Impact of changes to reimbursement of fixed combinations of inhaled corticosteroids and long-acting β₂-agonists in obstructive lung diseases: a population-based, observational study

U. S. Björnsdóttir, S. T. Sigurðardóttir, J. S. Jonsson, M. Jonsson, G. Telg, M. Thuresson, I. Naya, S. Gizurarson

SUMMARY

Background: In 2010, the Icelandic government introduced a new cost-saving policy that limited reimbursement of fixed inhaled corticosteroid/long-acting β₂-agonist (ICS/LABA) combinations. Methods: This population-based, retrospective, observational study assessed the effects of this policy change by linking specialist/primary care medical records with data from the Icelandic Pharmaceutical Database. The policy change took effect on 1 January 2010 (index date); data for the year preceding and following this date were analysed in 8241 patients with controlled/partly controlled asthma and/or chronic obstructive pulmonary disease (COPD) who had been dispensed an ICS/LABA during 2009. Oral corticosteroid (OCS) and short-acting β₂-agonist (SABA) use, and healthcare visits, were assessed pre- and post-index. Results: The ICS/LABA reimbursement policy change led to 47.8% fewer fixed ICS/LABA combinations being dispensed during the post-index period among patients whose asthma and/or COPD was controlled/partly controlled during the pre-index period. Fewer ICS monocomponents were also dispensed. A total of 48.6% of patients were no longer receiving any respiratory medications after the policy change. This was associated with reduced disease control, as demonstrated by more healthcare visits (44.0%), and more OCS (76.3%) and SABA (51.2%) dispensations. Conclusions: Overall, these findings demonstrate that changes in healthcare policy and medication reimbursement can directly impact medication use and, consequently, clinical outcomes and should, therefore, be made cautiously.

What's known
Changes in reimbursement policies that require patients to contribute a large amount towards the cost of their medication can have a negative impact on disease control. The use of separate inhaled corticosteroid (ICS) and long-acting β₂-agonist (LABA) inhalers results in reduced asthma control, compared with the use of a fixed ICS/LABA combination. In addition, non-consensual inhaler switches have been linked to reduced disease control in patients with previously controlled asthma.

What's new
Following changes in respiratory medication reimbursement policy in Iceland, fewer fixed ICS/LABA combinations were used by patients with previously controlled/partly controlled asthma and/or chronic obstructive pulmonary disease. Fewer ICS monocomponents were dispensed, and patients used more oral corticosteroids and short-acting β₂-agonists. This suggests that the policy change was associated with poorer disease control.

Background

Fixed inhaled corticosteroid/long-acting β₂-agonist (ICS/LABA) combination therapy is well documented in both asthma (1) and chronic obstructive pulmonary disease (COPD) (2) management guidelines to achieve and maintain control of symptoms, and reduce the risk of exacerbations. Randomised controlled trials in patients with controlled asthma show that discontinuing a fixed ICS/LABA combination in favour of ICS monotherapy results in a greater loss of asthma control compared with reducing the dose of the existing fixed ICS/LABA combination (3). Use of ICS and LABA monocomponents is associated with a higher risk of exacerbations and higher reliever use than fixed ICS/LABA combinations via a single inhaler (4).

Non-consensual inhaler switches in patients with controlled asthma have been linked with reduced disease control (5–7). Finally, using LABA monotherapy without a concurrent ICS leads to poorer outcomes in asthma and is associated with increased mortality; therefore, the use of separate inhalers should be avoided to prevent use of LABA monotherapy (8,9). Among patients with COPD, several studies have shown that the use of a fixed ICS/LABA combination is more effective at controlling COPD than ICS or LABA monotherapy (10–14). However, to our knowledge, the effects of non-consensual therapy switching on COPD control have not been studied.

In September 2008, the Icelandic national economy faced an unprecedented level of financial crisis, with the possibility of national bankruptcy (15). One
step taken by the Icelandic government to ensure economic survival was to place restrictions on various aspects of healthcare, including the use of specific medications, procedures and specialist care across a number of therapeutic areas — a cost-containment step that has been used in other European countries as a means of reducing expenditure (16). Particularly, on 1 January 2010, the Icelandic Ministry of Health introduced a new regulation regarding the reimbursement of fixed ICS/LABA combinations related to any diagnosis. This change in the regulation immediately moved the cost of continued therapy with fixed ICS/LABA combinations to the patient (unless a special reimbursement of the medication cost was applied for and approved) or forced physicians and patients to find alternative regimens and/or treatment strategies, such as receiving the two medications via separate inhalers.

Changes in reimbursement policies that require patients to contribute a large amount towards the cost of their medication may result in a negative impact on overall adherence (17,18), as has been shown for asthma medications (19,20). In addition, the use of separate ICS and LABA inhalers results in reduced asthma control, compared with the use of a fixed ICS/LABA combination (4). The same is true when asthma patients change from a fixed ICS/LABA combination to ICS monotherapy (3,21).

Ascertaining whether the revised reimbursement policy in Iceland led to changes in medication use, loss of disease control or an increased risk of exacerbations in patients with asthma and COPD is of clinical interest. The current observational study investigated the impact of the policy change on medication and healthcare utilisation in patients diagnosed with asthma and/or COPD that was previously controlled/partly controlled. Patients with uncontrolled disease were excluded from this analysis as changes in medication use among these patients were more likely to be because of medical reasons than the reimbursement policy.

Methods

Study design

This was a population-based, retrospective, observational, registry study (NCT01369810). The study was approved by the Icelandic Bioethics Committee (reference VSNb2010110021), the Icelandic Data Protection Committee (reference 2011030368), the Bioethics Committee of the Landspitali University Hospital (reference 16 Hf/ei) and the Icelandic Directorate of Health (reference 2010110080).

Data were collected from both medical records and the Icelandic Pharmaceutical Database. Data derived from medical records included: date of birth; gender; diagnoses [International Classification of Diseases, 10th Edition, Clinical Modification (ICD-10-CM) codes]; and number of healthcare contacts. The pharmaceutical database provided data on: date of birth; gender; dispensed drugs; drug name; drug strength; number of doses; number of defined daily doses (the assumed average maintenance dose per day for a drug used for its main indication in adults); and date of collection.

The linking of data from patient medical records and the Icelandic Pharmaceutical Database was performed by the Icelandic Directorate of Health. The linked database is held by the Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland.

The index date was 1 January 2010 (the date of the reimbursement changes); data for this study were collected from 1 January 2009 to 31 December 2010.

Patient population

Data were collected for all patients in the Icelandic Pharmaceutical Database (N = 46,269) who had been dispensed at least one fixed ICS/LABA combination at any time during 2009. Patients were classified as having controlled/partly controlled disease if they had been dispensed ≤1 oral corticosteroid (OCS) course and ≤2 short-acting β₂-agonists (SABAs) during 2009. Patients exceeding these limits were considered to be uncontrolled and were excluded from the analysis; patients who did not have a diagnosis of either asthma and/or COPD were also excluded.

Outcome measures

The impact of the reimbursement policy change on controlled/partly controlled patients was assessed using the following outcomes: number of fixed ICS/LABA combinations, ICS, LABAs, OCS and SABAs dispensed pre- and post-index; and number of healthcare visits for any reason (visits to general practitioners, pulmonary specialists and allergists/asthma specialists; data for private care visits were not available) in the 1-year period before and after the index date. Visits or admissions to hospitals were not possible to extract in this study. To assess the impact of the volcanic ash cloud that affected Iceland in April 2010 on medication use and healthcare visits, we performed a sensitivity analysis in which these outcomes were also assessed for a 3-month period (August–October) during 2009 and 2010.

The medication possession ratio [MPR; i.e. (number of dispensed defined daily doses/365) × 100] was used to determine the use of fixed ICS/LABA combinations in the pre-index period (i.e. in 2009).
The MPR was used to categorise patients as follows: continuous users (≥ 80%); intermediate users (40–80%); occasional users (< 40%). Patients were also stratified according to age: adolescents/children (aged < 18 years), adults (aged 18–65 years) or elderly patients (aged ≥ 65 years).

Statistical analyses
The main statistical analyses for this study were descriptive, for which data are presented using standard summary statistics such as mean (with standard deviation) and frequency (%). The risk of stopping fixed-combination ICS/LABA treatment and of having uncontrolled disease during the post-index period (2010) was analysed using a logistic regression analysis; the independent factors in the model were diagnosis (asthma and/or COPD), age and gender. The results are presented as odds ratios with corresponding 95% confidence limits and p-values. The statistical analyses were performed using R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results
Patients
From the database of 46,269 individuals, 13,814 patients received a fixed ICS/LABA combination during 2009. Of these, 1895 (13.7%) were uncontrolled based on our predefined criteria (dispensed > 1 OCS course and > 2 SABAs during 2009) and were, therefore, excluded. In addition, another 3678 patients were excluded because they had not been diagnosed with either asthma or COPD. The remaining 8241 patients were considered to be controlled/partly controlled (mean age, 47.0 years; 58.4% females) and were included in the analysis (Figure 1). The majority of the controlled/partly controlled patients had a diagnosis of asthma (n = 6142; 74.5%), 1340 (16.3%) patients had COPD, while 759 (9.2%) had a diagnosis of both asthma and COPD (Table 1).

Prior to the index date, the majority of patients were considered to be occasional users of fixed ICS/LABA combinations (62.0%; n = 5111), while 25.9% (n = 2134) were intermediate users and 12.1% (n = 996) were continuous users. Mean age was highest among continuous users and lowest among occasional users. Similarly, continuous users had more healthcare visits and asthma- and COPD-related healthcare visits, compared with occasional or intermediate users (Table 2). In addition, occasional users were more likely to be OCS free during the pre-index period than continuous or intermediate users of fixed ICS/LABA combinations.

Medication use
The total use of respiratory medications 6 months after the index date was 51.4% (Figure 2). A total of 48.6% of the patients who were controlled/partly controlled prior to index were not dispensed any respiratory medications during the post-index period: 54.0% of patients with asthma, 27.0% of those with diagnoses of both asthma and COPD, and 35.7% of those with COPD.

Overall, there were 47.8% fewer fixed ICS/LABA combinations dispensed after the index date (mean change from 197.5 to 103.1 fixed ICS/LABAs dispensed per 100 patient-years); this included 34.4% fewer ICS/LABA combinations dispensed in continuous users (from 450.9 to 296.0 per 100 patient-years), 39.8% fewer in intermediate users (from 254.2 to 153.0 per 100 patient-years) and 64.1% fewer in occasional users (from 124.4 to 44.7 per 100 patient-years; Figure 3A). There were 68.0% fewer dispensed ICS monocomponents (from 127.9 to 40.9 per 100 patient-years), although more LABA monocomponents were dispensed (611.8%; from 1.7 to 12.1 per 100 patient-years).

Figure 1 Patient flow. COPD, chronic obstructive pulmonary disease; ICS/LABA, inhaled corticosteroid/long-acting β2-agonist; OCS, oral corticosteroid; SABA, short-acting β2-agonist.
Occasional and intermediate users of fixed ICS/LABA combinations and adolescents/children were significantly more likely to discontinue ICS/LABA combination therapy during the post-index period (all p < 0.001 vs. continuous users and adult patients, respectively; Table 3). Elderly patients and those with a COPD or asthma/COPD diagnosis were significantly more likely to continue fixed ICS/LABA treatment post-index than adult patients and those with an asthma diagnosis only, respectively (all p < 0.001). The same factors were predictive of having uncontrolled disease during the post-index period (all p ≤ 0.001; Table 4).

Measures of disease control
More OCS and SABAs were dispensed during the post-index period, compared with pre-index (Figure 3B and C). In the overall patient population, there were 76.3% more OCS and 51.2% more SABAs dispensed (from 16.0 to 28.2 and from 37.5 to
56.7 dispensations per 100 patient-years, respectively). The same pattern was seen in the continuous, intermediate and occasional users subgroups for the number of OCS dispensations [ranging from 64.3% (from 12.6 to 20.7 per 100 patient-years) to 88.8% more dispensations (from 25.9 to 48.9 per 100 patient-years)] and SABA dispensations [ranging from 38.7% (from 35.4 to 49.1 per 100 patient-years)]

Figure 2 Drugs collected during the first 6 months following the index date (1 January 2010). R03 class medications are defined as ‘Drugs for obstructive airway diseases’. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; SABA, short-acting β2-agonist

Figure 3 Comparison between medications dispensed [fixed ICS/LABA combinations (A), OCS (B) and SABAs (C)] and healthcare visits (for any reason) (D) per 100 patient-years in the pre- (2009) and post-index (2010) period in continuous, intermediate and occasional users and in all patients combined. Error bars represent 95% confidence intervals. ICS/LABA, inhaled corticosteroid/long-acting β2-agonist; OCS, oral corticosteroid; SABA, short-acting β2-agonist
Changes to reimbursement of fixed ICS/LABAs

By contrast, the volcanic ash cloud may have impacted healthcare visits, as somewhat different findings were observed when data for August–October of the pre- and post-index periods were compared. Overall, there were 10.9% fewer healthcare visits (from 29.3 to 26.1 visits per 100 patient-years); this was primarily driven by the fact that there were 27.7% fewer healthcare visits in the occasional users subgroup (from 25.3 to 18.3 visits per 100 patient-years). More healthcare visits were seen in continuous and intermediate users (16.1%, from 40.9 to 47.5 visits per 100 patient-years and 3.9%, from 33.6 to 34.9 visits per 100 patient-years, respectively).

Discussion

This population-based, retrospective, observational study shows that the Icelandic government’s policy change regarding respiratory medications, whereby reimbursement of fixed ICS/LABA combinations was limited, resulted in fewer dispensations of fixed ICS/LABA combinations. While somewhat more LABA monotherapies were also dispensed, this change was not large enough to compensate for the lower ICS/LABA use, and fewer ICS monotherapies were dispensed. Notably, a marked proportion of patients with asthma and/or COPD were no longer receiving any respiratory medications at all. Deterioration in disease control was observed following the policy change, as demonstrated by more OCS and SABA dispensations and more healthcare visits.

Occasional users, the patient subgroup who had the fewest fixed ICS/LABA combinations dispensed before the index date, were the least likely to receive}

| Table 3  | Patient characteristics associated with a change in the risk of not receiving previously prescribed fixed ICS/LABA combination therapy (Yes/No) post-index (during 2010) as a dependent variable |
|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Characteristic | OR (95% CL) | p-value |
| Diagnosis of asthma and COPD | 0.45 (0.37, 0.54) | < 0.001 |
| Diagnosis of COPD | 0.76 (0.65, 0.88) | < 0.001 |
| Adolescent/child | 1.54 (1.33, 1.79) | < 0.001 |
| Elderly | 0.69 (0.61, 0.78) | < 0.001 |
| Men | 1.03 (0.93, 1.15) | 0.517 |
| Occasional users | 12.88 (10.73, 15.55) | < 0.001 |
| Intermediate users | 2.72 (2.25, 3.32) | < 0.001 |

CL, confidence limit; COPD, chronic obstructive pulmonary disease; ICS/LABA, inhaled corticosteroid/long-acting β2-agonist; OR, odds ratio. *vs. an asthma only diagnosis. †vs. adult patients (aged 18–65 years). ‡vs. female patients. §vs. continuous users. OR values > 1.0 indicate an increased or decreased risk, respectively, of discontinuing fixed ICS/LABA therapy.

Healthcare visits (for any reason)

During the post-index period, there were 44.0% more total healthcare visits (from 79.8 to 114.9 visits per 100 patient-years) in the overall patient population (Figure 3D); this change was particularly high in the occasional users subgroup (71.0%; from 54.8 to 93.7 visits per 100 patient-years).

Sensitivity analysis

Healthcare utilisation in August–October of the pre- and post-index periods was assessed to exclude the potential confounding effect of the volcanic ash cloud that affected Iceland during April 2010. In these analyses, data for the pre- and post-index periods regarding the number of fixed ICS/LABAs, OCS and SABAs dispensed were similar to those obtained for the whole study period: overall, there were 49.7% fewer fixed ICS/LABAs dispensed (from 51.5 to 25.9 dispensations per 100 patient-years); in the occasional users subgroup, there were 69.0% fewer fixed ICS/LABA dispensations (from 34.8 to 10.8 per 100 patient-years). In the total population, there were 75.6% more OCS dispensed (from 4.1 to 7.2 dispensations per 100 patient-years) and 41.4% more SABA dispensations (from 9.9 to 14.0 per 100 patient-years) during the post-index, vs. the pre-index, period.

By contrast, the volcanic ash cloud may have impacted healthcare visits, as somewhat different findings were observed when data for August–October of the pre- and post-index periods were compared. Overall, there were 10.9% fewer healthcare visits (from 29.3 to 26.1 visits per 100 patient-years); this was primarily driven by the fact that there were 27.7% fewer healthcare visits in the occasional users subgroup (from 25.3 to 18.3 visits per 100 patient-years). More healthcare visits were seen in continuous and intermediate users (16.1%, from 40.9 to 47.5 visits per 100 patient-years and 3.9%, from 33.6 to 34.9 visits per 100 patient-years, respectively).

Discussion

This population-based, retrospective, observational study shows that the Icelandic government’s policy change regarding respiratory medications, whereby reimbursement of fixed ICS/LABA combinations was limited, resulted in fewer dispensations of fixed ICS/LABA combinations. While somewhat more LABA monotherapies were also dispensed, this change was not large enough to compensate for the lower ICS/LABA use, and fewer ICS monotherapies were dispensed. Notably, a marked proportion of patients with asthma and/or COPD were no longer receiving any respiratory medications at all. Deterioration in disease control was observed following the policy change, as demonstrated by more OCS and SABA dispensations and more healthcare visits.

Occasional users, the patient subgroup who had the fewest fixed ICS/LABA combinations dispensed before the index date, were the least likely to receive
these medications after the reimbursement change, which may, in part, have been because of an unwillingness to pay for their own medication. These patients were, on average, younger than intermediate or continuous users, and were most likely to be OCS free during the pre-index period. The patients most likely to receive ICS/LABA treatment post-index were the continuous users, suggesting that physicians and healthcare providers exercised good judgement by concentrating the use of this class of drug in patients likely to have the greatest need for the fixed combination. Nonetheless, although continuous users had a smaller relative reduction in fixed ICS/LABA combination use, compared with occasional and intermediate users, they had a greater increase in OCS and SABA use, showing the greatest loss of disease control. This increase was apparent despite higher baseline OCS and, to a certain extent, SABA use in the continuous than occasional users of ICS/LABA and, therefore, suggests that these changes are not explained by potential regression to the mean, but perhaps that continuous-use patients had the highest level of underlying disease activity. In addition, the occasional users had the greatest relative increase in healthcare visits, an effect that may stem from a lack of preparation regarding the switch of medication. However, these visits could be because of a number of reasons, and may not have been in response to respiratory symptoms.

It is particularly worrisome that 27–54% of patients diagnosed with asthma, COPD or both were no longer receiving any respiratory medications at all during the post-index period, as this will inevitably lead to loss of disease control, especially in patients with COPD. This suggests that there are inconsistencies between recommended disease management and actual clinical practice, an observation that has been noted elsewhere (22,23).

Our results are similar to those observed following changes to the reimbursement schedule for cardiovascular medications implemented by the Icelandic Ministry of Health in 2009. Specifically, changes in the reimbursement policy for statins were associated with increases in cholesterol levels in patients with hyperlipidaemia and heart disease (24). Other studies in the setting of asthma and COPD have drawn similar conclusions to ours (19,20). A study in children with asthma in the USA found that an increase in out-of-pocket medication costs led to a reduction in adjusted medication use and increased asthma-related hospitalisations in children (19). In Canada, a significant reduction in the use of inhaled medications was seen following the implementation of cost-sharing policies, mostly because of a reduction in treatment initiation and greater treatment discontinuation (20).

The results of this study raise the question of whether any reimbursement reductions made by the government with the intent to save cost are partially or completely offset by increases in other healthcare resource use. There was more OCS and SABA use, as well as more healthcare visits, after the reimbursement change. A complete assessment of the health-economic and financial consequences of this change in reimbursement policy was beyond the scope of this study.

A strength of this study is that it was performed in a large group of patients without any restrictions in factors such as age, employment status, concomitant medications and comorbidities or healthcare insurance. Observational studies using clinical databases enable outcomes to be assessed in a real-life, non-interventional, naturalistic setting (25). As a result, the management, prescribing patterns and adherence to guidelines in clinical practice may be effectively studied and characterised. However, such a construct is not without its weaknesses; as with all database studies, data retrieval is limited to the variables included in the databases, and potential unknown confounding factors may still reside in the data. In addition, the fact that patients with uncontrolled asthma or COPD were excluded from this analysis could have led to an overestimation of the effect of the reimbursement change. However, it was necessary to exclude these patients as they were more likely to switch medications because of medical reasons than patients with controlled/partly controlled disease.

A significant environmental change that coincided with the study period was the volcanic eruption in Iceland and subsequent ash cloud that may have confounded the results. It is not known whether the ash particles in the atmosphere had an effect on respiratory conditions or influenced the availability of, or access to, healthcare resources (e.g. because of disruptions in travel). We controlled for this potential confounding factor by assessing data from a 3-month period during 2009 and a 3-month period in 2010 during which the ash cloud had dissipated (August–October); the results of this sensitivity analysis indicated that the volcanic ash cloud did not markedly influence the full 12-month outcomes.

In this study, the validity of the asthma and COPD diagnoses could not be verified, and the study was limited by the inability to perform further evaluations involving more detailed clinical characteristics of the patients (e.g. hospital data and categorisation by disease severity or lung function measurements). Such further evaluation would have permitted more detailed examination of the relationship between poor compliance and disease outcomes; however, it was beyond the scope of the current analysis to sub-
divide the continuous users group into balanced subgroups by severity to quantify if the degree of change in continuous use correlated with the degree of deterioration in disease activity. In addition, it was not known if some patients had non-eosinophilic asthma. As the role of ICS therapies in these patients is controversial, the presence of patients with non-eosinophilic asthma could have had an impact on the results of this analysis (26, 27).

In conclusion, among patients with previously controlled/partly controlled asthma and/or COPD in Iceland, the use of fixed ICS/LABA combinations was lower following a reimbursement policy change, but the use of ICS and LABA monotherapy was not comparably higher. There were, however, more OCS and SABAs dispensed and more healthcare visits, suggesting decreased disease control. The results of this study indicate that changes to healthcare policy and medication reimbursement should be made cautiously, since they can lead to unintended clinical consequences. The Icelandic Ministry of Health has now reversed this reimbursement policy change.

Acknowledgments
This article was funded by AstraZeneca. AstraZeneca was involved in the design of the study, the collection and analysis of the data, and in the writing of the report. It was the decision of the authors to submit the paper for publication. The corresponding author had full access to all the data and final responsibility to submit for publication. The authors thank Anna Mett and Katharine Williams of inScience Communications, Springer Healthcare, for providing editorial support in the preparation of this manuscript. This support was funded by AstraZeneca.

Author contributions
U.S.B., S.T.S., J.S.J., M.J., G.T., M.T., I.N. and S.G. all contributed to conceiving, writing and revising the manuscript. M.T. was responsible for statistical analyses.

References
1 Global Strategy for Asthma Management and Prevention. 2012. http://www.ginasthma.org/ (accessed 7 February 2014).
2 Global Strategy for Diagnosis, Management, and Prevention of COPD. 2011. http://www.goldcopd.org/ (accessed 7 February 2014).
3 Brozek JL, Kraft M, Krishnan JA et al. Long-acting beta-agonist step-off in patients with controlled asthma: systematic review with meta-analysis. Arch Intern Med 2012; 172: 1365–75.
4 Angus R, Reagan R, Cheesbrough A. Short-acting beta 2-agonist and oral corticosteroid use in asthma patients prescribed either concurrent beclomethasone and long-acting beta 2-agonist or salmeterol/fluticasone propionate combination. Int J Clin Pract 2005; 59: 156–62.
5 Doyle S, Lloyd A, Williams A et al. What happens to patients who have their asthma device switched without their consent? Prim Care Respir J 2010; 19: 131–9.
6 Thomas M, Price D, Chrystyn H et al. Inhaled corticosteroids for asthma: impact of practice level device switching on asthma control. BMC Pulm Med 2009; 9: 1.
7 Bjornsdottir US, Gizurarson S, Sabale U. Potential negative consequences of non-consented switch of inhaled medications and devices in asthma patients. Int J Clin Pract 2013; 67: 904–10.
8 Perrin K, Williams M, Wijeysinghe M et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting beta-agonist inhaler therapy in asthma. J Allergy Clin Immunol 2010; 126: 505–10.
9 Cockcroft DW, Sears MR. Are inhaled longacting β2 agonists detrimental to asthma? Lancet Respir Med 2013; 1: 339–46.
10 Calverley PM, Boonsawat W, Caeke Z et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003; 22: 912–9.
11 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.
12 Rennard SI, Tashkin DP, McElhatten J et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs 2009; 69: 549–65.
13 Tashkin DP, Rennard SI, Martin P et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. Drugs 2008; 68: 1975–2000.
14 Sharafkhaneh A, Southard JG, Goldman M et al. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomised study. Respir Med 2012; 106: 257–68.
15 Haarde GH. Address to the Nation, 2008. http://eng.forsaetisraduneyti.is/news-and-articles/nr/5935 (accessed 7 February 2014).
16 Vogler S, Zimmermann N, Loepold G, de Joncheere K. Pharmaceutical policies in European countries in response to the global financial crisis. South Med Rev 2011; 4: 69–79.
17 Schneeweiss S, Patrick AR, Machure M et al. Adherence to statin therapy under drug cost sharing in patients with and without acute myocardial infarction: a population-based natural experiment. Circulation 2007; 115: 2128–35.
18 Kim YA, Rascati KL, Prasla K et al. Retrospective evaluation of the impact of copayment increases for specialty medications on adherence and persistence in an integrated health maintenance organization system. Clin Ther 2011; 33: 596–607.
19 Karaca-Mandic P, Jena AB, Joyce GF, Goldman DP. Out-of-pocket medication costs and use of medications and health care services among children with asthma. JAMA 2012; 307: 1284–91.
20 Dormuth CR, Glynn RJ, Neumann P et al. Impact of two sequential drug cost-sharing policies on the use of inhaled medications in older patients with chronic obstructive pulmonary disease or asthma. Clin Ther 2006; 28: 964–78.
21 O’Hagan RA, Morton R, Eid N. Loss of asthma control in pediatric patients after discontinuation of long-acting Beta-agonists. Pulm Med 2012; 2012: 894063.
22 Craig RM, Kraus CK, Chewing BA, Davis JE. Quality of care for older adults with chronic obstructive pulmonary disease and asthma based on comparisons to practice guidelines and smoking status. BMC Health Serv Res 2008; 8: 144.
23 Rand CS, Wise RA. Measuring adherence to asthma medication regimens. Am J Respir Crit Care Med 1994; 149: 569–76.
24 Gizurarson S, Bjornsdottir LR, Einarsdottir R et al. Clinical consequences following regulatory changes in respect to reimbursement of statins cost by the Icelandic Social Insurance Administration. Scand J Public Health 2012; 40: 663–7.
25 Price D, Chisholm A, van der Molen T et al. Reassessing the evidence hierarchy in asthma: evaluating comparative effectiveness. Curr Allergy Asthma Rep 2011; 11: 526–38.
26 Pavord ID. Non-eosinophilic asthma and the innate immune response. Thorax 2007; 62: 193–4.
27 Green RH, Brightling CE, McKenna S et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002; 360: 1715–21.

Paper received February 2014, accepted May 2014