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Possible protection by inhaled budesonide against ischaemic cardiac events in mild COPD

A post-hoc evaluation of the EUROSCOP study

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Abstract

Background: Epidemiological studies have indicated that chronic obstructive pulmonary disease (COPD) may be associated with an increased incidence of ischaemic cardiac events.

Methods: We performed a post-hoc analysis of the EUROSCOP study – a 3-year, placebo-controlled study of an inhaled corticosteroid budesonide 800 μg/day in smokers (mean age 52 years) with mild COPD. We evaluated whether long-term budesonide treatment attenuates the incidence of ischaemic cardiac events, including angina pectoris, myocardial infarction, coronary artery disorder and myocardial ischaemia.

Results: Among the 1175 patients evaluated for safety, 49 patients (4.2%) experienced 60 ischaemic cardiac events. Patients treated with budesonide had a significantly lower incidence of ischaemic cardiac events (18 out of 593; 3.0%) than those receiving placebo (31 out of 582; 5.3%; $p<0.05$).

Conclusions: These results support the hypothesis that treatment with inhaled budesonide reduces ischaemic cardiac events in patients with mild COPD.

Word count: 143

Key words: ischaemic cardiac events, COPD, budesonide

Introduction

Tobacco smoking is one of the major causative agents for a number of morbidities such as chronic obstructive pulmonary disease (COPD), cardiovascular disease and lung cancer. COPD affects approximately 600 million people [1], and the mortality from COPD continues to increase and is expected to be the third largest cause of death worldwide by 2020 [2]. The relentless progression of COPD leads to an increasing loss of lung function, increased symptoms and deteriorating health-related quality of life. Exacerbations have been identified as one key driver of this progression, and are a major independent factor of poor prognosis and death in COPD [3]. Recent studies have indicated that COPD also has a considerable systemic inflammatory component [4–6]. Further, a reduced lung function and COPD are independent risk factors for cardiovascular morbidity and mortality [7–9].

Current guidelines for the management of COPD recommend the use of an inhaled corticosteroid (ICS) alongside a long-acting bronchodilator to prevent acute exacerbations in patients with severe COPD [2, 10–12]. Furthermore, retrospective analyses and a meta-analysis reported that ICS reduce the number of hospitalisations and the overall mortality rate associated with COPD [6, 13–15]. Next to effects on exacerbations in COPD, there is suggestive evidence that ICS reduce elevated C-Reactive Protein (CRP) levels [16–18], a marker of inflammation that is associated with reduced lung function [19–22], and with ischaemic cardiac disease [23].

Based on the above findings, we performed a post-hoc analysis of the EUROSCOP study [24] to investigate whether long-term budesonide

treatment (800 μg/day) attenuates the incidence of ischaemic cardiac events, such as angina pectoris and myocardial infarction, in patients with mild COPD and a low rate of ischaemic cardiac disease at inclusion. The EUROSCOP study was not designed for assessment of exacerbations; therefore a well-recognised surrogate marker for severe exacerbations, courses of oral corticosteroids, was analysed in order to explore any association of acute exacerbations with ischaemic cardiac events.

Methods

The EUROSCOP study was a 3-year, double-blind, randomised, multicentre, placebo-controlled study of budesonide (Pulmicort® administered via Turbuhaler®) 800 μg/day in current smokers with mild COPD and conducted in 9 Western European countries.

Patients

Patient inclusion criteria have been reported previously [24]. In short, current smokers (≥5 cigarettes/day) were included who had smoked for at least 10 years or had a smoking history of at least 5 pack-years, a post-bronchodilator forced expiratory volume in 1 second (FEV_1) of 50–100% of the predicted normal value, a ratio of prebronchodilator FEV_1 to slow vital capacity of <70% and reversibility of FEV_1 with 1 mg inhaled terbutaline of <10% (as per cent of predicted FEV_1). Patients with a history of asthma, allergic rhinitis or allergic eczema, a concomitant disease that could interfere with the interpretation of the study, those who used β-receptor antagonists, and those who had used oral glucocorticoids for more than 4 weeks during the preceding 6 months were excluded from the study.

Study assessments

A hypothesis-based post-hoc analysis was performed using the 3-year safety database from the EUROSCOP study. The following adverse events and serious adverse events as spontaneously reported by the responsible physician were considered relevant in the analysis of the incidence of ischaemic cardiac events: *angina pectoris*, *myocardial infarction*, *coronary artery disorder* and *myocardial ischaemia* (these are the preferred terms from

the Adverse Event dictionary used in the trial [AstraAED, based on WHOART]. A verbatim term reported by the investigator [e.g. coronary insufficiency] will be coded in the dictionary to the included term with closest resemblance to the reported term [ischaemic heart disease], which belongs to the corresponding preferred term [coronary artery disorders] used in the study report) . Baseline demographic and disease characteristic data of the overall study population was compared with that of the population experiencing any ischaemic cardiac adverse event in order to identify any potential prognostic factor. This included an analysis of courses of oral corticosteroids as a surrogate marker for severe exacerbations. Patients were followed for 3 years.

Statistical analyses

All analyses were conducted using the safety population. Descriptive statistics are presented for the baseline demographic and disease characteristics comparison. The incidence of the pre-defined first-time ischaemic cardiac adverse events was compared among patients receiving budesonide and those receiving placebo using the chi-square test. The total number of ischaemic cardiac events and the total number of courses of oral corticosteroids was compared between groups using Poisson regression with time in study as an offset variable. A Kaplan–Meier survival analysis was also performed.

Results

Of a total of 1277 randomised patients, 1275 were included in the intention-to-treat analysis. No data point regarding safety was collected for 100 of these patients and they were not considered evaluable for safety according to current database rules. Therefore 1175 patients were included in the safety evaluation (budesonide n=593, placebo n=582); , The baseline demographics and disease characteristics of the study population have been reported elsewhere (Pauwels et al 1999) and were comparable between the treatment groups as were the total number of treatment years, the discontinuations due to adverse events and the reasons for discontinuations; Among the 1175 evaluated patients 132 discontinued due to an adverse event (budesonide n=70, placebo n=62) and 131 discontinued due to other reasons (budesonide n=65, placebo n=66)

At baseline, 32 (2.7%; 15 on budesonide, 17 on placebo) had a previous medical history of ischaemic cardiac events. Among these 32 patients, 4 developed an ischaemic cardiac event during the trial (1 patient on budesonide, 3 patients on placebo). During the study, there were 18 deaths (8 budesonide vs. 10 placebo). 3 of these were myocardial infarctions (2 budesonide vs. 1 placebo). The most common cause of death was pulmonary carcinoma (3 budesonide vs. 3 placebo). Only one case of death was “unspecified” and reported as “sudden death” (placebo).

Incidence of ischaemic cardiac events

Forty-nine patients (4.2%) had a total of 60 ischaemic cardiac events. As stated above, 3 patients died by myocardial infarction, no other deaths occurred among the 49 patients with ischaemic cardiac disease. Significantly fewer patients treated with budesonide (18/593, 3.0%) experienced at least one ischaemic cardiac event during the 3 years of the study compared with those who received placebo (31/582, 5.3%; p=0.048, 95% confidence interval [CI]: –4.7, -0.0%). The 18 patients treated with budesonide experienced a total of 22 ischaemic cardiac events while the 31 patients who received placebo experienced a total of 38 events. The Poisson regression analysis resulted in an estimated ratio of ischaemic cardiac event rate of 0.58 (95% CI: 0.35, 0.98; p=0.043) (Figure 1). As can be seen in Figure 1 the specific events of angina pectoris, myocardial infarction and coronary artery disease are lower for budesonide in addition to the observation overall incidence of ischaemic cardiac events was lower with budesonide than with placebo.

Kaplan–Meier survival analysis of the fraction of patients experiencing an ischaemic cardiac event showed a clear distinction between the budesonide and placebo groups (Figure 2).

Of the 60 reported ischaemic cardiac events, 30 (budesonide n=13, placebo n=17) were serious (e.g. death, hospitalization) and 30 (budesonide n=9, placebo n=21) were non-serious.

On the basis of these findings, the number needed to treat with budesonide to prevent one ischaemic cardiac event is 95.

Potential prognostic factors

The baseline demographic and disease characteristics including lung function measures and pack-years smoking of the patients who experienced ischaemic cardiac events during the EUROSCOP study were similar to those of the overall population (Table 1). The yearly rate of severe exacerbations (estimated from courses of oral corticosteroids) was reduced in the budesonide group vs placebo group by 37% (0.05 vs 0.07, p = 0.002); corresponding to a yearly exacerbation rate ratio of 0.63 (95% CI: 0.47, 0.85). Among the 49 patients with ischaemic cardiac events, 7 received at least 1 course of oral corticosteroids (14%) compared with 8% in the remaining patients (non-significant).

Discussion

Results of the post-hoc analysis of data from the EUROSCOP study show that significantly fewer patients treated with budesonide 800 μg/day experienced ischaemic cardiac events than those who received placebo (18 vs 31, respectively; $p<0.05$). Similar results were observed when the absolute number of events was compared between the two treatment groups: 22 events among budesonide-treated patients compared with 38 events among those who received placebo ($p<0.05$).

The difference in the incidence of first-time ischaemic cardiac event between patients treated with budesonide and those who received placebo was not a result of differences in baseline characteristics. These were similar in the two treatment groups and also similar to those of the overall patient population, as were the total number of treatment years, the discontinuations due to adverse events and the reasons for discontinuations. Of importance to the results is that the baseline prevalence of ischaemic cardiac events was low in the EUROSCOP study, and that the overall mortality was lower than expected from reference populations [25], 18 observed cases versus 34.4 cases ($p=0.0052$).

At the time of the EUROSCOP study relatively little was known about the systemic component of COPD. Epidemiological studies have since indicated that COPD is not solely a disease of the respiratory tract but may also involve the cardiovascular system, resulting in an increased incidence of cardiovascular events [7, 8, 26]. The cause behind the association between COPD and cardiovascular disease is still unknown but one explanation could

be that the systemic inflammation in COPD increases the risk for cardiovascular events. Elevated CRP levels, a marker of inflammation that is associated with reduced lung function, is also associated with ischaemic cardiac disease [23]. Thus, it would be plausible that inhaled steroids, like budesonide, reduce the local inflammation and subsequent cardiovascular morbidity [27]. In this case, a local effect on the lung resulting in diminished spill-over of inflammation systemically to the cardiovascular system is an attractive hypothesis, since systemic steroids may have a dose-dependent harmful effect on the risk for ischaemic heart disease [28]. An alternative explanation may be that acute exacerbations of COPD may precipitate cardiovascular disease [29]. It has been shown that inhaled steroids reduce the rate of acute exacerbations in advanced COPD [30].The EUROSCOP study was not designed for assessment of exacerbations but, using courses of oral corticosteroids as a surrogate marker, a reduction was seen corresponding to a yearly decrease of 37% in the budesonide group versus placebo (p=0.0022). This study could not investigate whether exacerbations and ischaemic cardiac events were associated in this respect, since it did not have power to reveal this, though there was a trend towards a higher frequency in those with ischaemic cardiac events.

When evaluating these results it is important to note that the EUROCOP population was about 10 years younger than other similar studies in the field [10, 12, 31, 32]. The population also had much milder disease, as the mean FEV_1 was 76% of predicted normal compared with 36–50% in the studies mentioned earlier. Thus, this study population represents a much earlier phase in the natural history of COPD than many comparable studies.

The dose-dependent risks of systemic corticosteroids for cardiac disease reported in an observational large study [28], and the general vulnerability of COPD patients given their high age and frequent comorbidity require a well-documented safety profile for any intervention. The design and duration of the 3-year EUROSCOP study has provided a reassuring safety profile for long-term use of budesonide at a daily dose of 800 μg [24, 33].

The data presented here suggest that ischaemic cardiac events among patients with relatively mild COPD could be significantly reduced by inhaled budesonide. Further studies are required to verify this finding and to study the mechanisms involved.

References

1. World Health Organization. The World Health Report 1998. Life in the 21st Century. A vision for all. World Health Organization, Geneva, 1998.

2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO report 2005.

3. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925–931.

4. Agusti A. COPD, a multicomponent disease: implications for management. *Respir Med* 2005; 99: 670–682.

5. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005; 2: 8–11.

6. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* 2005; 127: 1952–1959.

7. Dankner R, Goldbourt U, Boyko V, Reicher-Reiss H. Predictors of cardiac and non-cardiac mortality among 14,697 patients with coronary heart disease. *Am J Cardiol* 2003; 91: 121–127.

8. Engström G, Lind P, Hedblad B, et al. Lung function and cardiovascular risk. Relationship with inflammation-sensitive plasma proteins. *Circulation* 2002; 106: 2555–2560.

9. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002; 166: 333–339.

10. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: 912–919.

11. Sin DD, Man SFP. Inhaled corticosteroids in the long-term management of patients with chronic obstructive pulmonary disease. *Drugs Aging* 2003; 20: 867–880.

12. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 74–81.

13. Sin DD, Wu L, Anderson J, et al. Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. *Thorax* 2005; 12: 992–997.

14. Soriano JB, Kiri VA, Pride NB, Vestbo J. Inhaled corticosteroids with/without long-acting beta-agonists reduce the risk of rehospitalisations and death in COPD patients. *Am J Respir Med* 2003; 2: 67–74.

15. Tkacova R, Toth S, Sin DD. Inhaled corticosteroids and survival in COPD patients receiving long-term home oxygen therapy. *Respir Med* 2006; 100: 385–392.

16. Man SFP, Sin DD. Effect of corticosteroids on systemic inflammation in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 78–82.

17. Pinto Plata VM, Müllerova H, Toso JF, Feudjo Tepie M, Soriano JB, Vessey RS, Celli BR. C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax* 2006; 61: 23–28.

18. Sin DD, Lacy P, York E, Man SF. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 760–765.

19. Broekhuizen R, Wouters EF, Creutzberg EC, Schols AM. Raised CRP levels mark metabolic and functional impairment in advanced COPD. *Thorax* 2006; 61: 17–22.

20. Donaldson GC, Seemungal TA, Patel IS, et al. Airway and systemic inflammation and decline in lung function in patients with COPD. *Chest* 2005; 128: 1995–2004.

21. Gislason T, Olafsdottir IS, Thjooleifsson B, et al. High sensitivity C-reactive protein (Hs-CRP) is associated with COPD and a faster decline in FEV_1 – a multicentre epidemiological study. *Eur Respir J* 2005; 26 (Suppl. 49): 51s.

22. Kony S, Zureik M, Driss F, et al. Association of bronchial hyperresponsiveness and lung function with C-reactive protein (CRP): a population based study. *Thorax* 2004; 59: 892–896.

23. Ridker PM: High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. *Am Heart J* 2004; 148 (Suppl. 1): S19–S26.

24. Pauwels RA, Löfdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 1999; 340: 1948–1953.

25. World Health Organization. 1991 World Health Statistics Annual. Geneva, Swtizerland: World Health Organization; 1992.

26. Kiechl S, Werner P, Egger G, Oberhollenzer F, Mayr M, Xu Q, Poewe W, Willeit J. Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis. Prospective results from the Bruneck Study. *Stroke* 2002; 33: 2170–2176.

27. Sin DD, Man SF. Can inhaled steroids mend a broken heart in chronic obstructive pulmonary disease? *Eur Respir J* 2005; 4: 589–590.

28. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med* 2004; 141: 764–770.

29. Wedzicha JA, Seemungal TA, MacCallum PK, Paul EA, Donaldson GC, Bhowmik A, Jeffries DJ, Meade TW. Acute exacerbations of chronic

obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb Haemost* 2000; 84: 210–215.

30. Calverley PMA. Reducing the frequency and severity of exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2004; 1: 161–166.

31. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C; TRial of Inhaled STeroids ANd long-acting beta2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449–456.

32. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.

33. Johnell O, Pauwels R, Lofdahl CG, Laitinen LA, Postma DS, Pride NB, Ohlsson SV. Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler. *Eur Respir J* 2002; 19: 1058–1063.

Table 1: Baseline demographics and disease characteristics of patients experiencing at least one ischaemic cardiac event compared with the overall study population

Parameter	Patients experiencing ischaemic cardiac events (n=49)	Overall EUROSCOP study population (n=1277)
Males/females, %	86/14	73/27
Age, years	54.7(32–64)	52.5 (25–66)
Body mass index	25.7 (20–32)	24.8 (15–44)
Pack-years	40 (18–111)	36 (0–171)
FEV_1, L	2.5 (1.4–3.6)	2.5 (1.0–4.7)
FEV_1, % of predicted	74.3 (51–99)	76.9 (42–103)
Inspiratory vital capacity, L	4.1(2.2–5.9)	4.1 (1.9–7.8)

Data presented as mean (range) except pack-years, which is median (range).

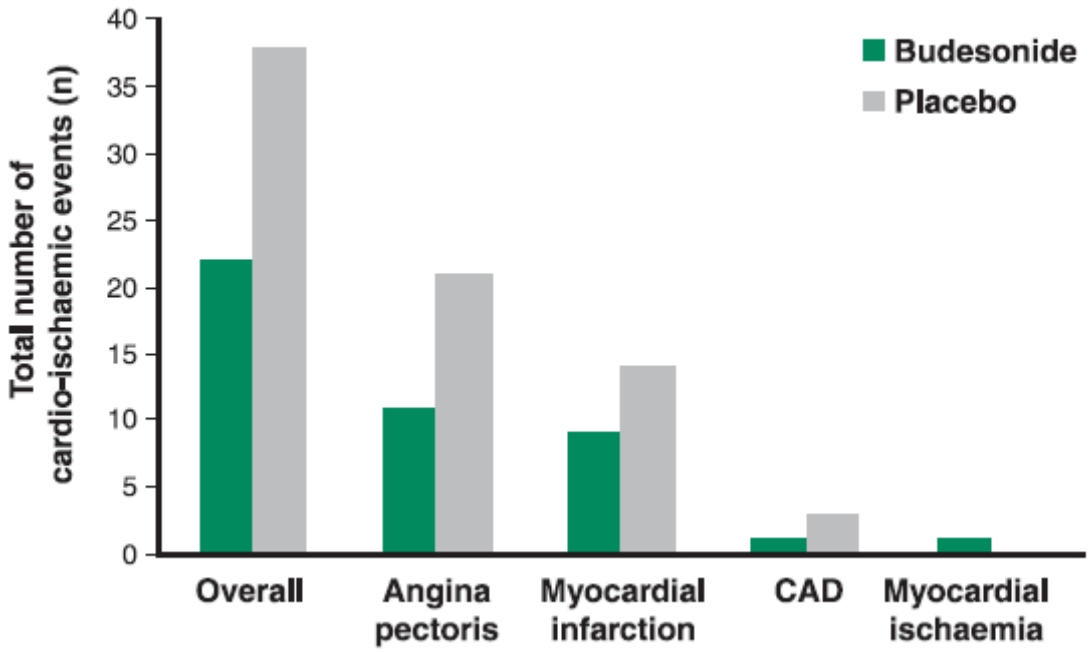
FEV_1: forced expiratory volume in 1 second.

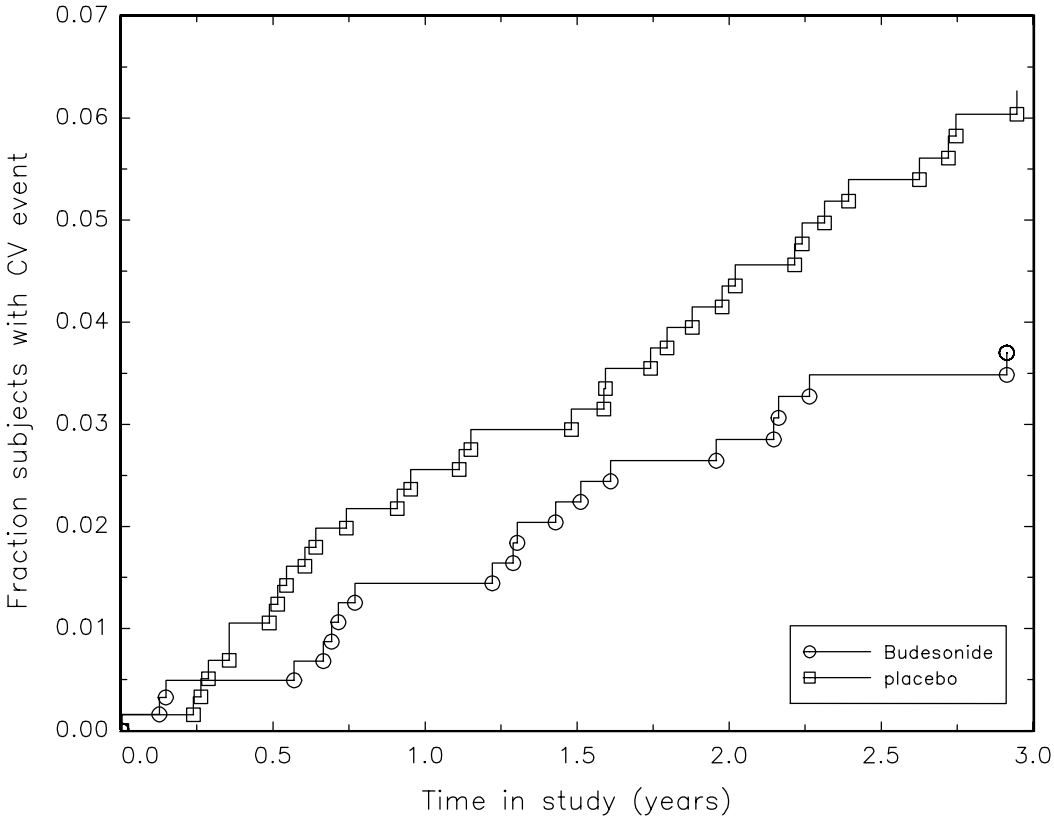
Figure legend

Figure 1: Distribution of ischaemic cardiac events among adult patients with COPD randomised to receive budesonide 800 μg/day or placebo for up to 3 years. CAD: coronary artery disease

Figure 2: Kaplan–Meier survival analysis of proportion of experiencing an ischaemic cardiac event during treatment with budesonide 800 μg/day or placebo for up to 3 years.

Figure 1


Budesonide
Placebo
Total number of cardio-ischaemic events (n)
40
35
30
25
20
15
10
5
0
Overall
Angina pectoris
Myocardial infarction
CAD
Myocardial ischaemia


Fraction subjects with CV event
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Time in study (years)
Budesonide
placebo