

**Title:** Clinical and economic implications of therapeutic switching of Angiotensin Receptor Blockers to Angiotensin-Converting Enzyme Inhibitors: A population-based study

**Short title:** Switching of antihypertensive drugs

**Authors:**

Amanj I B KURDI, PhD<sup>a, b</sup>

Rachel A ELLIOTT, PhD<sup>c</sup>

Li-Chia CHEN, PhD<sup>d</sup>

<sup>a</sup>Strathclyde Institute of Pharmacy and Biomedical Science, University of Strathclyde, Glasgow, UK; Email address: [amanj.baker@strath.ac.uk](mailto:amanj.baker@strath.ac.uk)

<sup>b</sup>Department of Pharmacology, College of Pharmacy, Hawler Medical University, Erbil, Iraq.

<sup>c</sup>Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; Email address: [Rachel.A.Elliott@manchester.ac.uk](mailto:Rachel.A.Elliott@manchester.ac.uk)

<sup>d</sup>Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; Email address: [Li-Chia.Chen@manchester.ac.uk](mailto:Li-Chia.Chen@manchester.ac.uk)

**Previous presentations of the whole or part of the work**

Part of this work has been presented as an oral presentation at the Health Services Research & Pharmacy Practice Conference 2016 at the University of Reading and as a poster at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management 2016 in Dublin, as the following citations:

*Amanj Baker*, Li-Chia Chen, Rachel Elliott. The impact of switching patients with primary hypertension from Angiotensin Receptor Blockers (ARBs) to Angiotensin-Converting Enzyme Inhibitors (ACEIs) on medication adherence and blood pressure control: a

retrospective cohort study. *International Journal of Pharmacy Practice*, 2016; 24(Suppl. 1): 5-6

*Amanj Baker*, Li-Chia Chen, Rachel Elliott. Switching of Angiotensin Receptor Blockers to Angiotensin-Converting Enzyme Inhibitors in Patients with Hypertension: Is It a Cost-Saving Strategy? *Pharmacoepidemiology and Drug Safety*, 2016;25 (Suppl. 3): 576

### **Conflicts of Interest and Source of Funding**

The authors declare no conflict of interests. The lead author (Amanj Kurdi) was funded by the Higher Committee for Education Development in Iraq for a PhD studentship. Li-Chia Chen was granted the Early Career Research and Knowledge Transfer Award from the University of Nottingham from 2010 to 2012 that supported accessing the CPRD dataset.

### **Corresponding author:**

Amanj Kurdi

Strathclyde Institute of Pharmacy and Biomedical Science, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, Scotland, UK

**Telephone:** +44(0)141 548 2181

**Fax number:** +44(0) 141 552 2562

**Email:** [amanj.baker@strath.ac.uk](mailto:amanj.baker@strath.ac.uk)

**Total word count:** 5,217 (excluding tables and legends)

**Number of tables:** 6

**Number of figures:** 1

1 **Abstract**

2 **Objective**

3 To evaluate the clinical and cost impact of switching Angiotensin Receptor Blockers (ARBs)  
4 to Angiotensin-Converting Enzyme Inhibitors (ACEIs) in patients with hypertension.

5 **Methods**

6 This study used the UK Clinical Practice Research Datalink, linking with the Hospital Episode  
7 Statistics (April-2006 to March-2012). Adults with hypertension (n=470) were followed from  
8 the first ARBs prescription date to the switching date (pre-switching period); then from the  
9 switching date to the date when study ended, patient left the dataset or died (post-switching  
10 period). Patients were divided into ACEIs-combined (n=369) and ACEIs-monotherapy (n=101)  
11 groups by whether additional antihypertensive drugs were prescribed with ACEIs in the post-  
12 switching period. Proportion of Days Covered (PDC), clinical outcomes and costs were  
13 compared between the pre- and post-switching periods using a multilevel regression.

14 **Results**

15 Overall, in the post-switching period, there was a significant increase in the proportion of non-  
16 adherence (PDC<80%) (OR: 2.4; 95%CI: 1.6, 3.7), but a significant reduction in mean SBP  
17 (mean difference [MD]: -2.3; 95CI: -3.4, -1.2mmHg) and mean DBP (MD: -1.9; 95%CI: -2.6,  
18 -1.2mmHg). However, these results were only observed in the ACEIs-combined group. There  
19 was no post-switching significant difference in either the incidence of individual or composite  
20 HT-related complications (OR: 0.9; 95%CI: 0.4, 2.0). There was a significant reduction in the  
21 overall annual medical cost per patient by £329 (95%CI: -534, -205).

22 **Conclusions**

23 Switching of ARBs to ACEIs monotherapy appeared to be clinically-effective and a cost-  
24 saving strategy. The observed changes in the ACEIs-combined group are assumed to be related  
25 to factors other than the ARBs switching.

26

27 **Keywords**

28 Therapeutic switching; ACEIs/ARBs; Hypertension; Cost-saving strategies; Clinical Practice  
29 Research Datalink (CPRD)

30

31 **List of Abbreviations**

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ACEIs	Angiotensin-Converting Enzyme Inhibitors
ARBs	Angiotensin Receptor Blockers
BCBV	Better Care Better Value
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular Disease
DBP	Diastolic blood pressure
HES	Hospital Episode Statistics
HT	Hypertension
PDC	Proportion of Days Covered
SBP	Systolic blood pressure

---

32

33 **Introduction**

34 Angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) are  
35 recommended as the first-line treatment of hypertension (HT) by most of the international  
36 guidelines[1, 2]. Their increasing utilisation has accounted for a significant part of total  
37 medicine use across Europe. From 2001-2007, ACEIs/ARBs utilisation significantly increased  
38 across six European countries[3] and contributed to a major part of the total increase of  
39 medicine expenditure[4]. In 2011, they accounted for 6% of all the prescribed medicines in the  
40 UK[5]. Consequently, many countries worldwide have initiated prescribing efficiency  
41 strategies to optimise the use of ACEIs/ARBs[3].

42

43 In 2009, a Better Care Better Value (BCBV) prescribing indicator for ACEIs/ARBs was  
44 implemented in the UK,[6] which encouraged prescribers to initiate adults with hypertension  
45 on ACEIs and actively switch established ARB users to ACEIs when appropriate. A cost-  
46 saving was expected to achieve by switching ARBs to ACEIs due to the differential cost  
47 between ARBs and ACEIs[7]. However, since ACEIs and ARBs have comparable effects in  
48 reducing cardiovascular disease (CVD) mortality and morbidity[8], it was also assumed that  
49 the ‘therapeutic switching’ between these two classes with a different mechanism of actions  
50 and active chemical entities[9] would not compromise the quality of care. However, this  
51 assumption is neither evidence-based nor has it been tested.

52

53 Previous studies demonstrated that policy-induced changes in prescribing patterns may not  
54 always translate into expected changes in patient outcomes[10]. Therefore, rigorous assessment  
55 of effects on patient outcomes is especially crucial given General Practitioners’ (GPs’)  
56 concerns over potential deterioration in patients’ quality of care that some anticipated to result  
57 from the policy-promoted switching of patients from ARBs to ACEIs[11]. Various factors that

58 lead to failure in therapeutic switching and consequently jeopardise the clinical effectiveness  
59 of therapy[9] have been suggested in previous literature, including the lack of guidance for  
60 prescribers to implement the switching, and post-switching reduction in patients' adherence  
61 due to switching to a drug with a lower adherence profile[12], patient's confusion and concerns  
62 resulting from changes in the drug's package, taste and/or appearance[13], and patients'  
63 negative expectations about switching (nocebo effect)[14]. These factors could also apply to  
64 the switching of ARBs to ACEIs.

65

66 Consequently, the overall cost-saving from switching to a cheaper drug may be offset by  
67 spending elsewhere in the health care system, resulting from the implementation or  
68 management of the adverse consequences of the switching[15]. For example, administration  
69 costs, additional visits for dose titration, follow-up and laboratory tests required to implement  
70 the switching, and hospitalisation costs needed to manage the consequence of inadequate blood  
71 pressure (BP) control[15]. Therefore, due to the lack of empirical evidence to support the  
72 therapeutic switching of ARBs to ACEIs, this study aimed to investigate the unanticipated  
73 impact of switching ARBs to ACEIs in adults with hypertension on adherence to ARBs and  
74 ACEIs, clinical effectiveness and overall changes in the National Health Service (NHS) costs.

## 75 **Methods**

### 76 **Study design and data source**

77 This retrospective cohort study used the UK primary care dataset – the Clinical Practice  
78 Research Datalink (CPRD)[16] in linkage with the hospitalisation dataset in England – the  
79 Hospital Episode Statistics (HES)[17] from April-2006 to March-2012. CPRD contains  
80 longitudinal electronic records (including patient demographics, medical diagnosis, and  
81 prescribed medications) for about 8.5% of the UK population. It has been considered broadly  
82 representative regarding practice and patient characteristics in the UK[18]. In addition, 65% of  
83 the English practices in the CPRD consent to data linkage with the HES[19]. The study protocol  
84 was approved by the Independent Scientific Advisory Committee of CPRD (protocol number  
85 13-150).

86

### 87 **Study cohort**

88 Adults ( $\geq 18$  years old) with primary hypertension, without a previous CVD and chronic kidney  
89 disease (CKD), and registered in the HES-consenting practices were identified by relevant  
90 Read codes (standard clinical terminology system used in the CPRD). Eligible patients who  
91 were issued with ARB during the study period were followed from their first ARB prescription  
92 date (index date) to the date when they switched to ACEIs (pre-switching period), and then  
93 from the switching date to the date when study ended, patient left the dataset or died (post-  
94 switching period) whichever happened first. According to previous literature, switching was  
95 defined as discontinuation of ARBs therapy and starting of ACEIs within a ‘switching window’  
96 to equal the duration of one prescription supply [20], which was 30 days on average in this  
97 study.

98

99 During the pre-switching period, the study cohort was prescribed with only ARBs as  
100 antihypertensive treatment. Considering the effect of combining additional antihypertensive  
101 medications with ACEIs in the post-switching period, the study cohort was sub-grouped by  
102 whether other antihypertensive medicines were prescribed to ACEIs in the post-switching  
103 period into the ACEIs-combined and ACEIs-monotherapy group, respectively.

104

105 All the seven ARBs (losartan, candesartan, valsartan, telmisartan, irbesartan, olmesartan,  
106 eprosartan) and the 11 ACEIs (ramipril, enalapril, lisinopril, captopril, cilazapril, quinapril,  
107 fosinopril, imidapril, moexipril, trandolapril, Perindopril) that were available in the UK during  
108 the study period were included in this study. As this study aimed to evaluate the impact of  
109 switching between the ARB and ACEI classes rather than individual ARBs and ACEIs, the  
110 types and daily dosages of the individual ARBs and ACEIs were not specified in the analysis.  
111 Given the relatively uncomplicated dosing schedules for ARBs and ACEIs in treating  
112 hypertension and evidence that GPs in the UK generally follow the recommendations in British  
113 National Formulary (BNF)[21, 22] , we assumed that ARBs/ACEIs were prescribed according  
114 to their recommended doses in the BNF.

115

### 116 **Outcome measures**

117 Adherence to antihypertensive medications, BP, HT-related complications and healthcare  
118 resource utilisation and costs (**Table 1**) were measured in both the ‘pre-switching’ and ‘post-  
119 switching’ period of the two study subgroups.

120

121 The proxy for adherence - the proportion of Days Covered (PDC) for ARBs and ACEIs were  
122 measured in the pre- and post-switching period, respectively, by dividing the total number of  
123 days covered by the drug prescription by the number of days in the follow-up time in each



124 period, and was truncated at 100% [23]. A standard cut-off point of 80% was applied to  
125 categorise the patient as adherent ( $PDC \geq 80\%$ ) and non-adherent ( $PDC < 80\%$ )[24], then the  
126 proportion of non-adherent patients was estimated.

127 In each period, mean systolic (SBP) and diastolic (DBP) BP were calculated as the average of  
128 the last three measurements. Furthermore, the incidence of individual and composite HT-  
129 related complications, including stroke, myocardial infarction (MI), angina, heart failure, and  
130 chronic kidney diseases were identified by applying previously validated ICD-10 diagnosis  
131 codes[25] to hospitalisation episodes in HES. HT-related healthcare resource utilisation was  
132 collected from primary and secondary care settings (**Table 1**). Individuals' resource utilisation  
133 was multiplied by the assigned unit cost to obtain the overall direct annual medical cost for  
134 each patient in each period.

135

### 136 **Covariates**

137 Patients' baseline characteristics including demographics (age, gender), and clinical  
138 characteristics, e.g. SBP, DBP, smoking status, body mass index, serum cholesterol and  
139 comorbidity measured using the Charlson comorbidity index (CCI)[26] were obtained at the  
140 index date. Prevalent HT patients and prevalent ARBs uses were defined as having any HT  
141 diagnosis codes or prescribed ARBs in the year before the index date; otherwise classified as  
142 incident HT patients and user, respectively.

143

### 144 **Data analysis**

145 Baseline characteristics were reported by descriptive statistics (mean and standard deviation  
146 for continuous variables; frequency and proportions for categorical variables) and the  
147 differences between subgroups were tested by the unpaired t-test and Chi-square test.  
148 Univariate analyses were undertaken in a self-controlled pre- and post- comparison framework

149 by applying appropriate statistical tests suitable for the outcome variables (**Table 1**).  
150 Furthermore, multilevel, mixed-effects regression modelling[27] was used to compare  
151 adherence, BP and HT-related complications pre- and post-switching, while adjusting for  
152 covariates. The results were presented as adjusted odds ratio (aOR) or adjusted mean difference  
153 (aMD) with their 95% confidence interval (CI). Patient's baseline characteristics (**Table 2**)  
154 such as age, gender, and smoking were not included in the adjustment models as individuals  
155 acting as a control for themselves.

156 **Results**

157 **Baseline characteristics**

158 About 5% (n=2,304) of patients (n=46,193) who switched their antihypertensive medications  
159 were ARBs switchers; of which 45.7% (n=1,053) switched from ARBs to ACEIs during the  
160 study period; of which, only 44.6% (n=470) patients were identified in the practices linked  
161 with HES, and hence were eligible for inclusion in this study. Patients in the ACEIs-combined  
162 (n=369; 78.5%) and ACEIs-monotherapy groups (n=101; 21.5%) had similar characteristics  
163 (**Table 2**), except for significantly more non-smokers in the ACEIs-combined group (58.0%  
164 vs. 47.5%, p<0.05).

165

166 **Proportion of days covered and proportion of non-adherent patients**

167 Comparing the post-switching against pre-switching period, the significant difference in  
168 adherence to antihypertensive medicating was only observed in the ACEIs-combined group.  
169 For example, the median PDC was significantly lower (99.2% vs. 97.9%, p<0.001) (Table 3);  
170 similarly, the proportion of non-adherent patients (PDC<80%) was significantly higher (17.3%  
171 vs. 29.0%, p<0.001), and consistently, a significantly higher post-switching likelihood of being  
172 non-adherent (aOR: 2.6; 95%CI: 1.6, 4.1) was found in the multivariate regression (Table 3).

173

174 **Blood pressure**

175 Likewise, a significant reduction in the mean SBP and DBP in the post-switching period were  
176 only observed in the ACEIs-combined group (Table 3); consistently, a significant post-  
177 switching reduction in both mean SBP (aMD [mmHg]: -2.2; 95%CI: 3.5, -1.0) and DBP (aMD:  
178 -2.1; 95%CI: -2.9, -1.4) after adjusting for covariates was only observed in the ACEIs-  
179 combined group (Table 3).

180 **Incidence of hypertension-related complications**

181 Of the 70 HT-related events identified from 40 patients; there was no significant difference in  
182 the incidence of individual or composite HT-related complications comparing post-switching  
183 against the pre-switching period, except for a significantly lower incidence of MI in the post-  
184 switching period (13% vs. 3%,  $p < 0.001$ ), which was only observed in the ACEIs-combined  
185 group. Consistently, the multivariate regression indicated no significant difference in risk of  
186 individual and composite HT-related complications, except for a significantly lower risk of MI  
187 (aOR: 0.1; 95%CI: 0.04, 0.6) the post-switching period (Table 4).

188

189 **Healthcare resource utilisation and costs**

190 There was higher healthcare resource use identified in the post-switching period, except for a  
191 lower and non-significant number of hospitalisations (Table 5). Overall, the median number of  
192 GP consultations was higher in the post-switching period compared with the pre-switching  
193 period, but this was statistically non-significant (4.1 vs. 3.6,  $p > 0.05$ ). The total direct cost of  
194 healthcare resource utilisation was significantly lower in the post-switching period (Figure 1).  
195 The bootstrapping analysis indicated a significantly lower total mean annual cost per patient in  
196 the post-switching period (£630 vs. £300.9; MD: -£329.2; 95%CI: -534.6, -205.7), regardless  
197 of stratifying the analysis by ACEIs-combined (MD: -£393.2; 95%CI: -665.3, -242) or ACEIs-  
198 monotherapy group (MD: -£95.1; 95%CI: -132.1, -39.0) (Table 6). This overall cost reduction  
199 was driven mainly by the significant decrease in the cost of antihypertensive drugs in the post-  
200 switching period. The costs of GP consultations and outpatient clinic attendance were not  
201 significantly different between the pre- and post-switching period.

202

203 **Discussion**

204 This study investigated a crucial prescribing issue which affects a large number of adult  
205 patients under the care of GPs by assessing the clinical and economic impact of the ARBs  
206 switching promoted by the BCBV policy. This study found that switching ARBs to ACEIs in  
207 adults with primary hypertension in current practice had no negative impact on medication  
208 adherence, clinical outcomes, and resulted in an overall direct medical cost saving. The results  
209 suggested there was no concern over compromising patients' quality of care caused by ARBs  
210 switching to ACEIs[11].

211

212 The small number of 'switchers' identified in this study indicates that switching hypertensive  
213 patients from ARBs to ACEIs appears to be uncommon in the UK. This could be attributed to  
214 the lack of an effective, national switching policy to promote switching ARB to ACEIs actively.  
215 Our previous study has shown that the BCBV indicator was ineffective[28] due to several  
216 implementation barriers[29]. Furthermore, the superior tolerability profile[30] and strong  
217 pharmaceutical marketing of ARBs[31] could also contribute to the low ARBs switching rate.

218

219 Although the previous literature has found that switching of antihypertensive drugs was  
220 associated with lower medication adherence; in this study, a significant reduction in post-  
221 switching adherence was only observed in the ACEIs-combined group, which suggests that the  
222 reduced adherence was primarily associated with the additional antihypertensive drugs  
223 prescribed, i.e. the complexity of therapeutic regime rather than the switching. The negative  
224 association between adherence and increasing the complexity of a therapeutic regimen[32] as  
225 a result of increasing the number of prescribed antihypertensive drugs[33] has been well-  
226 documented in the literature.

227

228 In addition, the comparable adherence profile between ACEIs and ARB[12, 31, 34] and the  
229 increasing patient involvement in their healthcare decision that in UK healthcare settings[35,  
230 36] could attribute to the lack of association between switching and adherence to ARB found  
231 in this study. The increase of patient involvement has been observed in several UK studies[37,  
232 38] that evaluated medication switching, including the switching of antihypertensive drugs,  
233 and involving patients in their treatments is believed to improve patients' engagement and  
234 adherence to treatment regimen.

235

236 Similar to the effect of ARBs switching on adherence, the significant reduction of both SBP  
237 and DBP was only observed in the ACEIs-combined group after switching. Since ARBs and  
238 ACEIs have similar efficacy in lowering BP[39], this result also indicates that the reduction of  
239 BP may be related to factors other than the switching, such as the additional or synergic effects  
240 of combining other antihypertensive drugs with ACEIs leading to a higher BP reduction[40].

241

242 At first glance, the observed significant reduction in BP (better BP control) in the ACEIs-  
243 combined group despite a significant decrease in medicine adherence (poor adherence) after  
244 switching seems to contradict the notion that poor adherence leads to suboptimal BP control[2].  
245 However, a statistically significant reduction in adherence may not always result in clinically  
246 relevant BP control[41].

247

248 It was not surprising to find that ARBs switching did not significantly impact on patients' HT-  
249 related complications in the ACEI-monotherapy group due to the small sample and tiny  
250 changes in adherence and BP in the post-switching period. In contrast, the significant reduction  
251 of the MI risk in the ACEIs-combination group could result from the significant reduction in  
252 BP after switching[42].

253 Although it has been reported that cost-savings from medication switching could be potentially  
254 offset by spending elsewhere in the healthcare system[9, 15], switching of ARBs to ACEIs in  
255 this study was not associated with any additional costs to offset the cost-saving resulted from  
256 ARBs switching to ACEIs. Recently, several generic ARBs were launched which might  
257 moderate the observed switching-related cost-saving in this study. However, currently, generic  
258 ACEIs are still cheaper than generic ARBs[43]; according to the UK national list prices[43],  
259 the cost of 28-day treatment supply of generic candesartan, irbesartan, and valsartan is 16%,  
260 41% and 148% higher than generic ramipril, respectively.

261

262 Furthermore, although there was no significant difference in the median of numbers of GP  
263 consultations between the pre- and post-switching period, the total number of GP consultations  
264 was higher in the post-switching period, but the total cost was lower. This difference in cost  
265 could be related to the different type and/or length of consultations (face to face vs. telephone  
266 consultations) between the pre- and post-switching period; for instance, there was a greater  
267 proportion of telephone consultations and shorter face to face consultations (mean duration:  
268 11.2 vs. 12.4 minutes) in the post-switching period compared with the pre-switching period.

269

270 Watman (2013) evaluated the impact of switching ARBs to ACEIs in 435 patients with primary  
271 hypertension[37] and reported similar findings to this study regarding insignificant changes in  
272 BP, hospitalisation, and overall cost-saving. However, Watman (2013) only followed up  
273 patients for 12 months and considered only drug acquisition costs and staff costs involved in  
274 implementing the switching[37]. Therefore, it did not demonstrate the complete picture of the  
275 full clinical and economic implications of switching ARBs to ACEIs.

276

277 This is the only population-based study that has assessed the full clinical and economic  
278 consequences of switching from ARBs to ACEIs, considering both short-term surrogate  
279 markers (adherence and BP), longer-term clinical outcomes (HT-related complications) and  
280 healthcare costs. The self-control design has been suggested to have higher statistical power  
281 compared with the parallel two-sample design (intervention vs control)[44], and this study had  
282 sufficient power to detect the significant difference in the outcomes of SBP, DBP and overall  
283 cost. It was not possible to identify the reasons for ARBs switching. Switching could occur for  
284 clinical (intolerance, treatment failure and development of other comorbid conditions[20]) or  
285 cost-saving reasons, all rarely or inconsistently recorded in the databases. Switching due to  
286 intolerance to ARBs is considered relatively unlikely given their better[13, 45] or at least  
287 similar[12, 31] tolerability profile compared with ACEIs. Switching due to treatment  
288 failure/clinical ineffectiveness is also regarded as unlikely as ARBs and ACEIs have  
289 comparable clinical efficacy[8, 39]. ACEIs have similar or broader license indications than  
290 ARBs,[46] so it is doubtful that GPs would switch patients from ARBs to ACEIs in response  
291 to the development of new comorbid conditions.

292

293 Therefore, after ruling out these clinical reasons, cost-saving is assumed to underpin most of  
294 these switching activities. This study was limited in size by only including patients from HES-  
295 consenting practices. Nevertheless, patients from HES-consenting practices have shown to be  
296 representative of the whole CPRD registrants regarding demographics, major prescriptions and  
297 hospitalisations[19]. The number of patients included in this study was higher than the amounts  
298 reported in previous clinical trials or observational studies[37, 38, 47], which evaluated the  
299 clinical and economic impact of antihypertensive drug switching other than ARBs to ACEIs.

300



301 Arguably, the study findings might be limited by the small number of CV events and the  
302 relatively medium follow-up period; however, it is unlikely that a longer follow-up time would  
303 have affected the results since there was no increase in BP, which is the typical, most reliable  
304 and well-evaluated surrogate marker for CVD[48]. As this study used healthcare databases, it  
305 was not possible to include the cost of implementing ARBs switching. The cost of staff  
306 involved in implementing the switching would not persist over time, whereas the overall cost-  
307 saving of ARBs switching is a continuous cost-saving generated from the chronic, lifetime use  
308 of cheaper ACEIs once switched from more expensive ARBs[37].

309

310 It is possible that this study results might be extrapolated to other drug classes or molecules,  
311 including other antihypertensive drug classes, which, similar to ARBs and ACEIs, have  
312 comparable clinical efficacy, safety profile, and dosing schedule. However, due to the complex  
313 and multifactorial nature of the switching process and disease conditions, the extrapolation of  
314 this research findings needs further investigation.

315

## 316 **Conclusions**

317 Switching adults with hypertension from ARBs to ACEIs appeared to do not compromise  
318 patients' adherence and clinical outcomes but resulted in overall cost-savings. Therefore, on  
319 this occasion and in this setting, it could be concluded that switching of ARBs to ACEIs can  
320 be considered a safe and clinical-effective cost-containment strategy, which could be used as  
321 evidence by clinicians and policymakers to make informed, more confident decisions about  
322 therapeutic switching of ARBs to ACEIs.

323 **References**

- 324 1. The National Institute of Health and Clinical Excellence. 2011, Hypertension: The  
325 clinical management of primary hypertension in adults, clinical guideline 127. Available at:  
326 <http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf>. Accessed 15<sup>th</sup> May, 2012.
- 327 2. Mancia, G, Fagard, R, Narkiewicz, K, Redon, J, Zanchetti, A, Böhm, M, et al. 2013  
328 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the  
329 management of arterial hypertension of the European Society of Hypertension (ESH) and of  
330 the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159-2219.
- 331 3. Voncina, L, Strizrep, T, Godman, B, Bennie, M, Bishop, I, Campbell, S, et al. Influence  
332 of demand-side measures to enhance renin-angiotensin prescribing efficiency in Europe:  
333 implications for the future. *Expert Rev Pharmacoecon Outcomes Res* 2011;11:469-479.
- 334 4. Moon, J, Flett, A, Godman, B, Grosso, A and Wierzbicki, A. Getting better value from  
335 the NHS drug budget. *Br Med J* 2010;341:30-32.
- 336 5. Health and Social Care Information Centre. 2012, Prescription Cost Analysis England  
337 2011. Health and Social Care Information Centre Available at:  
338 <http://www.hscic.gov.uk/catalogue/PUB05807/pres-cost-anal-eng-2011-rep.pdf>. Accessed  
339 24<sup>th</sup> September, 2014.
- 340 6. The NHS Institute for Innovation and Improvement. 2009, MeReC Stop Press; NPC  
341 Rapid Review- Resources relating to Better Care Better Value indicators. The NHS Institute for  
342 Innovation and Improvement Available at: <http://www.npc.nhs.uk/rapidreview/?p=328>.  
343 Accessed 23<sup>rd</sup> June, 2012.
- 344 7. Godman, B, Campbell, S, Suh, H, Finlayson, A, Bennie, M and Gustafsson, L. Ongoing  
345 measures to enhance prescribing efficiency across Europe: implications for other countries. *J*  
346 *Health Tech Assess* 2013;1:27-42.

- 347 8. Reboldi, G, Angeli, F, Cavallini, C, Gentile, G, Mancia, G and Verdecchia, P.  
348 Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor  
349 blockers on the risk of myocardial infarction, stroke and death: a meta-analysis. *J Hypertens*  
350 2008;26:1282-1289.
- 351 9. Johnston, A, Stafylas, P and Stergiou, G. Effectiveness, safety and cost of drug  
352 substitution in hypertension. *Br J Clin Pharmacol* 2010;70:320-334.
- 353 10. Serumaga, B, Ross-Degnan, D, Avery, AJ, Elliott, RA, Majumdar, SR, Zhang, F, et al.  
354 Effect of pay for performance on the management and outcomes of hypertension in the United  
355 Kingdom: interrupted time series study. *BMJ* 2011;342:d108.
- 356 11. Baker, A, Chen, L-C and Elliott, R. Lessons on the failure of the "Better Care Better  
357 Value" prescribing indicator for renin-angiotensin system drugs in treating hypertension: a  
358 qualitative study from general practitioners' perspectives. In: *The 44th Annual Scientific*  
359 *Meeting of the Society for Academic Primary Care (SAPC)*. 2015. University of Oxford,  
360 Oxford, UK. Available at: [https://sapc.ac.uk/conference/2015/abstract/lessons-failure-of-](https://sapc.ac.uk/conference/2015/abstract/lessons-failure-of-better-care-better-value-prescribing-indicator-renin)  
361 [better-care-better-value-prescribing-indicator-renin](https://sapc.ac.uk/conference/2015/abstract/lessons-failure-of-better-care-better-value-prescribing-indicator-renin)
- 362 12. Kronish, I, Woodward, M, Sergie, Z, Ogedegbe, G, Falzon, L and Mann, D. Meta-  
363 analysis: impact of drug class on adherence to antihypertensives. *Circulation* 2011;123:1611-  
364 1621.
- 365 13. Munger, M, Van, B and LaFleur, J. Medication nonadherence: an unrecognized  
366 cardiovascular risk factor. *Medscape general medicine* 2007;9:58-68.
- 367 14. Barsky, A, Saintfort, R, Rogers, M and Borus, J. Nonspecific medication side effects  
368 and the nocebo phenomenon. *J Am Med Assoc* 2002;287:622-627.
- 369 15. Johnston, A. Challenges of therapeutic substitution of drugs for economic reasons:  
370 Focus on CVD prevention. *Curr Med Res Opin* 2010;26:871-878.

- 371 16. The Medicines and Healthcare Products Regulatory Agency (MHRA). 2013, The  
372 Clinical Practice Research Datalink (CPRD). Available at: <http://www.cprd.com>. Accessed 10<sup>th</sup>  
373 March, 2013.
- 374 17. Health and Social Care Information Centre. 2014, Hospital Episode Statistics. Health  
375 and Social Care Information Centre Available at: <http://www.hscic.gov.uk/hes>. Accessed  
376 13<sup>th</sup> March, 2014.
- 377 18. Stergachis, A, Saunders, K, Davis, R, Kimmel, S, Schinnar, R, Chan, A, et al. Examples  
378 of Automated Databases. In: *Textbook of Pharmacoepidemiology*. By: Storm B. and Kimmel  
379 S.s,(Editors). 2006, John Wiley & Sons Ltd: England:204-207.
- 380 19. Gallagher, AM, Puri, S and Van Staa, TP. Linkage of the General Practice Research  
381 Database (GPRD) with Other Data Sources. *Pharmacoepidemiol Drug Saf* 2011;20:230-231.
- 382 20. Halpern, M, Khan, Z, Schmier, J, Burnier, M, Caro, J, Cramer, J, et al.  
383 Recommendations for evaluating compliance and persistence with hypertension therapy using  
384 retrospective data. *Hypertension* 2006;47:1039-1048.
- 385 21. Kendall, M and Enright, D. Provision of medicines information: the example of the  
386 British National Formulary. *Br J Clin Pharmacol* 2012;73:934-938.
- 387 22. Anonymous. 60 and counting. *Drug Ther Bull* 2010;48:48-133.
- 388 23. Raebel, M, Schmittiel, J, Karter, A, Konieczny, J and Steiner, J. Standardizing  
389 terminology and definitions of medication adherence and persistence in research employing  
390 electronic databases. *Med Care* 2013;51:S11-21.
- 391 24. Karve, S, Cleves, M, Helm, M, Hudson, T, West, D and Martin, B. Good and poor  
392 adherence: optimal cut-point for adherence measures using administrative claims data. *Curr*  
393 *Med Res Opin* 2009;25:2303-2310.

- 394 25. Signorovitch, J, Zhang, J, Wu, E, Latremouille-Viau, D, Yu, A, Dastani, H, et al.  
395 Economic impact of switching from valsartan to other angiotensin receptor blockers in patients  
396 with hypertension. *Curr Med Res Opin* 2010;26:849-860.
- 397 26. Charlson, M, Pompei, P, Ales, K and MacKenzie, R. A new method of classifying  
398 prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*  
399 1987;40:373-383.
- 400 27. Tabachnick, B and Fidell, L (Editors). *Using Multivariate Statistics*. 5<sup>th</sup> ed. 2008,  
401 Montreal: Pearson/A & B: Boston.
- 402 28. Baker, A, Chen, L-C, Elliott, RA and Godman, B. The impact of the 'Better Care Better  
403 Value' prescribing policy on the utilisation of angiotensin-converting enzyme inhibitors and  
404 angiotensin receptor blockers for treating hypertension in the UK primary care setting:  
405 longitudinal quasi-experimental design. *BMC Health Serv Res* 2015;15:367.
- 406 29. Baker, A, Chen, L-C and Elliott, R. Lessons on the failure of the "Better Care Better  
407 Value" prescribing indicator for renin-angiotensin system drugs in treating hypertension: a  
408 qualitative study from general practitioners' perspectives In: *The 44<sup>th</sup> Annual Scientific Meeting*  
409 *of the Society for Academic Primary Care (SAPC)*. 2015. University of Oxford, Oxford, UK.  
410 Available at: [https://sapc.ac.uk/conference/2015/abstract/lessons-failure-of-better-care-better-](https://sapc.ac.uk/conference/2015/abstract/lessons-failure-of-better-care-better-value-prescribing-indicator-renin)  
411 [value-prescribing-indicator-renin](https://sapc.ac.uk/conference/2015/abstract/lessons-failure-of-better-care-better-value-prescribing-indicator-renin)
- 412 30. Böhm, M, Baumhaekel, M, Mahfoud, F and Werner, C. From evidence to rationale:  
413 cardiovascular protection by Angiotensin II Receptor Blockers compared with Angiotensin-  
414 Converting Enzyme Inhibitors. *Cardiology* 2010;117:163-173.
- 415 31. Vegter, S, Nhu Ho, N, Visser, S, Postma, M and Boersma, C. Compliance, persistence,  
416 and switching patterns for ACE inhibitors and ARBs. *Am J Manag Care* 2011;17:609-616.

- 417 32. Choudhry, N, Fischer, M, Avorn, J, Liberman, J, Schneeweiss, S, Pakes, J, et al. The  
418 implications of therapeutic complexity on adherence to cardiovascular medications. *Arch*  
419 *Intern Med* 2011;171:814-822.
- 420 33. Hilleman, D. Adherence and health care costs with single-pill fixed-dose combination  
421 in hypertension management. *J Manag Care Pharm* 2014;20:93-100.
- 422 34. Evans, C, Eurich, D, Lu, X, Remillard, A, Shevchuk, Y and Blackburn, D. The  
423 association between market availability and adherence to antihypertensive medications: an  
424 observational study. *American Journal of Hypertension* 2013;26:180-190.
- 425 35. Coulter, A and Collins, A. Making shared decision-making a reality: no decision about me, without me.  
426 The King's Fund. fund, TKs, 2011. Available at: [http://www.kingsfund.org.uk/sites/files/kf/Making-](http://www.kingsfund.org.uk/sites/files/kf/Making-shared-decision-making-a-reality-paper-Angela-Coulter-Alf-Collins-July-2011_0.pdf)  
427 [shared-decision-making-a-reality-paper-Angela-Coulter-Alf-Collins-July-2011\\_0.pdf](http://www.kingsfund.org.uk/sites/files/kf/Making-shared-decision-making-a-reality-paper-Angela-Coulter-Alf-Collins-July-2011_0.pdf).  
428 Accessed 25<sup>th</sup> September, 2016
- 429 36. NICE. 2009, Medicines adherence: Involving patients in decisions about prescribed  
430 medicines and supporting adherence. National Institute for Health and Care Excellence  
431 Available at: <http://www.nice.org.uk/guidance/CG76>. Accessed 25<sup>th</sup> February, 2015.
- 432 37. Watman, G. Clinic to implement patient change from an Angiotensin Receptor Blocker  
433 (ARB) to an Angiotensin Converting Enzyme Inhibitor (ACEI) in general medical practices.  
434 *Pharmacy Management* 2013;29:19-24.
- 435 38. Usher-Smith, J, Ramsbottom, T, Pearmain, H and Kirby, M. Evaluation of the cost  
436 savings and clinical outcomes of switching patients from atorvastatin to simvastatin and  
437 losartan to candesartan in a Primary Care setting. *Int J Clin Pract* 2007;61:15-23.
- 438 39. Li, C, Heran, S and Wright, M. Angiotensin Converting Enzyme (ACE) Inhibitors  
439 versus Angiotensin Receptor Blockers for Primary Hypertension. *Cochrane Database of*  
440 *Systematic Reviews* 2014;8:CD009096.

- 441 40. Gradman, A, Basile, J, Carter, B and Bakris, G. Combination therapy in hypertension.  
442 *J Clin Hypertens* 2011;13:146-154.
- 443 41. Selak, V, Elley, C, Bullen, C, Crengle, S, Wadham, A, Rafter, N, et al. Effect of fixed  
444 dose combination treatment on adherence and risk factor control among patients at high risk of  
445 cardiovascular disease: randomised controlled trial in primary care. *Br Med J* 2014;348:g3318.
- 446 42. Yusuf, S, Hawken, S, Ôunpuu, S, Dans, T, Avezum, A, Lanas, F, et al. Effect of  
447 potentially modifiable risk factors associated with myocardial infarction in 52 countries (the  
448 INTERHEART study): case-control study. *Lancet* 2004;364:937-952.
- 449 43. British Medical Association. British National Formulary, 74. Royal Pharmaceutical  
450 Society of Great Britain: 2017
- 451 44. Lerman, J. Study design in clinical research: sample size estimation and power analysis.  
452 *Can J Anaesth* 1996;43:184-191.
- 453 45. The ONTARGET investigators. Telmisartan, ramipril or both in patients at high risk  
454 for vascular events. *N Engl J Med* 2008;358:1547–1559.
- 455 46. British Medical Association. British National Formulary, 71. Royal Pharmaceutical  
456 Society of Great Britain: London, 2016
- 457 47. McDonough, K, Weaver, R and Viall, G. Enalapril to lisinopril: economic impact of a  
458 voluntary Angiotensin-Converting Enzyme-Inhibitor substitution program in a staff-model  
459 health maintenance organization. *Ann Pharmacother* 1992;26:399-404.
- 460 48. Weintraub, WS, Lüscher, TF and Pocock, S. The perils of surrogate endpoints. *Eur*  
461 *Heart J* 2015;36:2212-2218.
- 462 49. Personal Social Services Research Unit. 2012, Unit Costs o Health and Social Care.  
463 Personal Social Services Research Unit Available at: [http://www.pssru.ac.uk/project-](http://www.pssru.ac.uk/project-pages/unit-costs/2012/#sections)  
464 [pages/unit-costs/2012/#sections](http://www.pssru.ac.uk/project-pages/unit-costs/2012/#sections). Accessed 14<sup>th</sup> March, 2014.

- 465 50. Briggs, A and Gray, A. The distribution of health care costs and their statistical analysis  
466 for economic evaluation. *J Health Serv Res Policy* 1998;3:233-245.
- 467 51. British Medical Association. British National Formulary, 63. Royal Pharmaceutical  
468 Society of Great Britain: London, March 2012
- 469 52. Department of Health. 2012, NHS reference costs: financial year 2011 to  
470 2012. Department of Health Available at: [https://www.gov.uk/government/publications/nhs-](https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012)  
471 [reference-costs-financial-year-2011-to-2012](https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012). Accessed 14<sup>th</sup> March, 2014.
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## **Figure legends**

**Figure 1. Mean total annual cost of healthcare resource use per patient, comparing post- and pre-switching periods**

## Tables

**Table 1. Summary of the study outcomes with their associated data sources and univariate analyses**

Outcome category	Outcome measures	Data source	Outcome	Univariate analysis
Adherence to antihypertensive medications	Proportion of Days Covered (PDC) by ARBs or ACEIs prescription	CPRD-Therapy file	Median and interquartile range (IQR) of PDC	Wilcoxon signed-rank sum test
			Proportion of non-adherence patients (PDC<80%)	McNemar's test
Blood pressure (BP)	Systolic blood pressure and diastolic blood pressure	CPRD-Medical file	Mean systolic and diastolic BP	Paired t-test
Hypertension (HT)-related complications	A composite of any event of a stroke, myocardial infarction, angina, heart failure, and chronic kidney diseases	HES-Inpatient dataset	Proportion of patients experienced any HT-related complications	McNemar's test
Healthcare resource utilisation	Number of HT-related GP visits and consultations	CPRD-Medical file	Median (IQR) of the outcome measures	Wilcoxon signed-rank sum test
	Number of prescriptions of antihypertensive medicines	CPRD-Therapy file		
	Number of HT-related hospital admissions	HES-Inpatient dataset		
	Number of HT-related outpatient attendance	CPRD-Referral file		
Cost	Cost/minute for HT-related GP consultations	PSSRU[49]	Annual costs from the bootstrapping approach	Paired t-test on the data generated from the bootstrapping approach[50]
	Cost of individual antihypertensive medication	BNF[51]		
	Cost/HT-related hospitalisation episode and attendance at outpatient clinics	NHS reference cost[52]		

**(Note)** CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics; PSSRU: Personal Social Services Research Unit; BNF: British National Formulary

**Table 2. Baseline characteristics of the study cohort and subgroups**

	<b>Total</b> (n=470)	<b>ACEIs-combined</b> <b>group</b> (n=369)	<b>ACEIs-</b> <b>monotherapy</b> <b>group</b> (n=101)
<b>Mean age (±SD)</b>	59.1±12.5	59.4±12.8	57.9±11.5
<b>Gender</b>			
Male	281 (59.8%)	225 (61.0%)	56 (55.5%)
Female	189 (40.2%)	144 (39.0%)	45 (44.5%)
<b>Mean BP (mmHg)</b>			
Mean SBP (±SD)	147.2±18.4	147.3±18.6	146.8±17.8
Mean DBP (±SD)	86.6±11.5	86.6±11.5	86.6±11.8
<b>Mean BMI (±SD)</b>	28.6±5.4	28.8±5.2	28.0±6.1
<b>Mean serum cholesterol (mmol/L)</b> (±SD)	5.1±1.1	5.1±1.2	5.2±1.0
<b>Charlson comorbidity index</b>			
0	286 (60.9%)	218 (59.1%)	68 (67.3%)
1	112 (23.8%)	92 (24.9%)	20 (19.0%)
≥2	72 (15.3%)	59 (16.0%)	13 (12.9%)
<b>Smoking status</b>			
Non- smokers	262 (55.7%)	214 (58.0%)*	48 (47.5%)*
Smokers	75 (16.0%)	52 (14.1%)	23 (22.8%)
Ex-smokers	133 (28.3%)	103 (27.9%)	30 (29.7%)
<b>Drug use status</b>			
Incident	146 (31.1%)	117 (31.7%)	29 (28.7%)
Prevalent	324 (68.9%)	252 (68.3%)	72 (71.3%)
<b>Hypertension status</b>			
Incident	116 (24.7%)	89 (24.1%)	27 (26.7%)
Prevalent	354 (75.3%)	280 (75.9%)	74 (73.3%)
<b>Mean follow-up time (years±SD)</b>			
Pre-switching	2.5±1.7	2.3±1.7	3.1±1.6
Post-switching	2.6±1.7	2.8±1.7	1.9±1.4
<b>(Note)</b> * p<0.05 Chi-square test; <b>SD</b> : standard deviation; <b>BP</b> : Blood pressure; <b>BMI</b> : Body mass index			

**Table 3. Proportion of Days Covered and blood pressure comparing post- and pre-switching periods**

	Total (n=470)		ACEIs-combined group (n=369)		ACEIs-monotherapy group (n=101)	
	Pre-switching	Post-switching	Pre-switching	Post-switching	Pre-switching	Post-switching
<b>Proportion of days covered (PDC)</b>						
Median PDC (IQR)	98.5% (89.5-100%) <sup>(a)</sup>	97.9% (74.7-100%) <sup>(a)</sup>	99.2% (89.5-100%) <sup>(a)</sup>	97.9% (70-100%) <sup>(a)</sup>	95.7% (90.5-100%)	98.0% (86.0-100%)
Proportion of patients with PDC<80%	17.0% <sup>(b)</sup>	27.0% <sup>(b)</sup>	17.3% <sup>(b)</sup>	29.0% <sup>(b)</sup>	15.8%	19.8%
aOR (95%CI) <sup>(c)</sup>	2.4 (1.6, 3.7)		2.6 (1.6, 4.1)		1.9 (0.6, 5.6)	
<b>Blood pressure (mmHg)</b>						
Mean SBP (±SD)	143.2±13.1 <sup>(d)</sup>	141.3±12.8 <sup>(d)</sup>	144.2±13.4 <sup>(d)</sup>	141.9±12.5 <sup>(d)</sup>	139.8±11.4	138.8±13.8
Mean DBP (±SD)	84.1±8.8 <sup>(d)</sup>	82.5±8.6 <sup>(d)</sup>	84.6±8.7 <sup>(d)</sup>	82.6±8.3 <sup>(d)</sup>	82.4±8.7	81.9±9.5
aMD (90%CI) of SBP	-2.3 (-3.4, -1.2) <sup>(e)</sup>		-2.2 (-3.5, -1.0) <sup>(e)</sup>		-2.0 (-4.8, 0.4)	
aMD (90%CI) of DBP	-1.9 (-2.6, -1.2) <sup>(e)</sup>		-2.1 (-2.9, -1.4) <sup>(e)</sup>		-1.0 (-2.7, 0.7)	
<b>(Note) SBP:</b> systolic blood pressure; <b>DBP:</b> diastolic blood pressure; <b>IQR:</b> interquartile range; <b>SD:</b> standard deviation; <sup>(a)</sup> <b>p&lt;0.001</b> (Wilcoxon signed-rank test); <sup>(b)</sup> <b>p&lt;0.001</b> (McNemar test); <sup>(c)</sup> <b>aOR:</b> adjusted OR for the proportion of non-adherent patients (PDC<80%), model was adjusted for patients' follow-up time; <b>aMD:</b> adjusted mean difference; <sup>(d)</sup> <b>p&lt;0.001</b> (paired t-test); <sup>(e)</sup> <b>p&lt;0.005</b> (regression models adjusted for follow-up time and PDC)						

**Table 4. Incidence of hypertension-related complications comparing post- and pre-switching periods**

Number of events (%)	Total (n=470)		aOR (95%CI) <sup>#</sup>	ACEIs-combined group (n=369)		aOR (95%CI) <sup>#</sup>	ACEIs-monotherapy group (n=101)		aOR (95%CI) <sup>#</sup>
	Pre-switching	Post-switching		Pre-switching	Post-switching		Pre-switching	Post-switching	
	<b>Composite</b>	19 (4.0%)		21 (4.5%)	0.9 (0.4, 2.0)		18 (4.9%)	18 (4.9%)	
<b>Stroke</b>	1 (0.2%)	2 (0.4%)	1.2 (0.08, 17.8)	0 (0.0%)	1 (0.3%)	NA	1 (1.0%)	1 (1.0%)	1.0 (0.08, 14.1)
<b>MI</b>	13 (2.8%)*	3 (0.6%)*	0.1 (0.04, 0.6)	13 (3.5%)*	3 (1.8%)*	0.1 (0.04, 0.6)	0 (0.0%)	0 (0.0%)	NA
<b>HF</b>	0 (0.0%)	1 (0.2%)	NA	0 (0.0%)	1 (0.3%)	NA	0 (0.0%)	0 (0.0%)	NA
<b>CKD</b>	0 (0.0%)	1 (0.2%)	NA	0 (0.0%)	1 (0.3%)	NA	0 (0.0%)	0 (0.0%)	NA
<b>Angina</b>	6 (1.3%)	7 (1.5%)	0.9 (0.2, 3.9)	6 (1.6%)	6 (1.6%)	0.7 (0.1, 3.3)	0 (0.0%)	1 (1.0%)	NA
<b>Atherosclerosis and other IHD</b>	4 (0.9%)	11 (2.3%)	2.1 (0.6, 7.3)	4 (1.1%)	10 (2.7%)	1.7 (0.5, 6.2)	0 (0.0%)	1 (1.0%)	NA

**(Note):** \*  $p < 0.001$  (McNemar test); <sup>#</sup>aOR: adjusted odds ratio, models were adjusted for patients' follow up time, PDC, systolic and diastolic BP, whether the patient developed the studied outcome of interest in the pre-switching period; **MI**: myocardial infarction; **HF**: heart failure; **CKD**: chronic kidney disease; **IHD**: ischaemic heart diseases; **NA**: non-applicable as study subgroups did not develop the complications before or after the switching.

**Table 5. Total healthcare resource utilisation and associated costs in the pre- and post-switching periods**

Healthcare resources category		Total (n=470)		ACEIs-combined group (n=369)		ACEIs-monotherapy group (n=101)	
		Pre-switching	Post-switching	Pre-switching	Post-switching	Pre-switching	Post-switching
<b>GPs consultation</b>	Quantity	4,359	5,734	3,277	5,075	1,082	659
	Cost	126,361	103,493	111,716	86,770	14,644	16,714
<b>Antihypertensive drug prescription</b>	Quantity	9,347	14,120	6,909	12,508	2,438	1,612
	Cost	95,543	12,216	79,979	10,603	15,563	1,614
<b>Hospitalisation</b>	Quantity	46	33	45	28	1	5
	Cost	73,147	23,800	73,931	21,237	216	2,563
<b>Outpatient attendance</b>	Quantity	17	44	12	42	5	2
	Cost	1060	1,891	878	1,786	182	105
<b>Total</b>	Quantity	13,769	19,931	10,243	17,653	3,526	2,278
	Cost	296,111	141,400	266,504	120,396	30,605	20,996

**(Note)** ACEIs: Angiotensin-Converting Enzyme Inhibitors

**Table 6. Mean total annual cost (in British Pounds) of healthcare resource utilisation per patient in the post-switching period compared with the pre-switching period**

	Total (n=470)		ACEIs-combined group (n=369)		ACEIs-monotherapy group (n=101)	
	Pre-switching	Post-switching	Pre-switching	Post-switching	Pre-switching	Post-switching
<b>GPs consultations</b>						
Mean cost <sup>(a)</sup>	268 (212.2 to 457.4)	220.2 (202.4 to 248)	302.8 (227.5 to 520)	235 (212.5 to 264)	145 (125 to 172.8)	165.5 (136 to 210)
Cost difference <sup>(a)</sup>	-48.7 (-227.4 to 10.0), P=0.382 <sup>(b)</sup>		-67.6 (-283.8 to 14.4), P=0.348 <sup>(b)</sup>		20.5 (-14.7 to 64.5), 0.315 <sup>(b)</sup>	
<b>Antihypertensive drugs prescriptions</b>						
Mean cost <sup>(a)</sup>	203.3 (173.8 to 272)	26.0 (27.0 to 28.5)	216.7 (181.8 to 317)	28.7 (26.1 to 31.8)	154.1 (146 to 162)	16.0 (14.6 to 18.1)
Cost difference <sup>(a)</sup>	-177.3 (-246.6 to -148.0), P=0.025 <sup>(b)</sup>		-188.0 (-288.0 to -153.4), P=0.021		-138.1 (-146.3 to -131.1), P<0.001 <sup>(b)</sup>	
<b>Hospitalisations</b>						
Mean cost <sup>(a)</sup>	155.6 (86.9 to 304.2)	50.6 (27.3 to 93.4)	197.6 (106.3 to 367)	57.6 (27.1 to 108.2)	2.2 (0.0 to 12.9)	25.4 (7.7 to 82.3)
Cost difference <sup>(a)</sup>	-105.0 (-251.0 to -31.1), P=0.028 <sup>(b)</sup>		-140.1 (-308.2 to -49.0), P=0.021 <sup>(b)</sup>		23.2 (-6.0 to 52.5), P=0.117 <sup>(b)</sup>	
<b>Outpatients attendance</b>						
Mean cost <sup>(a)</sup>	2.3 (1.2, 4.3)	4.0 (2.6, 6.7)	2.4 (1.1, 4.9)	4.8 (2.9, 8.6)	1.8 (0.4, 4.8)	1.0 (0.3, 4.3)
Cost difference <sup>(a)</sup>	1.8 (-0.5, 4.2), P=0.138 <sup>(b)</sup>		2.4 (-0.2, 5.4), P=0.10 <sup>(b)</sup>		0.8 (-3.6, 1.6), P=0.585 <sup>(b)</sup>	
<b>Total cost</b>						
Mean cost <sup>(a)</sup>	630.0 (506.7 to 844)	300.9 (269.3 to 350)	719.5 (565.8 to 979)	326.3 (288 to 387)	303 (281.6 to 329)	207.9 (172 to 274)
Cost difference <sup>(a)</sup>	-329.2 (-534.6 to -205.7); P=0.011 <sup>(b)</sup>		-393.2 (-665.3 to -242), P=0.01 <sup>(b)</sup>		-95.1 (-132.1 to -39.0); P=0.002 <sup>(b)</sup>	
<b>(Note)</b> <sup>(a)</sup> Bootstrapped bias-corrected and accelerated 95% confidence interval (95%CI); <sup>(b)</sup> Bootstrapped paired t-test p-value						

**Figure 1**

