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

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Abstract

Objective

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

Methods

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

Results

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

Conclusions

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

Keywords

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

List of Abbreviations

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

Introduction

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

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

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

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

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

Methods

Study design and data source

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

Study cohort

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

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

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

Outcome measures

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

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

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

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

Covariates

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

Data analysis

Baseline characteristics were reported by descriptive statistics (mean and standard deviation for continuous variables; frequency and proportions for categorical variables) and the differences between subgroups were tested by the unpaired t-test and Chi-square test. 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.

Results

Baseline characteristics

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

Proportion of days covered and proportion of non-adherent patients

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

Blood pressure

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

Incidence of hypertension-related complications

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

Healthcare resource utilisation and costs

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusions

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

References

1. The National Institute of Health and Clinical Excellence. 2011, Hypertension: The clinical management of primary hypertension in adults, clinical guideline 127.Available at: http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf. Accessed 15th May, 2012.

2. Mancia, G, Fagard, R, Narkiewicz, K, Redon, J, Zanchetti, A, Böhm, M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159-2219.

3. Voncina, L, Strizrep, T, Godman, B, Bennie, M, Bishop, I, Campbell, S, et al. Influence of demand-side measures to enhance renin-angiotensin prescribing efficiency in Europe: implications for the future. *Expert Rev Pharmacoecon Outcomes Res* 2011;11:469-479.

4. Moon, J, Flett, A, Godman, B, Grosso, A and Wierzbicki, A. Getting better value from the NHS drug budget. *Br Med J* 2010;341:30-32.

5. Health and Social Care Information Centre. 2012, Prescription Cost Analysis England 2011.Health and Social Care Information Centre Available at: http://www.hscic.gov.uk/catalogue/PUB05807/pres-cost-anal-eng-2011-rep.pdf. Accessed 24th September, 2014.

6. The NHS Institute for Innovation and Improvement. 2009, MeReC Stop Press; NPC Rapid Review- Resources relating to Better Care Better Value indicators.The NHS Institute for Innovation and Improvement Available at: http://www.npc.nhs.uk/rapidreview/?p=328. Accessed 23rd June, 2012.

7. Godman, B, Campbell, S, Suh, H, Finlayson, A, Bennie, M and Gustafsson, L. Ongoing measures to enhance prescribing efficiency across Europe: implications for other countries. *J Health Tech Assess* 2013;1:27-42.

8. Reboldi, G, Angeli, F, Cavallini, C, Gentile, G, Mancia, G and Verdecchia, P. Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis. *J Hypertens* 2008;26:1282-1289.

9. Johnston, A, Stafylas, P and Stergiou, G. Effectiveness, safety and cost of drug substitution in hypertension. *Br J Clin Pharmacol* 2010;70:320-334.

10. Serumaga, B, Ross-Degnan, D, Avery, AJ, Elliott, RA, Majumdar, SR, Zhang, F, et al. Effect of pay for performance on the management and outcomes of hypertension in the United Kingdom: interrupted time series study. *BMJ* 2011;342:d108.

11. Baker, A, Chen, L-C and Elliott, R. Lessons on the failure of the "Better Care Better Value" prescribing indicator for renin-angiotensin system drugs in treating hypertension: a qualitative study from general practitioners' perspectives. In: *The 44th Annual Scientific Meeting of the Society for Academic Primary Care (SAPC)*. 2015. University of Oxford, Oxford, UK. Available at: https://sapc.ac.uk/conference/2015/abstract/lessons-failure-of-better-care-better-value-prescribing-indicator-renin

12. Kronish, I, Woodward, M, Sergie, Z, Ogedegbe, G, Falzon, L and Mann, D. Meta-analysis: impact of drug class on adherence to antihypertensives. *Circulation* 2011;123:1611-1621.

13. Munger, M, Van, B and LaFleur, J. Medication nonadherence: an unrecognized cardiovascular risk factor. *Medscape general medicine* 2007;9:58-68.

14. Barsky, A, Saintfort, R, Rogers, M and Borus, J. Nonspecific medication side effects and the nocebo phenomenon. *J Am Med Assoc* 2002;287:622-627.

15. Johnston, A. Challenges of therapeutic substitution of drugs for economic reasons: Focus on CVD prevention. *Curr Med Res Opin* 2010;26:871-878.

16. The Medicines and Healthcare Products Regulatory Agency (MHRA). 2013, The Clinical Practice Research Datalink (CPRD).Available at: http://www.cprd.com. Accessed 10th March, 2013.

17. Health and Social Care Information Centre. 2014, Hospital Episode Statistics.Health and Social Care Information Centre Available at: http://www.hscic.gov.uk/hes. Accessed 13thMarch, 2014.

18. Stergachis, A, Saunders, K, Davis, R, Kimmel, S, Schinnar, R, Chan, A, et al. Examples of Automated Databases. In: *Textbook of Pharmacoepidemiology*. By: Storm B. and Kimmel S.s,(Editors). 2006, John Wiley & Sons Ltd: England:204-207.

19. Gallagher, AM, Puri, S and Van Staa, TP. Linkage of the General Practice Research Database (GPRD) with Other Data Sources. *Pharmacoepidemiol Drug Saf* 2011;20:230-231.

20. Halpern, M, Khan, Z, Schmier, J, Burnier, M, Caro, J, Cramer, J, et al. Recommendations for evaluating compliance and persistence with hypertension therapy using retrospective data. *Hypertension* 2006;47:1039-1048.

21. Kendall, M and Enright, D. Provision of medicines information: the example of the British National Formulary. *Br J Clin Pharmacol* 2012;73:934-938.

22. Anonymous. 60 and counting. *Drug Ther Bull* 2010;48:48-133.

23. Raebel, M, Schmittdiel, J, Karter, A, Konieczny, J and Steiner, J. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care* 2013;51:S11-21.

24. Karve, S, Cleves, M, Helm, M, Hudson, T, West, D and Martin, B. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin* 2009;25:2303-2310.

25. Signorovitch, J, Zhang, J, Wu, E, Latremouille-Viau, D, Yu, A, Dastani, H, et al. Economic impact of switching from valsartan to other angiotensin receptor blockers in patients with hypertension. *Curr Med Res Opin* 2010;26:849-860.

26. Charlson, M, Pompei, P, Ales, K and MacKenzie, R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383.

27. Tabachnick, B and Fidell, L (Editors). *Using Multivariate Statistics*. 5th ed. 2008, Montreal: Pearson/A & B: Boston.

28. Baker, A, Chen, L-C, Elliott, RA and Godman, B. The impact of the 'Better Care Better Value'prescribing policy on the utilisation of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for treating hypertension in the UK primary care setting: longitudinal quasi-experimental design. *BMC Health Serv Res* 2015;15:367.

29. Baker, A, Chen, L-C and Elliott, R. Lessons on the failure of the "Better Care Better Value" prescribing indicator for renin-angiotensin system drugs in treating hypertension: a qualitative study from general practitioners' perspectives In: *The 44th Annual Scientific Meeting of the Society for Academic Primary Care (SAPC)*. 2015. University of Oxford, Oxford, UK. Available at: https://sapc.ac.uk/conference/2015/abstract/lessons-failure-of-better-care-better-value-prescribing-indicator-renin

30. Böhm, M, Baumhaekel, M, Mahfoud, F and Werner, C. From evidence to rationale: cardiovascular protection by Angiotensin II Receptor Blockers compared with Angiotensin-Converting Enzyme Inhibitors. *Cardiology* 2010;117:163-173.

31. Vegter, S, Nhu Ho, N, Visser, S, Postma, M and Boersma, C. Compliance, persistence, and switching patterns for ACE inhibitors and ARBs. *Am J Manag Care* 2011;17:609-616.

32. Choudhry, N, Fischer, M, Avorn, J, Liberman, J, Schneeweiss, S, Pakes, J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Arch Intern Med* 2011;171:814-822.

33. Hilleman, D. Adherence and health care costs with single-pill fixed-dose combination in hypertension management. *J Manag Care Pharm* 2014;20:93-100.

34. Evans, C, Eurich, D, Lu, X, Remillard, A, Shevchuk, Y and Blackburn, D. The association between market availability and adherence to antihypertensive medications: an observational study. *American Journal of Hypertension* 2013;26:180-190.

35. Coulter;, A and Collins, A. Making shared decision-making a reality: no decision about me, without me. The King's Fund. fund, TKs, 2011. Available at:http://www.kingsfund.org.uk/sites/files/kf/Making-shared-decision-making-a-reality-paper-Angela-Coulter-Alf-Collins-July-2011_0.pdf. Accessed 25th September, 2016

36. NICE. 2009, Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence.National Institute for Health and Care Excellence Available at: http://www.nice.org.uk/guidance/CG76. Accessed 25th February, 2015.

37. Watman, G. Clinic to implement patient change from an Angiotensin Receptor Blocker (ARB) to an Angiotensin Converting Enzyme Inhibitor (ACEI) in general medical practices. *Pharmacy Management* 2013;29:19-24.

38. Usher-Smith, J, Ramsbottom, T, Pearmain, H and Kirby, M. Evaluation of the cost savings and clinical outcomes of switching patients from atorvastatin to simvastatin and losartan to candesartan in a Primary Care setting. *Int J Clin Pract* 2007;61:15-23.

39. Li, C, Heran, S and Wright , M. Angiotensin Converting Enzyme (ACE) Inhibitors versus Angiotensin Receptor Blockers for Primary Hypertension. *Cochrane Database of 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-
464 pages/unit-costs/2012/#sections. Accessed 14th March, 2014.

50. Briggs, A and Gray, A. The distribution of health care costs and their statistical analysis for economic evaluation. *J Health Serv Res Policy* 1998;3:233-245.

51. British Medical Association. British National Formulary, 63. Royal Pharmaceutical Society of Great Britain: London, March 2012

52. Department of Health. 2012, NHS reference costs: financial year 2011 to 2012.Department of Health Available at: https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012. Accessed 14th March, 2014.

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

	Total (n=470)	**ACEIs-combined group** (n=369)	**ACEIs-monotherapy group** (n=101)
Mean age (±SD)	59.1±12.5	59.4±12.8	57.9±11.5
Gender			
Male	281 (59.8%)	225 (61.0%)	56 (55.5%)
Female	189 (40.2%)	144 (39.0%)	45 (44.5%)
Mean BP (mmHg)			
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
Mean BMI (±SD)	28.6±5.4	28.8±5.2	28.0±6.1
Mean serum cholesterol (mmol/L) (±SD)	5.1±1.1	5.1±1.2	5.2±1.0
Charlson comorbidity index			
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%)
Smoking status			
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%)
Drug use status			
Incident	146 (31.1%)	117 (31.7%)	29 (28.7%)
Prevalent	324 (68.9%)	252 (68.3%)	72 (71.3%)
Hypertension status			
Incident	116 (24.7%)	89 (24.1%)	27 (26.7%)
Prevalent	354 (75.3%)	280 (75.9%)	74 (73.3%)
Mean follow-up time (years±SD)			
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

(Note) *** $p<0.05$ Chi-square test; **SD: standard deviation; **BP**: Blood pressure; **BMI**: 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**
Proportion of days covered (PDC)						
Median PDC (IQR)	98.5% (89.5-100%) [a]	97.9% (74.7-100%) [a]	99.2% (89.5-100%) [a]	97.9% (70-100%) [a]	95.7% (90.5-100%)	98.0% (86.0-100%)
Proportion of patients with PDC<80%	17.0% [b]	27.0% [b]	17.3% [b]	29.0% [b]	15.8%	19.8%
aOR (95%CI) [c]	2.4 (1.6, 3.7)		2.6 (1.6, 4.1)		1.9 (0.6, 5.6)	
Blood pressure (mmHg)						
Mean SBP (±SD)	143.2±13.1 [d]	141.3±12.8 [d]	144.2±13.4 [d]	141.9±12.5 [d]	139.8±11.4	138.8±13.8
Mean DBP (±SD)	84.1±8.8 [d]	82.5±8.6 [d]	84.6±8.7 [d]	82.6±8.3 [d]	82.4±8.7	81.9±9.5
aMD (90%CI) of SBP	-2.3 (-3.4, -1.2) [e]		-2.2 (-3.5, -1.0) [e]		-2.0 (-4.8, 0.4)	
aMD (90%CI) of DBP	-1.9 (-2.6, -1.2) [e]		-2.1 (-2.9, -1.4) [e]		-1.0 (-2.7, 0.7)	

(Note) SBP: systolic blood pressure; **DBP**: diastolic blood pressure; **IQR**: interquartile range; **SD**: standard deviation; [a] **p<0.001** (Wilcoxon signed-rank test); [b] **p<0.001**(McNemar test); [c] **aOR**: adjusted OR for the proportion of non-adherent patients (PDC<80%), model was adjusted for patients' follow-up time; **aMD**: adjusted mean difference**;** [d] **p<0.001** (paired t-test); [e] **p<0.005** (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)[#]	ACEIs-combined group (n=369)		aOR (95%CI)[#]	ACEIs-monotherapy group (n=101)		aOR (95%CI)[#]
	Pre-switching	Post-switching		Pre-switching	Post-switching		Pre-switching	Post-switching	
Composite	19 (4.0%)	21 (4.5%)	0.9 (0.4, 2.0)	18 (4.9%)	18 (4.9%)	0.7 (0.3,1.6)	1 (1.0%)	3 (3.0%)	4.4 (0.4, 50.2)
Stroke	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)
MI	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
HF	0 (0.0%)	1 (0.2%)	NA	0 (0.0%)	1 (0.3%)	NA	0 (0.0%)	0 (0.0%)	NA
CKD	0 (0.0%)	1 (0.2%)	NA	0 (0.0%)	1 (0.3%)	NA	0 (0.0%)	0 (0.0%)	NA
Angina	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
Atherosclerosis and other IHD	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); [#]**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**
GPs consultation	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
Antihypertensive drug prescription	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
Hospitalisation	Quantity	46	33	45	28	1	5
	Cost	73,147	23,800	73,931	21,237	216	2,563
Outpatient attendance	Quantity	17	44	12	42	5	2
	Cost	1060	1,891	878	1,786	182	105
Total	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

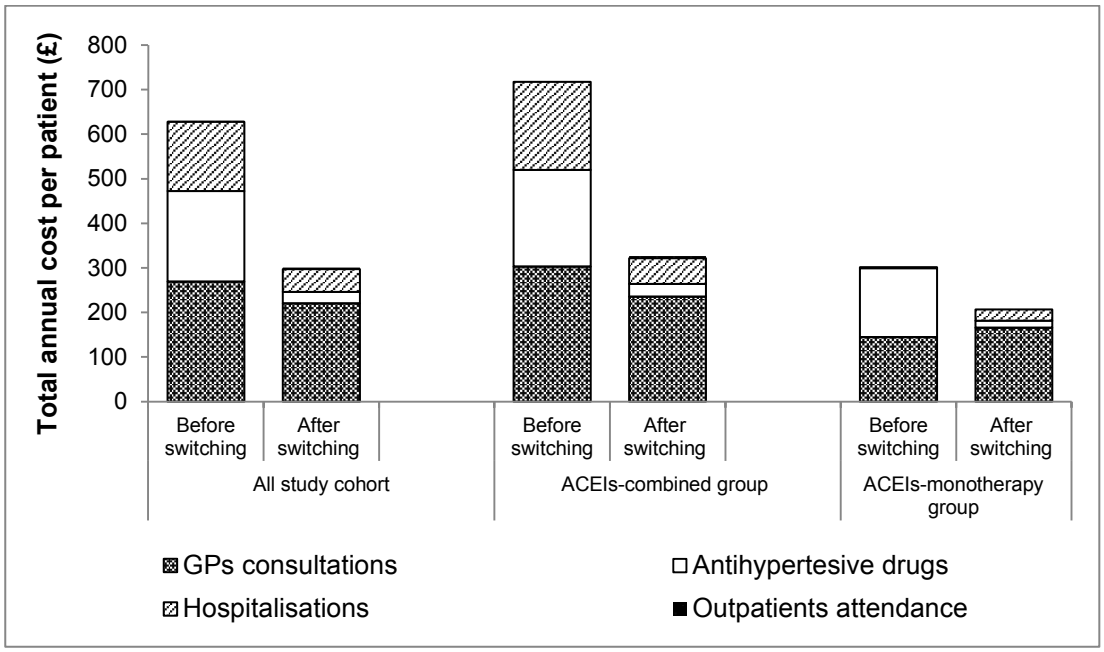
(Note) ACEIs: Angiotensin-Converting Enzyme Inhibitors

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**
GPs consultations						
Mean cost [(a)]	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 [(a)]	-48.7 (-227.4 to 10.0), P=0.382 [(b)]		-67.6 (-283.8 to 14.4), P=0.348 [(b)]		20.5 (-14.7 to 64.5), 0.315 [(b)]	
Antihypertensive drugs prescriptions						
Mean cost [(a)]	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 [(a)]	-177.3 (-246.6 to-148.0), P=0.025 [(b)]		-188.0 (-288.0 to-153.4), P=0.021		-138.1 (-146.3 to-131.1), P<0.001 [(b)]	
Hospitalisations						
Mean cost [(a)]	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 [(a)]	-105.0 (-251.0 to -31.1), P=0.028 [(b)]		-140.1 (-308.2 to -49.0), P=0.021 [(b)]		23.2 (-6.0 to 52.5), P=0.117 [(b)]	
Outpatients attendance						
Mean cost [(a)]	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 [(a)]	1.8 (-0.5, 4.2), P=0.138 [(b)]		2.4 (-0.2, 5.4), P=0.10 [(b)]		0.8 (-3.6, 1.6), P=0.585 [(b)]	
Total cost						
Mean cost [(a)]	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 [(a)]	-329.2 (-534.6 to -205.7); P=0.011 [(b)]		-393.2 (-665.3 to -242), P=0.01 [(b)]		-95.1 (-132.1 to -39.0); P=0.002 [(b)]	

(Note) [(a)] Bootstrapped bias-corrected and accelerated 95% confidence interval (95%CI); [(b)] Bootstrapped paired t-test p-value

Figure 1


Total annual cost per patient (£)
800
700
600
500
400
300
200
100
0
Before switching
After switching
Before switching
After switching
Before switching
After switching
All study cohort
ACEIs-combined group
ACEIs-monotherapy group
GPs consultations
Antihypertesive drugs
Hospitalisations
Outpatients attendance