Asthma phenotypes: do cough and wheeze predict exacerbations in persistent asthma?

Jaymin B. Morjaria[1,2], Alan S. Rigby[1] and Alyn H. Morice[1]

Affiliations: [1]Respiratory Medicine, Hull York Medical School, University of Hull, Castle Hill Hospital, Cottingham, UK. [2]Dept of Respiratory Medicine, Royal Brompton and Harefield NHS Trust, Harefield Hospital, Harefield, UK.

Correspondence: Alyn H. Morice, Hull York Medical School, University of Hull, Castle Hill Hospital, Castle Road, Cottingham HU16 5JQ, UK. E-mail: a.h.morice@hull.ac.uk

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MART has little impact on asthma symptoms when compared to salbutamol, despite reduction of exacerbation frequency http://ow.ly/aqAJ30eUN9y

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ABSTRACT Little is known of the long-term symptom profile in uncontrolled asthma and whether symptoms can predict distinct phenotypes. The primary objective of these analyses was to assess diurnal profile of cough and wheeze in an uncontrolled asthma population. Secondary outcomes were to examine how these symptom profiles influence response to treatment.

Twice-daily electronically recorded data from 1701 patients were examined in relation to the population demographics. Reliever treatment with salbutamol was then compared with extra-fine beclometasone/formoterol maintenance and reliever therapy (MART). Exacerbation frequency was then correlated with the symptom profile.

Symptoms were commoner in older patients with an increased body mass index. In most patients, reported cough and wheeze were closely correlated (r=0.73). Two phenotypes of cough- and wheeze-predominant patients were identified; the former were overweight, older females and the latter older males. Diurnal symptoms of cough and wheeze were similarly attenuated by both therapies. MART reduced exacerbation frequency by a third compared with salbutamol, and this effect was greatest in patients with fewest reported symptoms.

While cough and wheeze are highly correlated in uncontrolled asthma, some patients predominantly have cough whereas others wheeze. Symptoms and exacerbation frequency appear poorly associated, suggesting an alternative pathophysiology. MART may be the preferred option in those with fewest symptoms.

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Introduction

Inhaled corticosteroids (ICS) have been shown to improve symptoms, asthma control and reduce exacerbation frequency in mild persistent asthma [1]. When asthma remains uncontrolled with monotherapy, the addition of long-acting β_2-agonists (LABAs) is recommended [2, 3]. Optimisation of fixed-dose ICS/LABA combinations with short-acting β_2-agonists as required results in better asthma control and a reduction in exacerbation frequency when compared to monotherapy alone [4–6]. These and other observations have led to the hypothesis that exacerbation rate and asthma control are intimately related, with many contemporary management strategies directed at improving asthma by minimising symptoms and the risk of exacerbations.

Because of formoterol's rapid onset and long-lasting properties, its use in conjunction with budesonide as maintenance and reliever therapy has markedly diminished the frequency of asthma exacerbations when compared with various fixed-dose therapies [7–13]. Recently, beclometasone/formoterol (Fostair; Chiesi Farmaceutici, Parma, Italy) has similarly been reported to reduce exacerbation frequency by one-third when used as maintenance and reliever therapy (MART) [14]. In all seven of these studies the level of symptom control as measured by the asthma control questionnaire (ACQ) [15] or symptom scores were not significantly improved.

The concept of asthma control encompasses symptoms, lung function and use of reliever therapy [15–17]. The advent of electronic devices capable of contemporaneously recording indices of asthma control afforded us the opportunity to conduct an analysis of individual patient's reported symptom profile using data collected during the MART proof-of-concept study [14]. This large cohort of uncontrolled asthmatic subjects recorded diurnal symptoms of cough and wheeze for the 48 weeks of the study. We hypothesised that clinically important phenotypes of asthma may be revealed by the analysis of an individual's symptoms and that the relationship between the symptom score and exacerbation frequency may provide insights into the optimal management of such patients.

Methods

We performed a detailed *post hoc* analysis of the twice-daily symptoms score and exacerbation rate from a 48-week double-blind, multicentre, randomised (1:1 ratio), parallel-group trial comparing regular beclometasone/formoterol plus as-required salbutamol with beclometasone/formoterol as MART. The study, designed by Chiesi Farmaceutici, had a patient population that consisted of symptomatic adult asthmatics uncontrolled (partially controlled and/or uncontrolled) [2] on conventional medications who were non- or ex-smokers [14]. The study population, primary efficacy and safety end-points have been reported previously [14].

Subjective asthma symptoms were recorded once in the morning and evening, and rated using a four-point scale (0=no symptoms; 1=mild: symptoms not causing awakening; 2=moderate: discomfort enough to cause interference with daily activity; and 3=severe: incapacitating with inability to work/take part in usual activity). Data were stored on a portable electronic peak flow meter (Spirotel; Medical International Research, Rome, Italy) before diurnal peak expiratory flow (PEF) recording [14]. For the purposes of analysis, a symptom episode was defined as each occasion when a symptom of any severity was recorded in the electronic diary.

Severe exacerbations were defined as deterioration in asthma requiring hospitalisation or emergency-room treatment and/or the need for systemic corticosteroids for $\geqslant$3 days. Mild exacerbations were defined as the use of the as-needed reliever at least twice, 20% reduction in PEF compared to baseline and nocturnal asthma-related awakenings.

Statistical methods

The data were analysed according to intention-to-treat. Continuous data were summarised by the median (25th–75th centile) and categorical data by percentages. Incidence data (frequency of asthma exacerbations and number of cough and wheeze episodes) were analysed by Poisson regression. A key assumption of the Poisson model is that the variance of the outcome measure (*i.e.* number of episodes) should equal its mean. A common problem encountered with Poisson data is overdispersion, where the variance of the outcome measure is greater than its mean [18]. Poisson models were investigated and corrected for overdispersion where necessary [19]. The exposure variable in the Poisson models was the number of days in study. Incidence (episodes per unit time) was expressed per person-years of exposure. 95% confidence intervals were based on the robust variance. Pearson's correlation coefficient (r) was used to assess the degree of linear relationships on the scatter plots. The small number of missing values were analysed by case wise deletion. Given that this is a secondary analysis of an existing dataset, p-values (nominally set at 5%, two-tailed) were used sparingly. The data was analysed using Stata statistical software (release 10; StataCorp, College Station, TX, USA).

Results

Patient demographics

The demographics of the patient population has been reported previously [14]. Of relevance to the current analyses, the median age was 49 years, with more than three-fifths (n=1049) being female and 23% of the randomised patients (n=395) having a body mass index (BMI) ⩾30 kg·m^{-2}. The median individual duration of participation in the study was 322 days.

Symptom profile

Cough incidence

More than half a million cough episodes were reported during the study. An episode of cough was reported on a median of 323 days per year. Thus, the average rating of cough per episode (on the four-point scale) was 1.32. There were no significant sex differences.

Diurnal variation in cough

When daytime and night-time cough episodes and ratings were compared there was no significant difference; daytime incidence was 134 *versus* nocturnal 136. Both daytime and night-time cough were

TABLE 1 Incidence of cough and wheeze

	Symptoms per person-years	p-value
Daytime cough		
Age <40 years	192 (173–212)	
Age ⩾40 years	276 (260–292)	**<0.001**
BMI <30 kg·m^{-2}	243 (229–258)	
BMI ⩾30 kg·m^{-2}	281 (254–311)	**0.02**
Male	241 (221–264)	
Female	258 (229–293)	0.21
All	252 (239–265)	
As-needed BF	252 (234–271)	
As-needed salbutamol	251 (233–271)	0.93
Night-time cough		
Age <40 years	209 (190–230)	
Age ⩾40 years	287 (271–305)	**<0.001**
BMI <30 kg·m^{-2}	257 (243–274)	
BMI ⩾30 kg·m^{-2}	292 (244–289)	**0.03**
Male	237 (217–258)	
Female	258 (242–274)	0.25
All	250 (237–263)	
As-needed BF	247 (230–265)	
As-needed salbutamol	253 (235–271)	0.87
Daytime wheeze		
Age <40 years	176 (156–198)	
Age ⩾40 years	256 (238–275)	<0.001
BMI <30 kg·m^{-2}	224 (209–241)	
BMI ⩾30 kg·m^{-2}	264 (235–297)	0.025
Male	235 (214–257)	
Female	233 (215–252)	0.93
All	234 (220–248)	
As-needed BF	238 (218–260)	
As-needed salbutamol	229 (210–249)	0.51
Night-time wheeze		
Age <40 years	168 (150–188)	
Age ⩾40 years	245 (228–262.2)	<0.001
BMI <30 kg·m^{-2}	214 (201–230)	
BMI ⩾30 kg·m^{-2}	250 (223–281)	0.035
Male	221 (203–243)	
Female	224 (207–242)	0.90
All	223 (210–236)	
As-needed BF	224 (206–244)	
As-needed salbutamol	222 (204–241)	0.83

Data are presented as n (95% CI), unless otherwise stated. Bold type represents statistical significance. BMI: body mass index; BF: beclomethasone–formoterol. Rounding errors.

more common in those aged >40 years and in those with a higher BMI (table 1). An expanded analysis of the daytime and night-time cough by age in deciles showed a linear trend of increasing cough episodes to age 50–54 years, with a plateau thereafter (figure 1a)

Wheeze incidence

An episode of wheeze was reported on a median of 322 days per year. >450 000 wheeze episodes were recorded. Thus, the average rating (on the four-point scale) of wheeze per episode was 1.19. There were no significant sex differences.

Diurnal symptoms

When daytime and night-time wheeze episodes and ratings were compared there was no significant difference; daytime incidence was 102 *versus* nocturnal 96. Both daytime and night-time wheeze were more common in those aged >40 years and in those with a higher BMI (table 1). An expanded analysis of daytime and night-time wheeze by age in deciles showed a linear trend of increasing wheeze episodes to age 50–54 years, with a plateau thereafter (figure 1b).

Incidence of combined cough and wheeze symptoms

Figure 2 shows a scatter plot of total cough *versus* wheeze episodes with quartile reference lines drawn separately for both distributions. The correlation between the incidence of cough and wheeze was r=0.73 with many patients lying on the line of identity between the two symptoms. The quartile (Q) groups for cough incidence episodes were based on the following cut-points. Q1: 0–66 (n=417); Q2: 67–226 (n=429); Q3: 227–564 (n=428); and Q4: ⩾565 (n=427). The quartile groups for wheeze incidence episodes were based on the following cut-points. Q1: 0–34 (n =420); Q2: 35–168 (n=425); Q3: 169–503 (n=428); and Q4: ⩾504 (n=428). The incidence of cough was 377 (95% CI 360–395) which was greater than that of wheeze at 341 (322–360). When analysed in quarters, the top quartile had >525 incidences of cough (Q4) and >503 incidences of wheeze (Q4). 19% (n=316) of patients were in the top quartiles for both cough and wheeze (Q4 for both symptoms).

In contrast, few patients (n=8) were completely asymptomatic. However, many patients had relatively few symptoms, hence the high density of patients located in the lower left-hand section of figure 2. Indeed, just under half (747) of the patients reported <100 episodes of cough and/or wheeze. When present at low frequency, symptoms tended to be either predominantly cough or wheeze.

Table 2 shows demographic summary characteristics for cough/wheeze episodes. Patients in the top quartile (figure 2) were older (median 53 years *versus* 43 years) and heavier (median 27 kg·m^{-2} *versus* 23 kg·m^{-2}. While most patients reported both cough and wheeze at the same rate, two phenotypes stood out: 1) patients who had cough (Q4) and negligible wheeze (Q1); and 2) those with predominant wheeze (Q4) and minimal cough (Q1). Patients with predominant cough were mostly females with a high BMI, whereas those with isolated wheeze were predominantly males in the older age group. Cough-predominant asthmatics had a mean age of 57 years (study average 49 years), of whom 76% were female (study population 60%) and 31% were obese (study population 23%). Wheeze-predominant asthmatics had an average age of 53 years, of whom 70% were male.

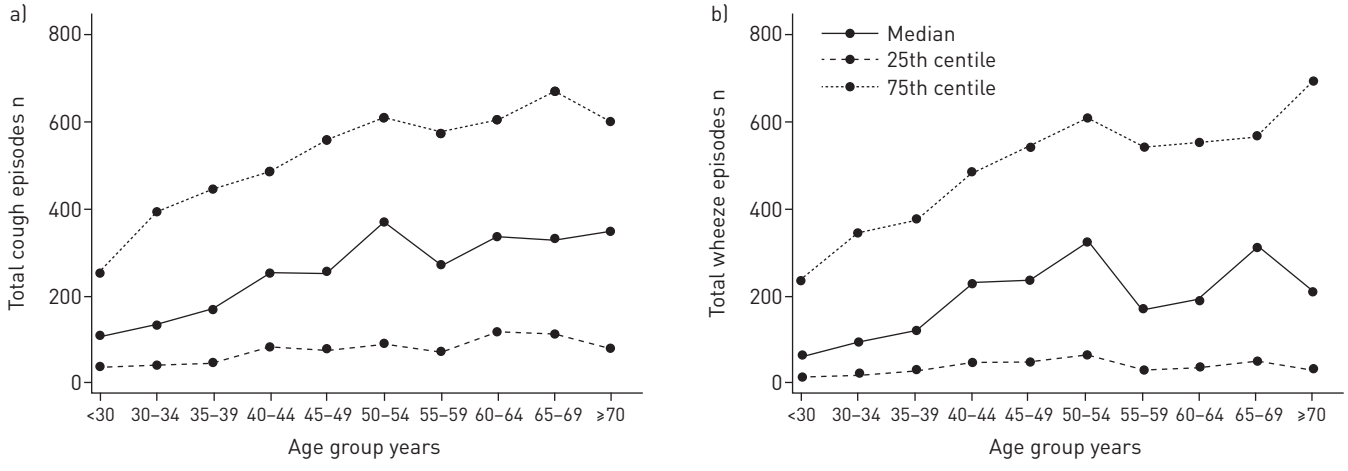

FIGURE 1 a) Distribution of total cough episodes by age; b) distribution of total wheeze episodes by age.

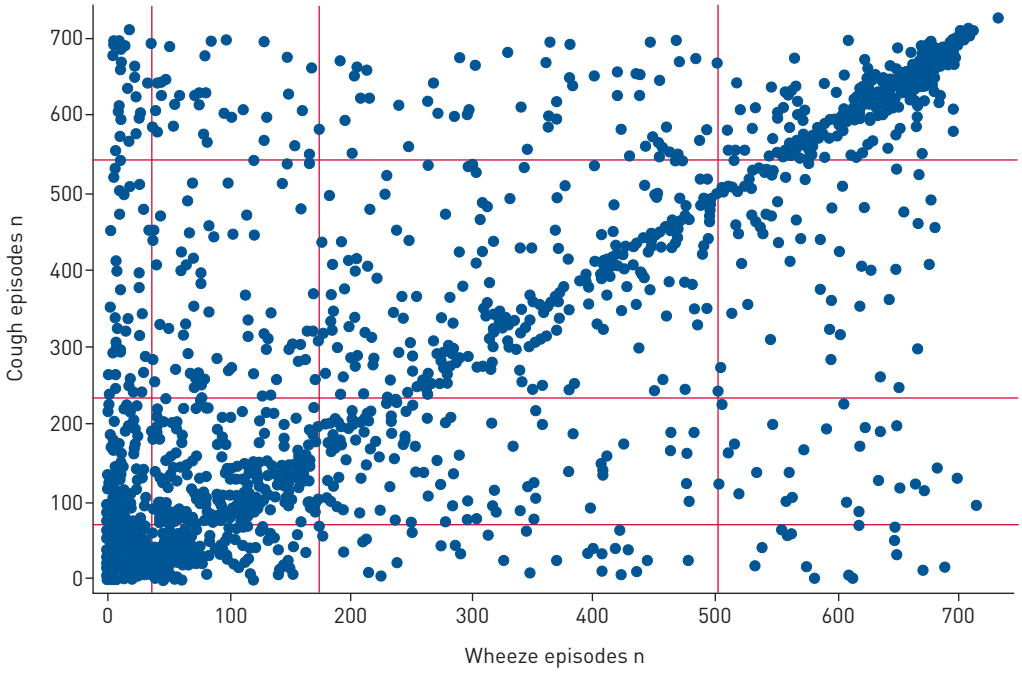

FIGURE 2 Scatter plot of the episodes of cough *versus* wheeze episodes with reference lines drawn at distribution quartiles.

Relationship between cough and wheeze with forced expiratory volume in 1 s and peak expiratory flow rate

Surprisingly, there was no linear relationship between either forced expiratory volume in 1 s (FEV_1) or PEF rate and the episodes of wheeze or cough. This was uninfluenced by sex and BMI.

The effect of treatment on symptoms

Both cough and wheeze symptom scores decreased by approximately one-quarter during treatment, with no significant difference observed between MART and as-required salbutamol. This was true of both nocturnal and daytime symptoms.

Exacerbations

In total there were 326 severe and 5636 mild asthma exacerbations contributing to an incidence rate of 0.26 (95% CI 0.22–0.29) and 4.62 (95% CI 4.35–4.90), respectively per-person-years (table 3). Patients in Q1 had a lower exacerbation rate (0.18) than more symptomatic patients (0.28; p=0.026), but there was no linear relationship between increasing degree of symptoms and exacerbation rate when viewed in Q2 (0.28), Q3 (0.36) and Q4 (0.23). Thus, worsening symptom scores were not closely linked to exacerbation frequency.

The incidence of exacerbations was significantly lower in the as-needed beclomethasone–formoterol group (0.20 per person-years) compared to the as-needed salbutamol group (0.31 per person-years) (p=0.002). There were 50% more severe exacerbations in symptomatic patients (Q2–Q4) when compared to relatively asymptomatic patients (Q1). The beneficial effect of MART on the number of severe exacerbations was unrelated to the severity of symptoms (table 4). Indeed, patients with the fewest symptoms appeared to gain the greatest positive effect from MART therapy.

Females had a greater trend in incidence of severe exacerbations than males (p=0.07), irrespective of treatment allocation.

ACQ scores

The median ACQ score at baseline was 1.8 (95% CI 1.4–2.4). There was a linear relationship between baseline quartiles of ACQ and the incidence of cough per person-years (p<0.001). The incidence of cough per quartile was Q1: 198 (95% CI 58–585); Q2: 353 (94–683); Q3: 444 (135–693); and Q4: 639 (247–712). In addition, there was a linear relationship between ACQ scores and the incidence of wheeze per

TABLE 2 Characteristics of cough/wheeze episodes by quartiles of respective distributions

Cough quartiles	Wheeze quartiles			
	Q1	Q2	Q3	Q4
Q4				
Age years	57 (44–59)	56 (47–62)	52 (39–61)	53 (45–60)
BMI kg·m^{-2}	27 (25–30)	27 (23–29)	26 (24–28)	27 (24–29)
Female %	76	63	52	61
Subjects n	25	32	54	316
Q3				
Age years	53 (45–58)	49 (40–58)	47 (36–56)	53 (46–60)
BMI kg·m^{-2}	27 (23–31)	26 (23–29)	26 (23–29)	27 (25–31)
Female %	66	69	61	60
Subjects n	41	65	250	72
Q2				
Age years	49 (36–59)	45 (32–56)	48 (40–59)	50 (42–58)
BMI kg·m^{-2}	26 (22–29)	26 (23–29)	27 (24–30)	28 (24–29)
Female %	74	66	69	56
Subjects n	101	203	98	27
Q1				
Age years	43 (3–55)	46 (35–55)	47 (40–53)	53 (41–62)
BMI kg·m^{-2}	23 (22–28)	26 (23–29)	27 (24–31)	26 (24–30)
Female %	60	55	38	31
Subjects n	253	235	26	13

Data are presented as incidence (95% CI) unless otherwise stated. Q1–Q4: distribution quartiles; BMI: body mass index.

person-years (p<0.001). The incidence of wheeze per quartile was Q1: 84 (95% CI 17–447); Q2: 199 (46–643); Q3: 386 (127–700); and Q4: 661 (222–726).

Discussion

The main objective of this *post hoc* analysis was to improve our understanding of the profile of symptoms experienced by patients with uncontrolled asthma. Cough and wheeze were recorded twice daily on a categorical 0–3 scale and, given that this population was recruited on the spirometric criteria of β-agonist reversibility, it is perhaps surprising that patients reported cough as the more predominant symptom. In the majority of patients, the occurrence of both symptoms was highly correlated; however, we have identified two phenotypic clusters: patients with an isolated chronic cough, and fewer patients with isolated wheeze as their main symptom. The chronic cough patients were predominantly older females with a high BMI. This observation is in keeping with reports from specialist cough clinics where females outnumber males in a ratio of 2:1 and obesity is a significant association [20]. It has been suggested that this female preponderance represents a sex-related heightened cough sensitivity [21, 22] that manifests as cough hypersensitivity syndrome [23]. We propose that this cluster corresponds to an unrecognised form

TABLE 3 Incidence of severe exacerbations

	Incidence per person-years	p-value
All patients	0.26 (0.22–0.29)	
As-needed BF	0.20 (0.16–0.26)	
As-needed salbutamol	0.31 (0.26–0.37)	**0.002**
Age <40 years	0.26 (0.19–0.35)	
Age ⩾40 years	0.26 (0.22–0.30)	0.79
BMI <30 kg·m^{-2}	0.25 (0.21–0.30)	
BMI ⩾30 kg·m^{-2}	0.27 (0.21–0.350)	0.63
Female	0.28 (0.24–0.33)	
Male	0.22 (0.17–0.28)	**0.07**

Data are presented as n (95% CI), unless otherwise stated. Bold type represents statistical significance. BF: beclomethasone–formoterol; BMI: body mass index.

TABLE 4 Incident rate ratios (IRR) of severe exacerbations based on individual symptom incidence scores (quartiles of table 3) overall and based on individualised randomised treatments

	IRR		
	All patients	**MART**	**As-required salbutamol**
Cough			
Q1	0.11	0.07	0.14
Q2	0.19	0.12	0.25
Q3	0.24	0.21	0.28
Q4	0.21	0.19	0.23
Wheeze			
Q1	0.12	0.08	0.17
Q2	0.18	0.12	0.23
Q3	0.22	0.15	0.28
Q4	0.23	0.24	0.22

MART: maintenance and reliever therapy; Q: quartile.

of cough-variant asthma that may require additional management strategies. Two previous studies have demonstrated a preponderance of females with higher BMI in patients with severe asthma [24, 25]. Subsequently, a cluster analysis by Haldar *et al.* [26] reported a discordance of symptoms and eosinophilic inflammation in obese females with late-onset asthma, suggesting the existence of alternative pathophysiological mechanisms. In contrast, those subjects in the current analysis with isolated wheeze were males aged >50 years.

Despite having to demonstrate uncontrolled asthma at entry to the study, neither of the symptoms was correlated with measures of lung function in any of the phenotypes identified. Symptoms per episode of cough or wheeze were rated as mild, with a mean rating of 1.32 and 1.19, respectively, out of a maximum of 3. This contrasts with retrospective surveys of asthma morbidity that claim patients such as those in the current analysis are highly symptomatic [27]. It is possible that recollection bias may influence retrospective surveys. Alternatively, the reduction of a quarter in recorded symptoms in both arms of this study may represent fatigue in the daily reporting of symptoms or a trial effect due to greater compliance. With cough it is now possible to compare objective measurement of cough counts with contemporaneously recorded subjective scores, and high correlations (r>0.6) are reported [28]. Until objective long-term measures of symptoms in asthma are developed, reliance on subjective reporting will remain our only available, if imperfect, tool.

Perhaps the most interesting findings of our analyses were the relationships between symptoms and exacerbations. In the original report by Papi *et al.* [14], MART reduced the number of severe exacerbations by one-third when analysed using a survival model of the time to first exacerbation. The Poisson regression of the total number of asthma exacerbations reported here confirms the marked reduction in exacerbations associated with MART therapy.

In multiple randomised controlled trials, budesonide–formoterol single (S)MART reduced exacerbations by 20–76% against conventional dosing of a variety of twice-daily therapies [8–10, 12, 14, 29]. The COMPASS study [10] compared conventional twice-daily high-dose budesonide–formoterol or fluticasone–salmeterol with SMART and found only the latter reduced exacerbation rates, despite a lower total drug exposure. Thus, it appears that the benefits of adjustable and maintenance treatment in reducing the exacerbation rate reside in the treatment regime itself rather than the specific drug combination used. The mechanism for this striking and reproducible effect is unknown, but conventional paradigms would predict an equally impressive effect on the asthma control. We did not find this to be the case.

In contrast to the large effect of MART on severe exacerbations, there was negligible treatment effect on daily scores of either cough or wheeze. We suggest that mild exacerbations, defined in the protocol as an increased PEF variability, nocturnal symptoms and/or reliever use are a composite of the objective and subjective measures of asthma control. When a highly effective LABA, such as formoterol, is measured against a composite end-point containing lung function then a reduction in the number of poorly controlled days is to be expected, as indeed was reported by Papi *et al.* [14]. Bateman *et al.* [30], using a Markov analysis of five studies of budesonide–formoterol SMART also showed no improvement in the

category of asthma control, except for a significant reduction in severe exacerbations. Indeed, in our analysis, the MART protocol appeared to be more effective in reducing exacerbations in patients with milder symptoms (table 4).

How might this apparent paradox of a marked therapeutic effect on severe exacerbations with minimal impact on daily symptom scores and asthma control be explained? While there is no doubt that in mild and moderate asthma exacerbation rate and asthma control are closely linked, perhaps in severe asthma the relationship between these two phenomena breaks down. There are several strands of evidence tp support this hypothesis. In 1999, Reddel *et al.* [31] first demonstrated the dissociation between indices of asthma control and exacerbations in patients established on high-dose inhaled corticosteroids. In addition, the effect of anti-asthma medication suggests that exacerbations and asthma control may be independent variables. In the FACET study [32] there was a marked reduction in exacerbation rate with higher doses of inhaled steroids, with little effect on asthma control. In contrast, formoterol improved asthma control with a lesser effect on exacerbations. Mepolizumab, an anti-interleukin-5 antibody, significantly reduced severe exacerbations and eosinophilic inflammation, but had no benefit on asthma symptoms, FEV_1 or airway hyperresponsiveness [33]. Green *et al.* [34] have compared a management strategy targeting eosinophilic inflammation with conventional guideline-based management aimed at improving asthma control. Marked reductions in asthma exacerbations and hospital admissions were seen with targeted management, but with no differences in any measures of asthma control, FEV_1 and bronchodilator use between the study arms.

There are some limitations to this study; chiefly, the lack of objective measures of symptoms such as cough counting and the absence of measures of airway inflammation. The latter would have been useful in the description of patient characteristics and the relationship with response to treatment.

In conclusion, we have demonstrated that patient-reported symptoms in asthma can be used to distinguish phenotypes that may benefit from individualised therapy, such as those directed against cough hypersensitivity. Thus, in contrast to the current concept of aggregating various parameters into a composite measure of "asthma control", it is possible that meaningful information may be simply derived in the clinic by assessing the profile of individual symptoms, prompting further detailed patient history and specific investigations. In our analysis symptoms proved to be poorly predictive of severe exacerbations. Asthma symptoms and exacerbations may not be intimately related, inferring the existence of different underlying pathophysiological mechanisms. MART was again demonstrated to be highly successful in reducing exacerbations, and this was particularly apparent in those with milder symptoms. Thus, MART therapy shows its greatest potential across the spectrum of symptoms in asthma and should not be reserved for those who are highly symptomatic.

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References

1 Boushey HA, Sorkness CA, King TS, *et al.* Daily *versus* as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005; 352: 1519–1528.
2 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/ Date last accessed: May 10, 2017. Date last updated: May 10, 2017.
3 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. SIGN 153. www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016/ Date last accessed: September 2016. Date last updated: September 2016.
4 Bateman ED, Boushey HA, Bousquet J, *et al.* Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004; 170: 836–844.
5 Papi A, Paggiaro P, Nicolini G, *et al.* Beclomethasone/formoterol *vs* fluticasone/salmeterol inhaled combination in moderate to severe asthma. *Allergy* 2007; 62: 1182–1188.
6 Papi A, Paggiaro PL, Nicolini G, *et al.* Beclomethasone/formoterol *versus* budesonide/formoterol combination therapy in asthma. *Eur Respir J* 2007; 29: 682–689.
7 Rabe KF, Pizzichini E, Ställberg B, *et al.* Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest* 2006; 129: 246–256.
8 O'Byrne PM, Bisgaard H, Godard PP, *et al.* Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005; 171: 129–136.
9 Scicchitano R, Aalbers R, Ukena D, *et al.* Efficacy and safety of budesonide/formoterol single inhaler therapy *versus* a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin* 2004; 20: 1403–1418.
10 Kuna P, Peters MJ, Manjra AI, *et al.* Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract* 2007; 61: 725–736.

11 Vogelmeier C, D'Urzo A, Pauwels R, *et al.* Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J* 2005; 26: 819–828.
12 Bousquet J, Boulet LP, Peters MJ, *et al.* Budesonide/formoterol for maintenance and relief in uncontrolled asthma *vs*. high-dose salmeterol/fluticasone. *Respir Med* 2007; 101: 2437–2446.
13 Buhl R, Kuna P, Peters MJ, *et al.* The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. *Respir Res* 2012; 13: 59.
14 Papi A, Corradi M, Pigeon-Francisco C, *et al.* Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med* 2013; 1: 23–31.
15 Juniper EF, Svensson K, Mörk AC, *et al.* Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005; 99: 553–558.
16 Nathan RA, Sorkness CA, Kosinski M, *et al.* Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004; 113: 59–65.
17 Schatz M, Sorkness CA, Li JT, *et al.* Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006; 117: 549–556.
18 Cox DR. Some remarks on overdispersion. *Biometrika* 1983; 70: 269–274.
19 Dean CB, Lawless JF. Tests for detecting overdispersion in Poisson regression models. *J Am Stat Assoc* 1989; 84: 467–472.
20 Ford AC, Forman D, Moayyedi P, *et al.* Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax* 2006; 61: 975–979.
21 Kastelik JA, Thompson RH, Aziz I, *et al.* Sex-related differences in cough reflex sensitivity in patients with chronic cough. *Am J Respir Crit Care Med* 2002; 166: 961–964.
22 Kelsall A, Decalmer S, McGuinness K, *et al.* Sex differences and predictors of objective cough frequency in chronic cough. *Thorax* 2009; 64: 393–398.
23 Morice AH, Faruqi S, Wright CE, *et al.* Cough hypersensitivity syndrome: a distinct clinical entity. *Lung* 2011; 189: 73–79.
24 The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J* 2003; 22: 470–477.
25 Varraso R, Siroux V, Maccario J, *et al.* Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005; 171: 334–339.
26 Haldar P, Pavord ID, Shaw DE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178: 218–224.
27 Partridge MR, van der Molen T, Myrseth SE, *et al.* Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006; 6: 13.
28 Faruqi S, Thompson R, Wright C, *et al.* Quantifying chronic cough: objective *versus* subjective measurements. *Respirology* 2011; 16: 314–320.
29 Rabe KF, Atienza T, Magyar P, *et al.* Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006; 368: 744–753.
30 Bateman ED, Reddel HK, Eriksson G, *et al.* Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol* 2010; 125: 600–608.
31 Reddel H, Ware S, Marks G, *et al.* Differences between asthma exacerbations and poor asthma control. *Lancet* 1999; 353: 364–369.
32 Pauwels RA, Löfdahl CG, Postma DS, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997; 337: 1405–1411.
33 Haldar P, Brightling CE, Hargadon B, *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360: 973–984.
34 Green RH, Brightling CE, McKenna S, *et al.* Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; 360: 1715–1721.