aPWV were observed in the FSC + tiotropium treatment group (\(n = 91\)) (mean (SE) change of 0.18 (0.16) m/s) or the placebo + tiotropium group (\(n = 96\)) (mean change of 0.18 (0.18) m/s) from week 12 to week 16. The statistically significant treatment difference between the FSC and placebo groups that was observed at week 12 was maintained at week 16 (least squares mean difference (SE) of 0.52 (0.25) m/s) (95%CI −1.01, 0.03; \(p = 0.037\)).

aPWV tertiles at baseline

We also performed a post hoc analysis of the change in aPWV between study groups in the three tertiles of baseline aPWV. The ranges of aPWV for tertiles 1, 2 and 3 were >8.7; >8.7−≤10.9; and >10.9, respectively. A description of patient characteristics by tertiles of aPWV at baseline is provided in Table 4. Patients in tertile 3 were older, more often former smokers, had greater total pack-years, lower FEV1/FVC ratio, and greater waist circumference and mean arterial pressure than those in tertiles 1 and 2. The least squares mean differences (SE) when comparing FSC with placebo for tertiles 1, 2 and 3 were −0.19 (0.33); \(p = 0.56\); 0.08 (0.48); \(p = 0.86\); and −1.10 (0.55); \(p = 0.050\) (Fig. 3).

Safety

Adverse events (AE) were reported for 58 (47%) patients in the FSC group and 48 (38%) patients in the placebo group. Serious adverse events (SAE) were reported for 8 (7%) and 8 (6%) patients in the FSC and placebo groups, respectively. The SAE reported with the highest incidence in the FSC group was pneumonia 3 (2%) and worsening of COPD 3 (2%) in the placebo group.

Discussion

Although many patients with COPD die from respiratory failure, CV disease is consistently a leading cause of death depending on the series and the severity of the patients’ underlying lung disease.\(^{20}\) Explanations for these observations have been difficult to elucidate though recent evidence suggests that the underlying mechanism may be in part explained by the fact that both CV disease and emphysema are associated with endothelial dysfunction and loss of extracellular matrix components like elastin.\(^{3,4}\) These processes in turn lead to abnormal vascular distensibility which can be assessed non-invasively by determining aPWV. Though a causal link between elevated

![Figure 2](image_url)
arterial stiffness and CV events has not been definitively established, their association raises the possibility that treatments that reduce aPWV may in turn improve cardiovascular outcomes. Proof that aPWV may serve as a surrogate for CV events in COPD is beyond the scope of the current trial which was designed to determine if FSC exerts biologically relevant effects on arterial stiffness. In this study FSC treatment did not meet the \( \textit{a priori} \) reduction in aPWV defined as clinically meaningful in the intention-to-treat population. However, compared with placebo FSC reduced aPWV in those who remained on study drug throughout the treatment period and this effect was more pronounced in those with greater baseline arterial stiffness. This is the first large scale efficacy trial to examine the impact of inhaled therapy on arterial stiffness in COPD and suggests that FSC may reduce aPWV. If confirmed in larger studies, and when combined with outcomes data linking reductions in aPWV to improvements in CV morbidity, these results may help explain prior observations suggesting that FSC reduces CV events in COPD.\(^1,12,13\)

The high prevalence of CV disease and death in COPD patients may result from traditional risk factors including cigarette smoking as well as recently recognized shared risks including systemic inflammation.\(^21\) Several studies have suggested that arterial stiffness, as assessed by PWV, is elevated in patients with COPD and that this is independent of cigarette smoking and perhaps FEV\(_1\).\(^4,8,22-24\) It has been argued that this results from an inflammatory process that occurs in both the vasculature and emphysematous lung leading to endothelial dysfunction and elastin degradation. Indeed, Coulson et al. have shown that COPD patients with elevated aPWV have increased aortic inflammation as

<table>
<thead>
<tr>
<th>Tertile 1 (\leq 8.7) m/s ((N = 81))</th>
<th>Tertile 2 (&gt; 8.7 - \leq 10.9) m/s ((N = 81))</th>
<th>Tertile 3 (&gt; 10.9) m/s ((N = 78))</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPWV, m/s</td>
<td>7.14 ± 1.24</td>
<td>9.84 ± 0.66</td>
</tr>
<tr>
<td>Males, %</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>Age, years</td>
<td>61.4 ± 8.1</td>
<td>61.7 ± 7.0</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>Pack-years</td>
<td>51.8 ± 25.2</td>
<td>53.0 ± 22.0</td>
</tr>
<tr>
<td>FEV(_1)% predicted</td>
<td>56.6 ± 15.2</td>
<td>56.2 ± 14.8</td>
</tr>
<tr>
<td>FEV(_1)/FVC ratio</td>
<td>0.56 ± 0.11</td>
<td>0.55 ± 0.10</td>
</tr>
<tr>
<td>Log hsCRP</td>
<td>0.77 ± 0.87</td>
<td>0.99 ± 1.00</td>
</tr>
<tr>
<td>Log BNP</td>
<td>3.02 ± 1.01</td>
<td>3.12 ± 0.87</td>
</tr>
<tr>
<td>Any CVD, %</td>
<td>52</td>
<td>70</td>
</tr>
<tr>
<td>LAA(%) – 950 HU</td>
<td>7.2 ± 9.4</td>
<td>9.8 ± 14.3</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>26.1 ± 4.3</td>
<td>26.6 ± 5.0</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>94.3 ± 12.6</td>
<td>96.2 ± 13.6</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122.0 ± 16.0</td>
<td>128.0 ± 14.2</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>76.9 ± 10.9</td>
<td>78.0 ± 9.5</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>45.1 ± 12.6</td>
<td>50.0 ± 12.2</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>91.9 ± 11.4</td>
<td>94.7 ± 9.7</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD unless otherwise indicated. \(P\)-values are from chi-square tests for categorical variables and from one-way ANOVA for continuous variables. aPWV = aortic pulse wave velocity. Log hsCRP = the log of high sensitivity c-reactive protein. Log BNP = log of B-type natriuretic peptide. CVD = cardiovascular disease. LAA (%) = low attenuation area%. MAP = mean arterial pressure.

\(^a\) \(p < 0.05\) Tertile 1 vs. Tertile 3.

\(^b\) \(p < 0.05\) Tertile 2 vs. Tertile 3.

\(^c\) \(p < 0.05\) Tertile 1 vs. Tertile 2.

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Figure 3  Change aPWV from baseline in the FSC group. Values are means ± SE. Open circles denote Tertile 1. Open triangles denote Tertile 2. Open squares denote Tertile 3. Tertile 1 was defined by having baseline aPWV measures <8.7 m/s; Tertile 2 was defined as having baseline aPWV >8.7 and <10.9 m/s and Tertile 3 was defined as having baseline aPWV >10.9 m/s. The least squares mean difference (SE) between FSC and placebo was \(-0.19\) (0.33), \(p = 0.56\) for Tertile 1, \(0.08\) (0.48), \(p = 0.86\) for Tertile 2, and \(-1.10\) (0.55), \(p = 0.050\) for Tertile 3.
assessed by $^{18}$F-FDG PET scanning as compared with healthy ex-smokers. $^{25}$ Sabit et al. $^{8}$ have also reported a correlation between serum IL-6 and aPWV ($r = 0.31$, $p < 0.01$) though McAllister et al. $^{22}$ found no relationship between PWV and serum CRP. In that study, a correlation was observed between PWV and the severity of CT emphysema ($r = 0.47$, $p < 0.001$) perhaps implicating a shared inflammatory process. In the current study we found univariate correlations between aPWV and both CT emphysema and hsCRP though these were not significant on multivariate testing. These data suggest that increased arterial stiffness in COPD may result from abnormalities in the vascular extracellular matrix and that this may be a systemic feature of the disease leading to increased CV risk.

Several prior studies have shown that both beta-agonists and corticosteroids can reduce arterial stiffness. $^{18,24}$ The effects of beta-agonists may be mediated via systemic stimulation of endothelial nitric oxide synthase while corticosteroids may reduce systemic inflammation which is known to contribute to atherosclerosis. $^{21}$ The impact of inhaled corticosteroids (ICS) and ICS/long-acting beta agonist combinations on markers of systemic inflammation has been debated. Though Sin et al. have shown that as compared with placebo, fluticasone propionate reduced serum CRP in patients with COPD $^{26}$ a subsequent trial of FSC demonstrated no such effect. $^{27}$ In a post hoc analysis of the TORCH study Calverley et al. $^{28}$ also found that after adjustment for drug exposure the probability of having a CV adverse event was lowest in patients taking FSC (20.8%) as compared with those taking fluticasone propionate or salmeterol alone and statistically lower than in patients taking placebo (24.2%; $p = 0.031$). Similarly, in a two year trial comparing FSC and tiotropium in patients with severe COPD, a lower rate of death due to CV events was observed in those in the FSC group (1% vs. 3%, $p > 0.05$). $^{13}$ Though our trial was not powered to directly compare the effects of tiotropium and FSC on arterial stiffness, the difference in aPWV observed at week 12 was maintained between FSC-tiotropium and placebo-tiotropium in the open label phase of the study.

Two prior studies have specifically examined the impact of active treatments on arterial stiffness in COPD. Vodtzev et al. have shown that PWV was reduced after 4 weeks of exercise in ten trained COPD patients (10.3 m/s−9.2 m/s; $p = 0.001$) as compared with seven untrained patients matched for age and lung function. $^{29}$ Though these data support the possibility that arterial stiffness can be modulated in COPD, the study was limited by its non-randomized design, the use of carotid-radial rather than the gold standard carotid-femoral PWV and the fact that the authors did not account for the reduction in systolic blood pressure that occurred with exercise. Blood pressure, both central and peripheral, is a major determinant of PWV and the 8 mm Hg reduction observed in the trained patients could explain the observed arterial stiffness improvements. Blood pressure improvements during the current study were minimal and the results were not altered in analyses adjusting for these changes. In the second small trial, Sabit et al. evaluated the effects of FSC in 14 patients with moderate-severe COPD and observed that treatment significantly reduced arterial stiffness at 8 weeks by 2.2 mm/s ($p < 0.01$). $^{19}$ This study provided the only preliminary data regarding the impact of FSC on aPWV in COPD and led us to select our estimated effect size of 1.5 m/s and to power the trial. There are several differences between the design of this prior trial and the current report that may explain why we were unable to demonstrate a statistically significant reduction in aPWV in our intention-to-treat population ($p = 0.065$). First, Sabit et al. utilized the 500/50 dose of FSC as compared with the 250/50 dose used in our study. Second, patients in the Sabit trial had more severe airflow limitation (mean FEV1 1.01 L vs. 1.65 L) and this may in part explain why they also had significantly higher resting aPWV (13 m/s vs. 10 m/s). This may have limited our power to detect an effect of active treatment on aPWV. Indeed, though limited by the post hoc analysis, a statistically significant reduction in arterial stiffness was observed in those in the highest tertile of baseline aPWV (>10.9 m/s). Though the change in aPWV with FSC was less than expected, Orlova et al. have reported that in patients with coronary artery disease any decrease in PWV over 6 months was associated with a four-fold reduction in the risk of major cardiac events over 3.5 years of follow-up. The association observed in this observational study cannot be used to determine the clinical relevance of the change in aPWV we observed. However this study can also not be excluded to the possibility that a small reduction in aPWV may be meaningful. $^{29}$

There are several limitations to our study. First, as we did not include study arms with the individual FSC components we were unable to determine the relative effects of each drug on aPWV. The use of ICS alone in COPD is currently not recommended however, and thus the relevant limitation is the lack of a salmeterol arm. Despite this, the published observational data suggest that the greatest benefits on CV outcomes are achieved with FSC as compared with either drug alone. Second, we did not find any reduction in AIx with FSC in either the intent-to-treat or post hoc analyses. This is of interest as AIx is correlated with long term CV outcomes though the relationship is not as robust as that for aPWV. $^{2,6,7}$ In addition, AIx is a complex parameter affected by arterial stiffness, systemic vascular resistance, and left ventricular function and thus may be less sensitive for the detection of the effects of FSC. This may be particularly relevant in our study population as AIx tends to plateau beginning at age 50 while aPWV continues to increase. $^{30}$ Third, though the tertile analysis suggested that FSC reduced arterial stiffness in patients with the highest baseline aPWV, it is also possible that the effect we observed in this subgroup was not the result of study drug but due to the regression of their elevated aPWV towards the mean. This is somewhat unlikely given that there was no reduction in aPWV in placebo treated patients in this subgroup. Fourth, it is also possible that a longer treatment period might be required to demonstrate a statistically significant reduction in aPWV. Lastly, though patients were excluded from the trial if they began or had been recently prescribed new medications that may impact aPWV, the overall use of proven cardioprotective drugs (e.g. beta-blockers, statins, angiotensin converting enzyme inhibitors) was relatively low despite the 60% prevalence of CV disease.

The mechanism by which FSC may lower aPWV remains unknown. Though beta-agonists and corticosteroids have
both been shown to reduce arterial stiffness\textsuperscript{16,18} the
systemic bioavailability of salmeterol and fluticasone propionate when delivered by inhalation is very low\textsuperscript{31} and
argues against a direct pharmacologic effect. As discussed, it
has been postulated that ICS may reduce systemic inflammation indirectly by downregulating airway derived
IL-6 which in turn reduces CRP expression by the liver\textsuperscript{26}
though not all reports support this hypothesis.\textsuperscript{27} It has
also been shown that patients with COPD have elevated
sympathetic activation even in the absence of hypoxemia
also been shown that patients with COPD have elevated
sympathetic activation even in the absence of hypoxemia
and that this may be driven by dyspnea or abnormal lung
hyperinflation.\textsuperscript{32} As sympathetic output has been directly
linked to aPWV,\textsuperscript{3} it is possible that aPWV is reduced in COPD
in response to the beneficial effects of FSC on lung hyper-
inflation and resulting improvements in shortness of breath
and respiratory mechanics. As has been noted recently,
emphysema and hyperinflation can have important
extrapulmonary effects including those on cardiac perfor-
ance.\textsuperscript{33,34} Additional studies would be required to better
examine this possibility.

In summary, this is the first large scale trial to accurately
examine the effect of inhaled anti-inflammatory and
bronchodilator therapy on aPWV in a well characterized
COPD population. Although the study did not meet the
primary endpoint, it does suggest FSC may reduce aPWV in
patients with the greatest abnormality in arterial stiffness
and provides preliminary data for future trials examining
the impact of COPD therapies on aPWV. When combined
with large outcome studies establishing a link between
reductions in aPWV and subsequent CV events, these
studies will allow a better understanding of the potential
CV impact of COPD treatments.

Conflict of interest

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related talks. JRC is a PI for the ARCADE Study and a member of GSK advisory board for GSK UK. RRT serves as
a consultant to GlaxoSmithKline, Merck and Novartis and receives royalties from UpToDate. HOC has received an
honorary fee for serving on the steering committee for the ECLIPSE project for GSK. In addition he was the co-
investigator on two multi-center studies sponsored by GSK
and has received travel expenses to attend meetings related to the project. He has a contract service agreement
with GSK to quantify the CT scans in subjects with COPD and
a service agreement with Spiriation Inc to measure changes
in lung volume in subjects with severe emphysema. He has
received a fee for speaking at a conference and related
tavel expenses from AstraZeneca (Australia). FJM has
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GSK, MedImmune/AstraZeneca, Ikaria, Merck, Pearl, Novartis, UBC, Forest/Almirall. He has consulted for
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Schering, HLS, Talecris, Comgenix, fb Communications,
BoomComm and Actelion. He has served on Speaker’s
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References

1. Sin DD, Wu L, Man SFP. The relationship between reduced lung
function and cardiovascular mortality: a population-based
study and a systematic review of the literature. Chest 2005;
2. Bolton CE, Cockcroft JR. Lung function and cardiovascular risk:
3. Barr RG, Mesia-Vela S, Austin JHM, Basner RC, Keller BM,
Reeves AP, et al. Impaired flow-mediated dilation is associated
with low pulmonary function and emphysema in ex-smokers:
the emphysema and cancer action project (EMCAP) study. Am
4. McAllister DA, Maclay JD, Mills NL, Mair G, Miller J, Anderson D,
et al. Arterial stiffness is independently associated with
emphysema severity in patients with chronic obstructive
pulmonary disease. Am J Respir Crit Care Med 2007;176(12):
1208–14.
5. Swierbiewska E, Hering D, Kara T, Kunicka K, Kruszweski P,
Bieniaszewski L, et al. An independent relationship between
muscle sympathetic nerve activity and pulse wave velocity in
Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C,
Wilkinson I, Struijker-Boudier H. Expert consensus document
on arterial stiffness: methodological issues and clinical appli-
7. Vlachopoulos C, Aznouridis K, Stefanadis C. Prediction of
cardiologic events and all-cause mortality with arterial
stiffness: a systematic review and meta-analysis. J Am Coll
8. Sabit R, Bolton CE, Edwards PH, Pettit RJ, Evans WD,
McEniery CM, et al. Arterial stiffness and osteoporosis in