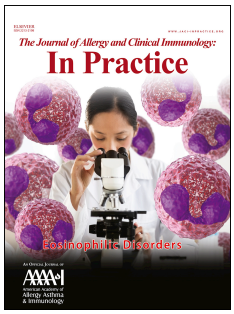
Journal Pre-proof



Intolerance to angiotensin converting enzyme inhibitors in asthma and the general population: a UK population-based cohort study

Daniel R. Morales, PhD, Brian J. Lipworth, MD, Peter T. Donnan, PhD, Huan Wang, PhD

PII: S2213-2198(21)00561-4

DOI: https://doi.org/10.1016/j.jaip.2021.04.055

Reference: JAIP 3605

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 24 August 2020

Revised Date: 21 April 2021

Accepted Date: 22 April 2021

Please cite this article as: Morales DR, Lipworth BJ, Donnan PT, Wang H, Intolerance to angiotensin converting enzyme inhibitors in asthma and the general population: a UK population-based cohort study, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: https://doi.org/10.1016/j.jaip.2021.04.055.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

Journal Pre-proof

Intolerance to angiotensin converting enzyme inhibitors in asthma and the general population: a UK population-based cohort study

Daniel R. Morales PhD, [1]Division of Population Health and Genomics, University of Dundee, UK. [2]Health Data Research (HDR)-UK Scotland. [3]Department of Public Health, University of Southern Denmark.

Brian J. Lipworth MD, Scottish Centre for Respiratory Research, University of Dundee, UK

Peter T. Donnan PhD, [1]Division of Population Health and Genomics, University of Dundee, UK. [2]Dundee and Epidemiology Biostatistics Unit, University of Dundee, UK

Huan Wang PhD, Division of Population Health and Genomics, University of Dundee, UK

Corresponding authors

Daniel R. Morales / Brian J Lipworth, Division of Population Health and Genomics, University of Dundee, Mackenzie Building, Kirsty Semple Way, Dundee, DD2 4BF. Tel: 01382 383475

Email: d.r.z.morales@dundee.ac.uk / b.j.lipworth@dundee.ac.uk

Short running title: Intolerance to ACE inhibitors in asthma

Word count: 2993

Funding/Conflict of interests

The project was supported by Tenovus (T15/59) that provided funded the role of HW. DM is supported by a Wellcome Trust Clinical Research Development Fellowship (Grant 214588/Z/18/Z). DM is a member of the European Medicines Agency Pharmacovigilance Risk Assessment Committee. BJL reports grants and personal fees from Sanofi, AstraZeneca, and Teva; reports personal fees from Cipla, Glenmark, and Lupin; reports grants, personal fees, and other from Chiesi, outside the submitted work.

ABSTRACT

Background: Angiotensin converting enzyme inhibitor (ACEI) intolerance commonly occurs requiring switching to an angiotensin-II receptor blocker (ARB). ACEI intolerance may be mediated by bradykinin potentially affecting airway hyper-responsiveness.

Objective: Assess the risk of switching to ARBs in asthma.

Methods: We conducted a new-user cohort study of ACEI initiators identified from electronic health records from the UK Clinical Practice Research Datalink. The risk of switching to ARBs in people with asthma, chronic obstructive pulmonary disease (COPD) and the general population were compared. Adjusted hazard ratios (HR) were calculated using Cox regression, stratified by British Thoracic Society (BTS) treatment step and ACEI type.

Results: Of 642,336 new-users of ACEI, 6.4% had active asthma. The hazard of switching to ARB was greater in people with asthma (HR1.16, 95%CI 1.14-1.18, p=<0.001) and highest in those at BTS step ≥3 (HR1.35, 95%CI 1.32-1.39 and 1.18, 95%CI 1.15-1.22, p=<0.001 for patients aged ≥60 years and <60 years respectively). Hazard was highest with enalapril (HR1.25, 95%CI 1.18-1.34, p=<0.001; HR1.44, 95%CI 1.32-1.58, p=<0.001 for BTS step ≥3 asthma). No increased hazard was observed in COPD or those younger than 60 years at BTS step 1/2. The NNT varied by age, gender and BMI ranging between 21 and 4, being lowest in older women with BMI ≥25.

Conclusions: People with active asthma are more likely to switch to ARBs after commencing ACEI therapy. The NNT varies by age, gender, BMI and BTS step. ARBs could potentially be considered first-line in people with asthma and in those with high-risk characteristics.

Journal Pre-proof

44 **Highlights box**

45 **1: What is already known on this topic?**

46 • Many people are intolerant to ACE inhibitors due to cough and require switching to an
47 angiotensin-II receptor blocker (ARB).
48 • ACE inhibitors may affect airway hyperresponsiveness in asthma, possibly mediated via
49 bradykinin or cough reflex sensitivity.

50 **2: What does this article add to our knowledge?**

51 • People with asthma are generally at increased risk of switching to ARBs from ACEI therapy and is
52 greatest in those with more severe asthma.
53 • The absolute risk of switching varies by age, sex and body mass index.

54 **3: How does this study impact current management guidelines?**

55 • ARBs could be considered first-line in older people with asthma or young people with more
56 severe asthma including in those with other high-risk characteristics.

Journal Pre-proof

Key words

Asthma

Angiotensin converting enzyme

Cough

Epidemiology

Hypertension

Journal Pre-proof

63 **Abbreviations**

64 ACEI Angiotensin converting enzyme inhibitor

65 AHR Airway hyper-responsiveness

66 ARB Angiotensin-II receptor blocker

67 BMI Body mass index

68 BTS British Thoracic Society treatment step

69 COPD Chronic obstructive pulmonary disease

70 CVS Cardiovascular

71 GP General Practitioner

72 HR Hazard ratio

73 ICS Inhaled corticosteroids

74 LABA Long-acting beta2-agonists

75 LKTA Leukotriene receptor antagonists

76 NNT Number needed to treat

77 SABA Short-acting beta2-agonists

78 UK United Kingdom

Journal Pre-proof

INTRODUCTION

Asthma is a highly prevalent disease causing significant morbidity, mortality and healthcare cost.[1] Comorbidity in asthma is common, and 62.6% of people with asthma reported to have ≥1 comorbidity, and the likelihood of having coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hypertension, diabetes and chronic kidney disease are all significantly greater in people with asthma compared to the general population.[2,3] Angiotensin-converting enzyme inhibitors (ACEI) are commonly prescribed medicines indicated for the management of these chronic diseases.[4] ACEI block the enzyme responsible for converting the peptide hormone angiotensin-I to angiotensin-II, which stimulates aldosterone release and causes vasoconstriction. Whilst ACEI have beneficial effects in the management of these chronic diseases, many patients are intolerant of long-term ACEI the most common reason of which is a dry persistent cough. This adverse drug reaction is thought to occur in around 10% of people treated with ACEI and may be related to increased levels of bradykinin.[5] This adverse reaction is considered a class effect of ACEI, suggesting that even low doses may also alter bradykinin levels in susceptible patients.

In people who develop ACEI intolerance from cough it is recommended that patients are switched to angiotensin-II receptor blocker (ARB) therapy.[5] ARBs have similar properties to ACEI but do not cause a persistent dry cough. ARBs inhibit angiotensin-II in a highly selective manner via a mechanism which does not alter bradykinin levels. However, irrespective of the cause having to switch treatments increases healthcare resource utilisation, treatment burden, treatment disutility, and may delay in establishing effective preventative therapy for the underlying indication. Despite being an important health economic factor many drug formularies and guidelines still recommend first-line treatment with ACEIs usually on cost grounds.[6]

A key tenet in the pathogenesis of asthma is airway hyper-responsiveness (AHR) which can be affected by a variety of environmental stimuli.[7,8] Bradykinin is a pro-inflammatory mediator that can cause bronchoconstriction and lung inflammation.[9] It is therefore plausible that treatment with ACEI may exacerbate asthma symptoms through bradykinin accumulation leading to worsening AHR, which may in turn increase the incidence of cough and switching to ARBs.[10] However, there is limited evidence studying the effect of ACEI exposure in patients with asthma. The aim of this study was to 1) examine ACEI drug utilisation in people with asthma, 2) assess the association of switching to ARBs in people with asthma compared to the general population and 3) characterise patients at greater risk.

111 **METHODS**

112 *Data source*

113 The UK Clinical Practice Research Datalink (CPRD) GOLD database was used to identify a large UK cohort
114 of people with active asthma. CPRD GOLD contains anonymised electronic medical records from >680
115 general practices covering >5 million people in the UK with linked health data about patient
116 demographics, prescriptions, diagnoses, hospitalisations and deaths. Patients are broadly representative
117 of the UK general population in terms of age, sex and ethnicity.[11] General practices and patients
118 within CPRD GOLD are required to meet defined quality standards in order to contribute data, with
119 diagnoses have high validity, including for asthma that has a positive predictive value for respiratory
120 disease of around 90%.[12,13] It has also been deemed to meet regulatory requirements to be used in a
121 regulatory context.[14]

122

123 *Study cohort*

124 An open cohort of adults aged 18 years and over was identified from January 1 1998 through to June 30
125 2014. This time period reflects the start of database availability and the latest data available at the time
126 of data extraction. Patients were required to be registered with a general practice providing up-to-
127 standard data for at least 1 year prior to cohort entry. The population was divided into patients with
128 active asthma with the remainder forming the rest of the general population. People with active asthma
129 were defined using a validated code list for asthma and the receipt of at least two asthma medications
130 with cohort follow-up commencing at the latest of these dates.[13] Asthma medicines were defined by
131 the use of: inhaled short-acting beta2-agonists (SABA); inhaled corticosteroids (ICS); inhaled long-acting
132 beta2-agonists (LABA); oral leukotriene antagonists (LKTA); and oral methylxanthines.[15] To reduce the
133 chance of misclassification, people with a diagnostic code for asthma who also had a diagnostic code for
134 COPD, interstitial lung disease or bronchiectasis were excluded from the active asthma population. For
135 examining drug utilisation, cohort exit (that results in right censoring) for all patients was defined as the
136 earliest of the following: end of study period; deregistration from the general practice; date of last data
137 collection from the general practice; or death. For the analysis examining the risk of switching to an ARB
138 following ACEI initiation, cohort entry was additionally defined by the date of the incident ACEI
139 prescription in people without any prior ACEI or ARB exposure and cohort exit was additionally defined
140 by the date of switching to an ARB or 180 days after ACEI discontinuation if no ARB had been initiated.
141 For the switching analysis, patients prescribed an ARB on or prior to the incident ACEI were excluded. To
142 test the robustness of the potential mechanism relating to asthma we also examined this association in

143 patients with COPD who acted as a negative control population. Patients with COPD are expected to be
144 unaffected by the underlying pathophysiological hypothesis targeting AHR and were identified also using
145 a validated code list.[16]
146
147 *Exposures*
148 All ACEI and ARB prescriptions were identified for patients within the cohort. The date of incident ACEI
149 therapy was defined as the first ever ACEI prescription occurring during cohort follow-up with no
150 previous prescription at any point prior to this time. ACEI discontinuation was defined by the date of an
151 ACEI prescription with no further ACEI prescription following at least six months of this date. Switching
152 to an ARB was defined by an incident ARB prescription issued within six months of the ACEI
153 discontinuation date, with the date of the ACEI discontinuation representing day 1 of this six month
154 period of follow-up (Online Repository Figure E1). The list of ACEI and ARB drug codes are provided in
155 the Online Repository Table E1. For people who switched, the maximal ACEI dose prescribed prior to
156 switching was calculated. ACEI doses were standardised using ramipril equivalent doses (please see
157 Online Repository Table E2).
158
159 *Outcomes*
160 The primary outcome was the relative hazard of switching from ACEI to ARB therapy in people with
161 active asthma compared to the general population, with trends in ACEI initiation and switching to ARBs
162 reported over the study period among the active asthma population. Patients could switch at any point
163 after initiating ACEI therapy providing they met the definition of switching and had not been censored
164 due to one of the cohort exit criteria.
165
166 *Analysis*
167 Trends in the quarterly prevalence of ACEI and ARB initiation and discontinuation were calculated for
168 the active asthma population. The start of each quarter was defined as January 01, April 01, July 01 and
169 October 01. The quarterly prevalence was age-standardised using the European standard
170 population.[17] The cohort analysis used Cox proportional hazards regression to calculate hazard ratios
171 (HR) for switching to an ARB after initiating ACEI therapy in people with asthma compared to the general
172 population. Time in this time to event analysis was the difference in days between the date of the
173 incident ACEI prescription and switching to an ARB or another cohort exit censoring event as described
174 above. Routine checks of the proportional hazards assumption were conducted by examining log-log

Journal Pre-proof

175 plots. We used the entire population available to use within the database that met our criteria. Based
176 upon a two-group survival analysis this cohort has 90% at alpha 0.01 to detect a difference in relative
177 hazard of 1.05 or greater. The Cox model was adjusted for the following baseline confounders: age; sex;
178 practice-level socioeconomic deprivation applied to the individual (defined by the Index of Multiple
179 Deprivation categorised into quintiles); smoking status (categorised into smoker, ex-smoker and non-
180 smoker); body mass index (BMI, categorised into <20, 20-24, ≥25); history of cardiovascular disease
181 (CVS); and history of hypertension. We selected variables based upon a search in the literature, known
182 differences in the characteristics of asthma patients and indications for ACEI. A full model was fitted
183 with using all variables as main effects. The active asthma cohort was categorized into three groups
184 according to baseline British Thoracic Society (BTS) asthma treatment step (1, 2 and ≥3) defined by
185 prescribed asthma medication as a potential marker of severity and included in the model.[1] The
186 cohort was stratified by the most frequently prescribed types of ACEI and analysed separately. Multiple
187 imputation was used to impute missing data on BMI, deprivation and smoking status. The imputation
188 model included all variables relating to clinical characteristics, medication exposure and switching
189 events. Multiple imputation used fully conditional specification, with linear regression for continuous
190 variables and logistic regression for categorical variables with five imputations analysed using Rubin's
191 rules.[18] We performed a complete case analysis to assess the impact of multiple imputation as a
192 sensitivity analysis. To calculate an absolute measure, the rate of switching per 1000 patients was first
193 calculated in the general cohort population, and was then multiplied by the adjusted hazard ratio to
194 calculate the expected number of switchers in asthma. The number of asthma patients needed to treat
195 (NNT) with an ACEI for one person to switch to an ARB was then calculated by taking the reciprocal of
196 this value. Data on absolute risk are presented stratified by age and sex as done elsewhere.[19,20]

Journal Pre-proof

RESULTS

The active asthma cohort consisted of 521,857 adults (57.8% female, mean age 39 years) of which 66,895 patients (12.8%) were prescribed ACEIs, 28,791 were prescribed ARBs (5.5%), and 16,203 were prescribed both (3.1%) individually at some point during cohort follow-up. Trends in ACEI and ARB prescribing are presented in the Online Repository Figure E2.

Among the entire population, a total of 642,336 patients initiating ACEIs were identified, of which 40,953 had active asthma (6.4%). The remainder formed the general population, of which 5.2% had COPD. Patient characteristics are shown in table 1. Fewer patients with active asthma were men, current smokers or had a history of CVS disease. The most commonly prescribed ACEIs were ramipril, followed by lisinopril, perindopril then enalapril. Overall, 17.4% of people with active asthma switched to an ARB following ACEI initiation compared to 14.6% from the general population. Among those who switched, the number of GP consultations and mean ramipril10-equivalent dose prior to switching were similar between the groups.

The hazard ratio for switching to an ARB in patients with active asthma was increased compared to the general population (HR 1.16, 95%CI 1.14-1.18) (table 2). In contrast it was decreased for patients with COPD (HR 0.89, 95%CI 0.87-0.91). When associations between other patient characteristics were examined, the hazard of switching to an ARB was greater in women compared to men (HR 1.46, 95%CI 1.45-1.47), with increasing age (HR 1.65, 95%CI 1.62-1.71 for patients ≥60 years) and in patients with BMI ≥25 (table 2). In contrast, the hazard of switching to an ARB was lower in patients with a history of smoking and in patients registered at general practices in more socioeconomically deprived areas.

The increased hazard of switching to an ARB with active asthma was similar when stratified by gender (HR 1.16, 95%CI 1.13-1.19 for men and HR 1.17, 95%CI 1.15-1.20 for women). Hazard ratios for switching to an ARB were greater among active asthma patients aged ≥60 years and among those at BTS step ≥3 (HR 1.35, 95%CI 1.32-1.39 and HR 1.18, 95%CI 1.15-1.22 for patients aged ≥60 years and <60 years respectively) (figure 1 and table 3). While the hazard ratio was elevated among asthma patients aged ≥60 years at BTS step 1 and 2, no increased hazard was observed for those aged <60 years. When stratified by the four most commonly prescribed ACEIs, the hazard ratio for switching to an ARB in patients with active asthma was consistently elevated for all ACEI types, being numerically largest with enalapril (HR 1.24, 95%CI 1.17-1.32) (table 4) and greatest in those at BTS step ≥3. Results of the

229 sensitivity analysis using a complete case analysis were in keeping with the main results (Online
230 Repository Table E3).
231
232 The overall incidence of switching to an ARB in the general population was 148 per 1000 patients with
233 an additional 24 per 1000 patients (95%CI 21-27) among people with active asthma. The NNT with an
234 ACEI for one person to switch to an ARB varied by age, sex, BMI and asthma severity (table 5). The NNT
235 in men with BMI <20 varied from 24 to 11 being lower with older patients at BTS step 3. Corresponding
236 numbers for men with BMI of ≥25 were lower ranging from 12 to 6 respectively. The NNT similarly
237 varied in women, ranging from 14 to 7 in women with BMI <20 and from 10 to 4 in women with BMI of
238 ≥25, being lower in older patients at BTS step 3. Corresponding numbers for the general population are
239 shown in the Online Repository Table E4.

Journal Pre-proof

240 **Discussion**

241 *Summary of findings*

242 We observed that people with active asthma have an increased risk of ACEI intolerance and switching to
243 ARB therapy compared to the general population. This association was greatest in those with more
244 severe asthma, with people above and below 60 years of age at BTS step ≥3 asthma having a 35%
245 increased hazard versus 18% increased hazard respectively. The hazard of switching to an ARB was
246 consistently elevated with all commonly prescribed ACEIs in our population and was largest following
247 treatment with enalapril, with BTS step ≥3 patients having a 44% increased hazard. However, patients
248 below 60 years of age at BTS step 1 or 2 asthma were not at increased risk. The number of asthma
249 patients needed to treat with ACEI for one person to switch was also significantly influenced by age, sex
250 and BMI, which ranged from 21 to 4, being lowest in older women with a BMI of ≥25 at BTS step 3.

251

252 *Comparison with previous literature*

253 AHR is an important determinant in the pathophysiology of asthma and is affected by a variety of stimuli
254 such as methacholine and bradykinin that can cause bronchoconstriction,.[7,8] Whereas methacholine
255 induces bronchoconstriction in normal and in asthmatic subjects, bradykinin-induced
256 bronchoconstriction is predominantly observed in asthmatics, suggesting the effect of bradykinin is
257 related to structural and/or to functional airway abnormalities that occur in asthma.[7] Bradykinin's
258 potent bronchoconstrictor effect in asthmatic patients is thought to be mediated via an indirect
259 mechanism related to the level of AHR and active airway inflammation.[9,10] Whilst the increased
260 hazard of switching in people with active asthma, but not COPD, would be in keeping with a specific
261 effect on AHR other mechanisms such as ACEI increasing cough reflex hypersensitivity, which is similarly
262 associated with female gender, cannot be excluded.[21]

263

264 Indirect acting AHR is related to the degree of aeroallergen sensitisation and occurs independently of
265 airway calibre or ICS use.[22] This in turn may explain why the effect of bradykinin due to ACEI may be
266 specific for asthma but not COPD, in addition to the presence of type 2 inflammation in the former. This
267 is because AHR is not a key feature in the pathogenesis of COPD perhaps unless patients have asthma-
268 COPD overlap syndrome. Indeed, fixed airway remodelling in COPD may be one reason why a decreased
269 hazard of switching was observed in this population. Our observation of increased ACEI intolerance in
270 patients with BTS step 3 and above is likely explained by such patients have more severe disease. Having
271 said that, AHR has been shown to be attenuated by drugs such as ICS, which would be more prevalent in

272 patients taking step 3/4 therapy.[23-25] Some studies have evaluated bronchial reactivity of captopril,
273 ramipril and enalapril in asthma patients and showed no change in reactivity.[26-31] However, the
274 cumulative number of patients from all of these studies is only n=71, which in addition to studies
275 employing different methods (ie. histamine, bradykinin or methacholine challenges or simply measuring
276 lung function) limits the generalisability of these findings.
277
278 Although several types of ACEIs are available for clinical use, it cannot be assumed they are all equally
279 effective or safe without head to head comparisons. In our study the hazard of switching to ARB with
280 enalapril was modestly larger in people with asthma compared to other ACEI. In a meta-analysis of
281 randomized controlled trials, ACEI cough had higher rates in hypertension and lowest rates in heart
282 failure suggesting these may differ by underlying cardiovascular condition.[32] Although differences
283 among users of different ACEI types remains possible, we adjusted for several of these factors and saw a
284 larger hazard ratio for hypertension compared to cardiovascular disease. Similarly, a network meta-
285 analysis of 29 randomized placebo controlled trials of ACEI therapy in heart failure patients also found
286 that enalapril had the highest incidence of cough, gastrointestinal discomfort, and greater deterioration
287 in renal function compared to other ACEIs.[33]
288
289 An increased risk of cough or switching to ARB therapy in people with asthma has recently been
290 reported.[32,34] However, no studies used an active asthma population, examined associations by
291 asthma severity or type of ACEI, or provided information relating to ACEI dose or the rate of healthcare
292 utilisation rate prior to switching. Meanwhile information on absolute risk is lacking but is necessary to
293 guide robust health economic and clinical decision is making. Women in the general population are
294 considered to have a 1.5 to 2.3-fold increased risk of switching to ARBs following ACEI therapy.[35-37]
295 However, the impact of increasing age has been less consistently reported and there remains a paucity
296 of data around the association with BMI.[38-40] We clearly show that all three characteristics are
297 relevant for people with asthma and are strong determinants of the NNT.
298
299 *Strengths and limitations*
300 This study has several strengths and limitations. First we analysed a large clinical population identified
301 using a validated data source and definitions. Although cough is by far the most common reason for
302 ACEI intolerance and switching to an ARB we were unable to directly measure ACEI-induced cough as an
303 outcome. This would be challenging as cough may not be recorded sufficiently well to distinguish

Journal Pre-proof

304 between cough related to ACEIs as opposed to another condition, particularly in patients with asthma.
305 Whilst cough is the predominant reason for ACEI intolerance in the general population, we cannot
306 exclude the possibility that other symptoms such as wheeze or dyspnoea may have occurred, which
307 have been reported among asthma patients using ACEIs.[40] However, switching to an ARB after ACEI
308 treatment is considered to be the best marker for identifying ACEI-induced adverse drug reactions in
309 electronic databases, having a positive predictive value of up to 90.5% with cough being the most
310 commonly reported adverse reaction.[42,43]
311
312 Whist there remains the potential for unmeasured confounding from potentially important unknown
313 patient factors not included in our model, we used a negative control population by examining the
314 association in patients with COPD. The null findings in patients with COPD provide additional evidence
315 suggesting our observed association is causal and that the increased hazard of switching observed in
316 people with active asthma are potentially related to changes in AHR due to bradykinin. However, these
317 results may not be generalizable to people with the asthma-COPD overlap syndrome. It would be
318 pertinent to further evaluate the putative impact of ACEI in patients with known AHR and markers of
319 type 2 inflammation such as fractional exhaled nitric oxide and blood eosinophils, as well as total and
320 specific IgE levels.[44,45]
321
322 *Clinical implications*
323 It is recognised that managing comorbidities in patients with asthma may be associated with additional
324 risk.[46-49] When evaluated for the management of hypertension, ARBs are thought to have similar
325 effects on blood pressure, mortality and CVS outcomes compared with ACEIs, yet fewer patients in the
326 general population withdraw from clinical trials due to adverse effects when treated with ARBs
327 compared to ACEIs.[50] Despite the potentially higher incidence of switching with enalapril, the largest
328 determinant on absolute risk in people with asthma appeared to be a person's age, gender and BMI.
329 Given the high prevalence of obesity in the population combined with increasing age of patients, such
330 factors are important determinants for considering whether ARBs should be recommended as first line
331 therapy. This would be particularly relevant in people with asthma, where discriminating ACEI-induced
332 cough from symptoms of uncontrolled asthma may be complex, potentially leading to unnecessary
333 asthma treatment if not immediately recognised. Many guidelines for the management of patients with
334 cardiovascular disease still recommend ACEIs as first-choice therapy, reserving ARBs as an alternative
335 when patients are intolerant to ACEIs. This has led to recent calls to change these recommendations

Journal Pre-proof

given the equal efficacy but fewer adverse reactions with ARBs.[51] This would potentially avoid unnecessary health care appointments, patient treatment disutility, and delays in establishing effective therapy for the underlying clinical condition.

In conclusion, our findings suggest that ACEIs are less well tolerated in people with asthma compared to the general population. The NNT is lower in asthma and in those with older age, are female and have a higher BMI. Consideration could potentially be given to recommending ARBs first-line in people with asthma or those with high risk characteristics when treatment with a renin-angiotensin system inhibitor is clinically indicated.

Journal Pre-proof

345 **Contributions**

346 DM and BJL conceived the idea. All authors were involved in the study design. HW and DM performed
347 the analysis and DM is the guarantor for the study. All authors contributed to the interpretation of
348 results, writing the manuscript and approved the final draft. The corresponding author attests that all
349 listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

350 **Disclaimer**

351 The views expressed in this article are the personal views of the author(s) and may not be understood or
352 quoted as reflecting the views of any organisation.

353 **Data sharing**

354 No data are available for sharing. Data can be accessed according to CPRD's standard terms and
355 conditions and payment for using the CPRD database.

356 **Study registration**

357 The study has been registered in the EU PAS Register (no. EUPAS35083) [www.encepp.eu)

358 **Ethical approval**

359 The study was approved by the Independent Scientific Advisory Committee for Medicines and
360 Healthcare products and Regulatory Agency (MHRA) (protocol 14_240R).

Journal Pre-proof

361 **References**

362 1. British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the
363 Management of Asthma. Thorax. 2008;63 Suppl 4:iv1-121.
364 2. Weatherburn CJ, Guthrie B, Mercer SW, Morales DR. Comorbidities in adults with asthma:
365 Population-based cross-sectional analysis of 1.4 million adults in Scotland. Clin Exp Allergy. 2017
366 Oct;47(10):1246-1252.
367 3. Steppuhn H, Langen U, Keil T, Scheidt-Nave C. Chronic disease co-morbidity of asthma and
368 unscheduled asthma care among adults: results of the national telephone health interview survey
369 German Health Update (GEDA) 2009 and 2010. Prim Care Respir J. 2014 Mar;23(1):22-9.
370 4. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and
371 Pharmaceutical Press. http://wwwmedicinescompletecom (accessed 1 Aug 2015).
372 5. British Hypertension Society. Drug classes: Angiotensin Converting Enzyme (ACE) Inhibitors (online).
373 https://bihsoc.org/wp-content/uploads/2017/11/Angiotensin-Converting-Enzyme-Final-2017.pdf
374 Accessed 12 Dec 2019.
375 6. National Health Service Tayside Area Formulary. Available at:
376 http://www.taysideformulary.scot.nhs.uk/chaptersSubDetails.asp?FormularySectionID=2&SubSecti
377 onRef=02.05&SubSectionID=A100 Accessed 12 Dec 2019.
378 7. Barnes PJ. Bradykinin and asthma. Thorax. 1992;47(11):979-83.
379 8. Fuller RW, Dixon CM, Cuss FM, Barnes PJ. Bradykinin-induced bronchoconstriction in humans. Mode
380 of action. Am Rev Respir Dis. 1987Jan;135(1):176-80.
381 9. Polosa, R., and S. T. Holgate. 1990. Comparative airway responses to inhaled bradykinin, kallidin,
382 and [des-Arg9] bradykinin in normal and asthmatic subjects. Am. Rev. Respir. Dis. 142:1367-1371.
383 10. Roisman GL, Lacronique JG, Desmazes-Dufeu N, Carré C, Le Cae A, Dusser DJ. Airway responsiveness
384 to bradykinin is related to eosinophilic inflammation in asthma. Am J Respir Crit Care Med. 1996
385 Jan;153(1):381-90.
386 11. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data Resource
387 Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun;44(3):827-36.
388 12. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the
389 General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69(1):4-14.
390 13. Nissen F, Morales DR, Mullerova H, Smeeth L, Douglas IJ, Quint JK. Validation of asthma recording in
391 the Clinical Practice Research Datalink (CPRD). BMJ Open. 2017 Aug 11;7(8):e017474.
392 14. Pacurariu A, Plueschke K, McGettigan P, et al. Electronic healthcare databases in Europe: descriptive
393 analysis of characteristics and potential for use in medicines regulation [published correction
394 appears in BMJ Open. 2019 Feb 22;8(11):e023090corr1]. BMJ Open. 2018;8(9):e023090.
395 15. Joint Formulary Committee. British National Formulary. Respiratory system – 3 (online) London: BMJ
396 Group and Pharmaceutical Press. http://wwwmedicinescompletecom (accessed 1 Aug 2015).
397 16. Quint JK, Müllerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, Davis K, Smeeth L. Validation
398 of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-
399 GOLD). BMJ Open. 2014 Jul 23;4(7):e005540.
400 17. Eurostat. Revision of the European Standard Population. 2013 Edition. Available at:
401 https://ec.europa.eu/eurostat/documents/3859598/5926869/KS-RA-13-028-EN.PDF/e713fa79-
402 1add-44e8-b23d-5e8fa09b3f8f Accessed 20/12/2019.
403 18. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification.
404 Stat Methods Med Res. 2007 Jun;16(3):219-42.

Journal Pre-proof

19. Morales DR, Flynn R, Kurz X. Addendum to: Relative and Absolute Risk of Tendon Rupture with Fluoroquinolone and Concomitant Fluoroquinolone/Corticosteroid Therapy: Population-Based Nested Case-Control Study. Clin Drug Investig. 2019 Jun;39(6):591-594.
20. Morales D, Pacurariu A, Slattery J, Pinheiro L, McGettigan P, Kurz X. Association Between Peripheral Neuropathy and Exposure to Oral Fluoroquinolone or Amoxicillin-Clavulanate Therapy. JAMA Neurol. 2019 Jul 1;76(7):827-833.
21. Fox AJ, Lalloo UG, Belvisi MG, Bernareggi M, Chung KF, Barnes PJ. Bradykinin-evoked sensitization of airway sensory nerves: a mechanism for ACE-inhibitor cough. Nat Med. 1996 Jul;2(7):814-7.
22. Currie GP, Jackson CM, Lee DK, Lipworth BJ. Allergen sensitization and bronchial hyper-responsiveness to adenosine monophosphate in asthmatic patients. *Clin Exp Allergy* 2003: 33(10): 1405-1408.
23. Currie GP, Jackson CM, Ogston SA, Lipworth BJ. Airway-stabilizing effect of long-acting beta2-agonists as add-on therapy to inhaled corticosteroids. *QJM : monthly journal of the Association of Physicians* 2003: 96(6): 435-440.
24. Currie GP, Lipworth BJ. Bronchoprotective effects of leukotriene receptor antagonists in asthma: A meta-analysis. *Chest* 2002: 122(1): 146-150.
25. Currie GP, Fowler SJ, Lipworth BJ. Dose response of inhaled corticosteroids on bronchial hyperresponsiveness: A meta-analysis. *Annals of Allergy, Asthma and Immunology* 2003: 90(2): 194-198.
26. Sala H, Abad J, Juanmiquel L, Plans C, Ruiz J, Roig J, et al. Captopril and bronchial reactivity. Postgrad Med J 1986;62(suppl 1):76-7.
27. Riska H, Stenius-Aarniala B, Sovijarvi AR. Comparison of the effects of an angiotensin converting enzyme inhibitor and a calcium channel blocker on blood pressure and respiratory function in patients with hypertension and asthma. J Cardiovasc Pharmacol 1987;10(suppl 10):S79-81.
28. Riska H, Sovijarvi AR, Ahonen A, Salorinne Y, Sundberg S, Stenius-Aarniala B. Effects of captopril on blood pressure and respiratory function compared to verapamil in patients with hypertension and asthma. J Cardiovasc Pharmacol 1990;15:57-61.
29. Kaufman J, Schmitt S, Barnard J, Busse W. Angiotensin-converting enzyme inhibitors in patients with bronchial responsiveness and asthma. Chest 1992;101:922-5.
30. Mue S, Tamura G, Yamauchi K, Fujimoto Y, Inoue H, Takishima T. Bronchial responses to enalapril in asthmatic, hypertensive patients. Clin Ther 1990;12:335- 43.
31. Dixon CM, Fuller RW, Barnes PJ. The effect of an angiotensin converting enzyme inhibitor, ramipril, on bronchial responses to inhaled histamine and bradykinin in asthmatic subjects. Br J Clin Pharmacol. 1987 Jan;23(1):91-3. doi: 10.1111/j.1365-2125.1987.tb03015.x.
32. Vukadinović D, Vukadinović AN, Lavall D, Laufs U, Wagenpfeil S, Böhm M. Rate of Cough During Treatment With Angiotensin-Converting Enzyme Inhibitors: A Meta-Analysis of Randomized Placebo-Controlled Trials. Clin Pharmacol Ther. 2019 Mar;105(3):652-660.
33. Sun W, Zhang H, Guo J, Zhang X, Zhang L, Li C, Zhang L. Comparison of the Efficacy and Safety of Different ACEIs in Patients With Chronic Heart Failure: A PRISMA-Compliant Network Meta-Analysis. Medicine (Baltimore). 2016 Feb;95(6):e2554.
34. Mahmoudpour SH, Asselbergs FW, Souverein PC, de Boer A, Maitland-van der Zee AH. Prescription patterns of angiotensin-converting enzyme inhibitors for various indications: A UK population-based study. Br J Clin Pharmacol. 2018 Oct;84(10):2365-2372.

Journal Pre-proof

35. Humbert X, Alexandre J, Sassier M, Default A, Gouraud A, Yelehe-Okouma M,Puddu PE, Fedrizzi S. Long delay to onset of ACEIs-induced cough: Reason of difficult diagnosis in primary care? Eur J Intern Med. 2017 Jan;37:e50-e51.
36. Brugts JJ, Arima H, Remme W, Bertrand M, Ferrari R, Fox K, DiNicolantonio J,MacMahon S, Chalmers J, Zijlstra F, Caliskan K, Simoons ML, Mourad JJ, Boersma E, Akkerhuis KM. The incidence and clinical predictors of ACE-inhibitor induced dry cough by perindopril in 27,492 patients with vascular disease. Int J Cardiol. 2014 Oct 20;176(3):718-23.
37. Mahmoudpour SH, Baranova EV, Souverein PC, Asselbergs FW, de Boer A, Maitland-van der Zee AH; PREDICTION-ADR consortium. Determinants of angiotensin-converting enzyme inhibitor (ACEI) intolerance and angioedema in the UK Clinical Practice Research Datalink. Br J Clin Pharmacol. 2016 Dec;82(6):1647-1659.
38. Morimoto T, Gandhi TK, Fiskio JM, Seger AC, So JW, Cook EF, Fukui T, Bates DW. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. J Eval Clin Pract. 2004 Nov;10(4):499-509.
39. Alharbi FF, Kholod AAV, Souverein PC, Meyboom RH, de Groot MCH, de Boer A, Klungel OH. The impact of age and sex on the reporting of cough and angioedema with renin-angiotensin system inhibitors: a case/noncase study in VigiBase. Fundam Clin Pharmacol. 2017 Dec;31(6):676-684.
40. Jamshed F, Jaffry H, Hanif H, Kumar V, Naz U, Ahmed M, Fareed S. Demographic and Clinical Characteristics of Patients Presenting With Angiotensin-converting Enzyme Inhibitors Induced Cough. Cureus. 2019 Sep 11;11(9):e5624.
41. Fox AJ, Lalloo UG, Belvisi MG, Bernareggi M, Chung KF, Barnes PJ. Bradykinin-evoked sensitization of airway sensory nerves: a mechanism for ACE-inhibitor cough. Nat Med. 1996 Jul;2(7):814-7.
42. Mahmoudpour SH, Asselbergs FW, de Keyser CE, Souverein PC, Hofman A, Stricker BH, de Boer A, Maitland-van der Zee AH. Change in prescription pattern as a potential marker for adverse drug reactions of angiotensin converting enzyme inhibitors. Int J Clin Pharm. 2015 Dec;37(6):1095-103.
43. Speirs C, Wagniart F, Poggi L. Perindopril postmarketing surveillance: a 12 month study in 47,351 hypertensive patients. Br J Clin Pharmacol. 1998 Jul;46(1):63-70.
44. Kuo CR, Spears M, Haughney J, Smith A, Miller J, Bradshaw T, Murray L, Williamson P, Lipworth B. Scottish consensus statement on the role of FeNO in adult asthma. *Respir Med* 2019: 155: 54-57.
45. Price DB, Bosnic-Anticevich S, Pavord ID, Roche N, Halpin DMG, Bjermer L, Usmani OS, Brusselle G, Ming SWY, Rastogi S. Association of elevated fractional exhaled nitric oxide concentration and blood eosinophil count with severe asthma exacerbations. *Clin Transl Allergy* 2019: 9: 41.
46. Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. BMC Med. 2017 Jan 27;15(1):18.
47. Morales DR, Dreischulte T, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blocker eye drops in asthma: population-based study and meta-analysis of clinical trials. Br J Clin Pharmacol. 2016 Sep;82(3):814-22.
48. Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. Allergy. 2015 Jul;70(7):828-35.
49. Morales DR, Jackson C, Lipworth BJ, Donnan PT, Guthrie B. Adverse respiratory effect of acute β-blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials. Chest. 2014 Apr;145(4):779-786.

492 50. Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin
493 receptor blockers for primary hypertension. Cochrane Database Syst Rev. 2014 Aug
494 22;(8):CD009096.
495 51. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-Converting Enzyme Inhibitors in
496 Hypertension: To Use or Not to Use? J Am Coll Cardiol. 2018 Apr 3;71(13):1474-1482.

497

498

499

500

501

502

503

504

505

Journal Pre-proof

506 Table 1. Demographic details and baseline covariates of people initiating ACEI therapy in the general population and in
507 those with active asthma.
508

Patient characteristics	Active asthma cohort (n = 40953)	General population (n = 601383)
Mean age, (SD)	58.7 (13.3)	64.4 (13.8)
Male sex (%)	17274 (42.2)	315463 (52.5)
Mean years of follow-up (SD)	3.0 (3.3)	3.3 (3.4)
Mean BMI at baseline (SD)	30.7 (6.7)	28.7 (5.9)
Missing BMI (%)	1314 (3.2)	39519 (6.6)
Practice level deprivation (%):		
1 (least deprived)	3712 (8%)	55612 (9.3)
2	5510 (14%)	81311 (13.5)
3	5273 (13%)	79094 (13.2)
4	5329 (13%)	87680 (14.6)
5 (most deprived)	5115 (13%)	77959 (13.0)
Missing	16014 (39.1)	219727 (36.5)
COPD (%)	0 (0)	31294 (5.2)
Hypertension (%)	27783 (67.8)	401,918 (66.8)
Cardiovascular disease (%)	8090 (19.8)	169805 (28.2)
Baseline smoking status (%)		
Non-smoker	20918 (55.7)	256732 (49.2)
Ex-smoker	11537 (30.7)	167358 (32.1)
Current smoker	5129 (13.7)	98001 (18.8)
Missing smoking status (%)	3369 (8.2)	79292 (13.2)
ACEI type (%)		
Ramipril	22600 (55.2)	324942 (54.0)
Lisinopril	10279 (25.1)	148389 (24.7)
Perindopril	5741 (14.0)	91054 (15.1)
Enalapril	1907 (4.7)	28760 (4.8)
Other*	426 (1.0)	8238 (1.4)
Number discontinuing ACEIs (%)	18973 (46.3)	271773 (45.2)
Number switching to an ARB (%)	7108 (17.4)	88980 (14.8)
Mean ACEI dose mg (SD)*	4.4 (2.9)	4.5 (3.0)
Mean no. GP consultations (SD)**	12.4 (21.1)	12.0 (18.9)

509 *Other = quinapril, trandolapril, captopril, fosinopril, imidapril, cilazapril or moexipril. **Standardised ramipril
510 equivalent dose prior to switching. ***Mean number of general practice (GP) surgery consultations between the
511 date of ACEI initiation and ARB initiation. SD=standardised difference. P-value for all comparisons <0.05 using Chi-
512 square test for counts and t-test for continuous variables.

Journal Pre-proof

513 Table 2. Hazard ratios for switching to an ARB following any ACEI therapy in people with active asthma compared to
514 the general population and other risk factors.

	Crude Hazard ratio (95% CI)	Crude P-value	Adjusted Hazard ratio (95% CI)	Adjusted P-value
Population				
General population	1.00		1.00	
Active asthma	1.22 (1.20-1.24)	<0.001	1.16 (1.14–1.18)	<0.001
COPD	0.79 (0.78-0.81)	<0.001	0.89 (0.87-0.91)	<0.001
Hypertension	1.34 (1.33-1.35)	<0.001	1.21 (1.20–1.22)	<0.001
Cardiovascular disease	0.81 (0.80-0.82)	<0.001	0.88 (0.87-0.89)	<0.001
Sex				
Male	1.00		1.00	
Female	1.53 (1.52-1.54)	<0.001	1.46 (1.45-1.47)	<0.001
Age at baseline				
<40	1.00		1.00	
40-49	1.34 (1.30-1.37)	<0.001	1.32 (1.29-1.36)	<0.001
50-59	1.53 (1.50-1.57)	<0.001	1.53 (1.49-1.57)	<0.001
>60	1.67 (1.63-1.71)	<0.001	1.66 (1.62-1.70)	<0.001
BMI category				
<20	1.00		1.00	
20-24	1.37 (1.34-1.40)	<0.001	1.43 (1.39-1.46)	<0.001
>=25	1.52 (1.49-1.56)	<0.001	1.55 (1.51-1.59)	<0.001
Smoking status				
Non-smoker	1.00		1.00	
Ex-smoker	0.89 (0.88-0.90)	<0.001	0.96 (0.95–0.97)	<0.001
Current smoker	0.64 (0.63-0.65)	<0.001	0.73 (0.72–0.74)	<0.001
Deprivation				
1 (Least deprived)	1.00		1.00	
2	1.07 (1.05-1.08)	<0.001	1.05 (1.04-1.06)	<0.001
3	1.13 (1.12-1.14)	<0.001	1.10 (1.09-1.11)	<0.001
4	1.17 (1.15-1.18)	<0.001	1.13 (1.12-1.15)	<0.001
5 (Most deprived)	1.24 (1.22-1.25)	<0.001	1.20 (1.18-1.21)	<0.001

515 BTS step=British Thoracic Society asthma treatment step. Adjusted model adjusted for gender, age, BMI, smoking
516 status, history of hypertension, cardiovascular disease, COPD and socioeconomic deprivation. Deprivation=Index of
517 multiple deprivation. CI=confidence interval.

518 Table 3. Overall adjusted cause-specific hazard ratios for switching to an ARB following ACEI therapy stratified by
519 British Thoracic Society asthma treatment step.

BTS asthma treatment step	Number with asthma (%)	Crude cause-specific Hazard ratio (95% CI)	Crude P value	Adjusted cause-specific Hazard ratio (95% CI)	Adjusted P value
Age >=60 years					
≥3	9057 (45.6)	1.47 (1.44-1.51)	<0.001	1.35 (1.32-1.39)	<0.001
2	5774 (29.1)	1.22 (1.18-1.26)	<0.001	1.13 (1.09-1.17)	<0.001
1	5026 (25.3)	1.23 (1.19-1.28)	<0.001	1.14 (1.09-1.19)	<0.001
Age <60 years					
≥3	9398 (44.6)	1.27 (1.23-1.30)	<0.001	1.18 (1.15-1.22)	<0.001
2	4982 (23.6)	1.09 (1.05-1.14)	<0.001	1.02 (0.96-1.07)	0.753
1	6716 (31.8)	0.97 (0.94-1.01)	0.193	0.96 (0.92-1.00)	0.146

520 BTS step=British Thoracic Society asthma treatment step. Adjusted model adjusted for gender, age, BMI, smoking status,
521 history of hypertension, history of cardiovascular disease, COPD and socioeconomic deprivation. CI=confidence interval.

Journal Pre-proof

Journal Pre-proof

522 Table 4. Overall adjusted cause-specific hazard ratios for switching to an ARB following different types of ACEI
523 therapy.

ACEI type	Crude Hazard ratio (95% CI)	Crude P value	Adjusted Hazard ratio (95% CI)	Adjusted P value
Enalapril				
BTS step ≥3	1.51 (1.39-1.64)	<0.001	1.44 (1.32-1.58)	<0.001
BTS step 2	1.29 (1.16-1.42)	<0.001	1.21 (1.08-1.35)	<0.001
BTS step 1	1.04 (0.92-1.17)	0.582	1.01 (0.89-1.16)	0.841
Overall	1.31 (1.24-1.39)	<0.001	1.25 (1.18-1.34)	<0.001
Ramipril				
BTS step ≥3	1.34 (1.30-1.37)	<0.001	1.27 (1.23-1.30)	<0.001
BTS step 2	1.16 (1.12-1.20)	<0.001	1.09 (1.05-1.14)	<0.001
BTS step 1	1.05 (1.01-1.09)	0.010	1.04 (1.00-1.08)	0.060
Overall	1.21 (1.19-1.24)	<0.001	1.16 (1.14-1.19)	<0.001
Lisinopril				
BTS step ≥3	1.32 (1.27-1.37)	<0.001	1.26 (1.21-1.31)	<0.001
BTS step 2	1.14 (1.08-1.19)	<0.001	1.09 (1.04-1.15)	0.001
BTS step 1	1.10 (1.04-1.16)	<0.001	1.10 (1.05-1.17)	<0.001
Overall	1.21 (1.18-1.24)	<0.001	1.17 (1.14-1.21)	<0.001
Perindopril				
BTS step ≥3	1.36 (1.30-1.43)	<0.001	1.27 (1.21-1.33)	<0.001
BTS step 2	1.09 (1.01-1.17)	0.026	1.03 (0.95-1.11)	0.456
BTS step 1	1.01 (0.93-1.09)	0.856	0.97 (0.89-1.05)	0.410
Overall	1.20 (1.16-1.25)	<0.001	1.13 (1.09-1.18)	<0.001

524 BTS step=British Thoracic Society asthma treatment step. Adjusted model adjusted for gender, age, BMI, smoking
525 status, history of hypertension, cardiovascular disease, COPD and socioeconomic deprivation. ACE=angiotensin
526 converting enzyme inhibitor. CI=confidence interval.

Journal Pre-proof

527 **Table 5. Number of asthma patients needed to treat with an ACEI for one person to switch to an ARB according**
528 **to age, sex, BMI and asthma severity.**

529

	Men				Women			
	Rate in non-asthmatics per 1000	**NNT Step 1 Asthma**	**NNT Step 2 Asthma**	**NNT Step ≥3 Asthma**	**Rate in non-asthmatics per 1000**	**NNT Step 1 Asthma**	**NNT Step 2 Asthma**	**NNT Step ≥3 Asthma**
BMI <20								
Age <40 years	9	24	24	21	74	14	14	11
Age 40-59 years	63	16	16	14	126	8	8	7
Age >=60 years	68	13	13	11	114	8	8	7
BMI 20-24								
Age <40 years	63	16	16	14	99	10	10	9
Age 40-59 years	91	11	11	9	149	7	7	6
Age >=60 years	114	8	8	7	176	5	5	4
BMI >=25								
Age <40 years	82	12	12	10	101	10	10	8
Age 40-59 years	118	9	9	7	171	6	6	5
Age >=60 years	135	7	7	6	192	5	5	4

530 Rate=Rate of switching to an ARB following ACEI initiation. BMI=Body mass index. NANT=Number with asthma needed to
531 treat with ACEI for a switch to ARB to occur. NNT calculated taking the reciprocal of rate in non-asthma population*hazard
532 ratio of switching in asthma by age and BTS step, rounded to the nearest whole number. Step=British Thoracic Society
533 asthma treatment step.

534

535

536

537

Journal Pre-proof

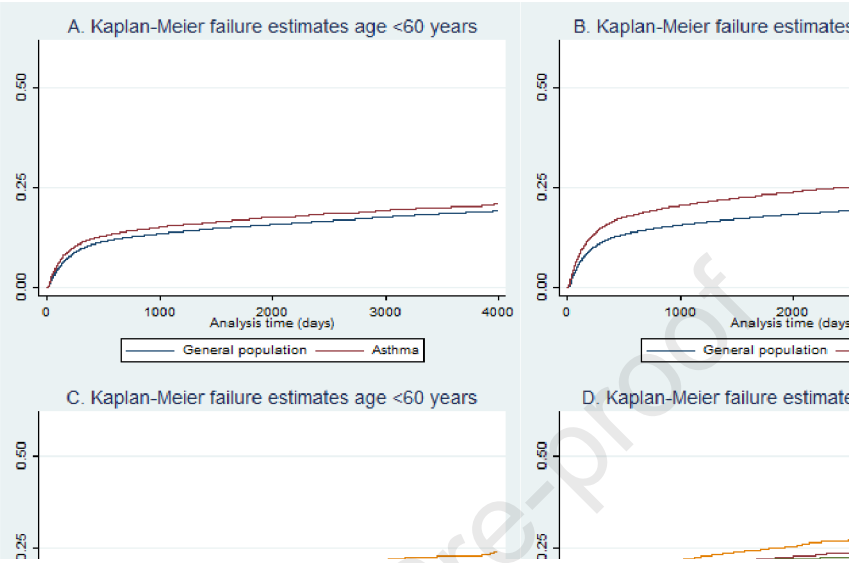
538 **Figure Legends**

539

540 **Figure 1. Kaplan-Meier failure plots for risk of switching to an ARB following treatment with ACEI in A) people**
541 **under 60 years with asthma, B) people under 60 years by BTS treatment step, C) people aged 60 years or older**
542 **with asthma, and D) people aged 60 years or older by BTS treatment step.**

543

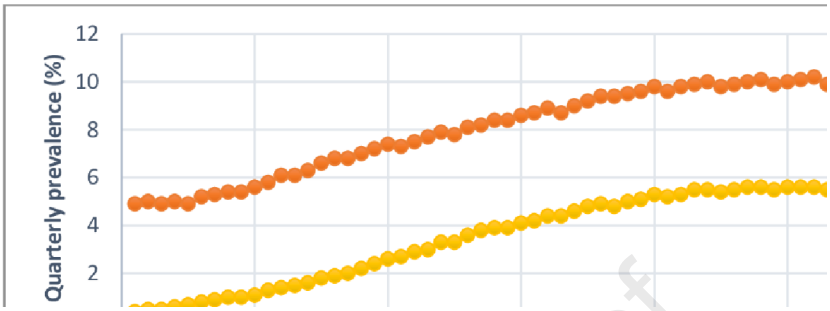
Journal Pre-proof



Journal Pre-proof

Aged ≥18 years
Registered with a general practice ≥1 year
Validated diagnostic code for asthma
≥2 asthma medication prescriptions

Journal Pre-proof



Journal Pre-proof

Journal Pre-proof

Supplementary Figure Legends

Figure E1. Diagram demonstrating the exposure windows used to define switching to ARB therapy following initiation of ACEI therapy.

Figure E2. Age-standardized quarterly prevalence of ACEIs and ARBs in patients with active asthma.

ACE=angiotensin converting-enzyme inhibitor. ARB=angiotensin-II receptor blocker. Q=quarter.

Journal Pre-proof