



SHORT COMMUNICATION

Impact of regulatory interventions to restrict the combined use of renin–angiotensin system blockers: A Danish nationwide drug utilisation study

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This study aimed to evaluate the impact of the risk minimisation measures issued by the European Medicines Agency in 2014 to restrict the combined use of renin–angiotensin system (RAS) blocking agents in Denmark. Data from the Danish National Prescription Registry covering all medications dispensed during January 2008–December 2018 was used. The outcome was monthly prevalence of patients codispensed RAS blockers. Autoregressive integrated moving average interrupted time series regression was used to evaluate dispensing trends. The prevalence of patients codispensed RAS blockers decreased from 0.01 to 0.0003%. Preintervention trend was declining and further decreased with an additional -0.45 (95% confidence interval $-0.66, -0.25$) codispensing per million population after the intervention. Overall, the intervention had minimal impact on the combined use of RAS blockers. However, as the combined use of RAS blockers is low, further interventions to restrict the combined use of RAS blockers may not be required in Denmark at this point.

KEYWORDS

angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, drug safety, drug utilisation, pharmacovigilance, renin–angiotensin system, risk management

1 | INTRODUCTION

Regulatory interventions aimed at preventing or reducing adverse drug reactions are vital for ensuring public safety. Moreover, when such risk minimisation measures have been implemented, it is important to evaluate their effectiveness to ensure that they are working as intended. If the evaluation shows that the risk minimisation measures are not effective, corrective actions must be taken.¹

In April 2014, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommended (referral procedure, Article 31 of Directive 2001/83/EC) restriction of combined use of different agents acting on the renin–angiotensin

system (RAS).² These agents, also called RAS blockers, act by blocking various stages of the renin–angiotensin system, which regulates blood pressure, systemic vascular resistance, and fluid and electrolyte balance. RAS blockers include **angiotensin-converting enzyme inhibitors (ACEIs)**, **angiotensin II receptor blockers (ARBs)** and direct renin inhibitors (e.g., **aliskiren**). They are used to treat hypertension, heart failure and diabetic nephropathy.³ Previously, combined use of 2 different RAS blockers had been employed to manage hypertension and was believed to be more efficacious than monotherapy. However, a detailed review by the PRAC, including data from large clinical trials and meta-analyses,^{4–7} demonstrated an increased risk of hypotension, hyperkalaemia and renal failure resulting from the combined

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use of RAS blockers compared to monotherapy. Moreover, no significant benefits of combined use were observed in patients without heart failure. Following the review of all available data, the PRAC implemented risk minimisation measures in 2014 in terms of updating the summary of product characteristics, including advice against the combined use of different RAS blockers. Exceptions were **candesartan** and **valsartan**, which are the only ARBs licensed as add-on therapy to ACEIs for symptomatic heart failure patients.

So far, research on the impact of the regulatory intervention in 2014 has been conducted only in the UK,⁸ and the wider impact of the measures across the EU remains unknown. Therefore, this study aimed to evaluate the effectiveness of the risk minimisation measures to restrict the combined use of different RAS blockers issued by the PRAC in 2014 in Denmark. Of note, the impact of the intervention in 2014 is restricted to the combined use of ACEIs and ARBs only because warnings against combining aliskiren with an ARB or ACEI was communicated by the EMA in 2012.

2 | METHODS

The predefined study protocol is registered and accessible under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), EU PASS Register No: 38752.

2.1 | Population and data sources

The study included nationwide secondary data from the National Prescription Registry⁹ covering all prescriptions dispensed by community pharmacies in Denmark. The study population included the full adult (≥ 18 y) population of Denmark.

2.2 | Outcomes

The primary outcome used to examine trends in coprescribing was monthly codispensing defined as an ACEI and an ARB dispensed the same day based on dispensing dates. We calculated the monthly prevalence of patients codispensed RAS blockers from 1 January 2008 to 31 December 2018 by dividing the number of patients with at least 1 codispensing within a given month by the number of the total adult population (aged ≥ 18 y) in Denmark in that month. The primary outcome was stratified according to sex and age groups (18–64 and ≥ 65 y). Secondary outcome was the prevalence of patients codispensed an ARB and an ACEI among users (i.e., patients dispensed an ARB or an ACEI or both).

2.3 | Data analysis

Since the intervention was a warning of combination therapy, but not an absolute contraindication, we assumed that the main effect is

What is already known about this subject

- In comparison to monotherapy, the combined use of renin–angiotensin system (RAS) blockers has been associated with an increased risk of hypotension, hyperkalaemia and renal failure.
- The European Medicines Agency recommends the restriction of combined use of RAS blockers.
- The pattern of combined use of RAS blockers in Denmark is not known.

What this study adds

- Risk minimisation measures had a minimal impact on the combined use of RAS blockers in Denmark.
- Codispensing of RAS blockers in Denmark is low indicating prescribing is in accordance with regulatory guidelines.
- No further interventions may be required in Denmark to restrict the combined use of RAS blockers.

merely a gradual effect rather than an abrupt effect. Hence, the main outcome was a change in slope before and after the intervention. The intervention time was defined as the PRAC advice issued in April 2014. We used the autoregressive integrated moving average (ARIMA) interrupted time series regression model outlined by the Cochrane Effective Practice and Organisation of Care (EPOC)¹⁰ to evaluate change in dispensing trends preintervention to postintervention.^{11,12} Linear trend was assessed by visual inspection of the preintervention data,¹³ and homogeneity of variance and normal distribution of residuals was used to check the assumptions of the linear regression model.¹⁴

To evaluate autocorrelation adequately, we used 24 data points before and 24 data points after the intervention and aimed for a minimum of 100 observations at each data point.¹⁴ We used summary statistics to identify any seasonal patterns and Durbin–Watson statistics to test for autocorrelation.¹⁴

Stata software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA: StataCorp LLC.) was used in data extraction and management on the remote servers of Statistics Denmark. The ARIMA analyses were performed in SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA.), and confidence intervals (CIs) were calculated using Microsoft Excel for Windows (2019). Graphic representation of fitted lines was performed using R statistical software (Foundation for Statistical Computing, Vienna, Austria).

2.4 | Sensitivity analyses

The following sensitivity analyses were carried out to test key assumptions.

- Twelve data points were used before and after the intervention instead of 24 data points.
- The intervention time was moved (i) 12 months back to the start of the referral procedure in June 2013; and (ii) to October 2014, which is 4 weeks after the European Commission's final decision in September 2014 where the public health communication is updated saying that the review is now final and translations in all official EU languages are published.
- Seven- and 30-day time windows were used to capture codispensing as some patients may be dispensed medications on different days. The date of codispensing was defined as the date of the latest dispensing of the 2 prescribed medicines.

TABLE 1 Number of patients (age ≥ 18 y) treated with an ACEI or ARB or both at study start in January 2008 and at end of study in December 2018

Drug	January 2008 general adult population ^a (n = 4 260 307)	December 2018 general adult population ^a (n = 4 645 061)
ACEI or ARB or both	156 521 (3.67%)	136 979 (2.95%)
ACEI	121 053 (2.84%)	105 108 (2.26%)
ARB	36 222 (0.85%)	32 070 (0.69%)
ACEI and ARB	468 (0.01%)	162 (0.003%)

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

^aGeneral population was age ≥ 18 years.

3 | RESULTS

On average, 315 patients were codispensed ACEIs and ARBs per month in the study period, representing 0.007% (315/4,442,400) of the adult Danish population. The absolute number of patients codispensed an ACEI and ARB decreased during the study from 468 patients in January 2008 to 162 patients in December 2018 (Table 1), representing 109/million and 35/million adults in Denmark (age ≥ 18 y), respectively (Figure 1, Table S1). Codispensing peaked in December 2008 with 525 (122/million) and was lowest in November 2018 at 133 (29/million).

3.1 | Interrupted time series results

Results of the interrupted times series are presented in Table 2. The preintervention baseline trend was declining and the trend further decreased after the intervention. The observed change in slope after the intervention of -0.45 (95% CI $-0.66, -0.25$) codispensing per million population per month was statistically significant. Also, we observed a nonsignificant rise (1.99, 95% CI $-0.90, 4.88$) in codispensing in the first month after the intervention. Similarly, the codispensing among users (secondary outcome) was already declining before the intervention and decreased further with a significant slope change after the intervention (Figure S4, Table 2).

Similar direction of trends in codispensing of ACEIs and ARBs were detected across age groups and sexes (Figure S5, Figure S6, Table S2). Downward preintervention trends and slope changes were somewhat more pronounced among those aged >65 years compared to the younger population.

FIGURE 1 Monthly prevalence (per 1 000,000 population) of angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker codispensing in Denmark from January 2008 to December 2018. The solid lines show trends in codispensing in the period from May 2012 to April 2016, that is 24 months before and 24 months after the regulatory intervention, and the dotted line represents the counterfactual trend that would be expected if the intervention had not been introduced. Codispensing was defined as an angiotensin-converting enzyme inhibitor and an angiotensin II receptor blocker dispensed the same day

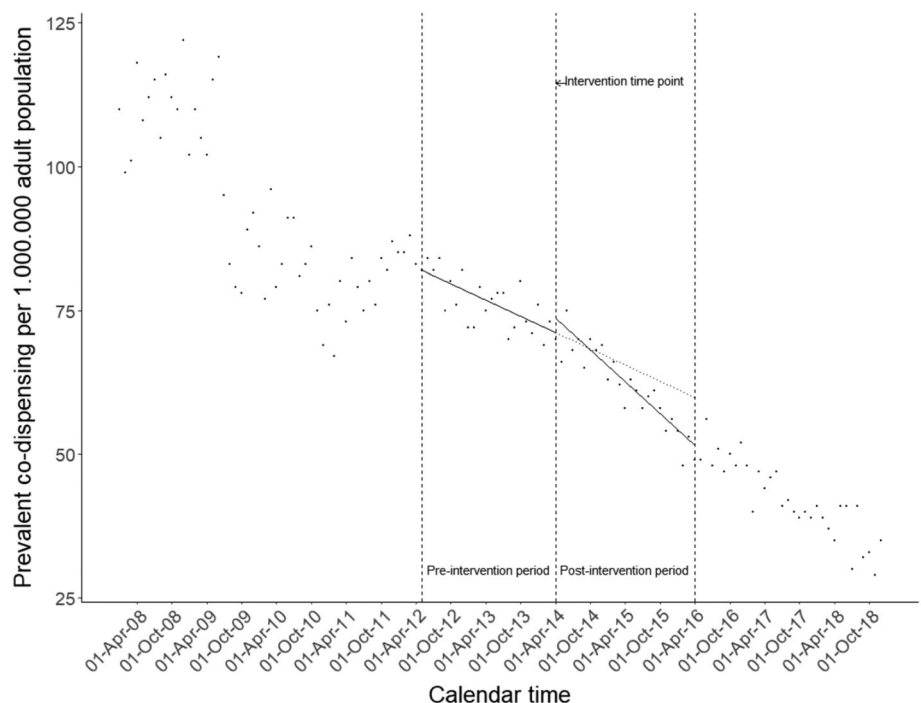


TABLE 2 Interrupted time series regression results for trends in prevalence of ACEI and ARB codispensing^a

Outcome	Preintervention slope (95% CI), P-value	Level change 1 mo after intervention (95% CI), P-value	Slope change after intervention (95% CI), P-value
Primary			
Monthly prevalence of codispensing per million population	-0.47 (-0.62, -0.32), <i>P</i> < .001	1.99 (-0.90, 4.88), <i>P</i> = .17	-0.45 (-0.66, -0.25), <i>P</i> < .001
Secondary			
Monthly prevalence of codispensing per million users of ACEI or ARB or both	-8.23 (-13.06, -4.40), <i>P</i> = .001	48.14 (-47.46, 143.74), <i>P</i> = .32	-13.19 (-19.97, -6.42), <i>P</i> < .001

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CI = confidence interval

^aCodispensing was defined as an ACEI and an ARB dispensed the same day.

Sensitivity analysis using 12 data points and moving the intervention time showed similar direction and magnitude as the primary outcome using same day codispensing, 24 data points and an intervention time point in April 2014. The sensitivity analyses using wider time windows (7- and 30-d) showed similar patterns and trends as the primary outcome but with higher codispensing rates (Table S3, Figure S9).

4 | DISCUSSION

Our results show a steadily declining trend in the prevalence of patients codispensed RAS blockers starting in July 2009, almost 5 years before the regulatory intervention in May 2014. When assessing the intervention's impact, we observed an additional decrease of approximately a half (-0.45) codispensing per million population per month after the intervention, compared to the preintervention period. However, in the sensitivity analyses, similar changes were observed when moving the intervention date forward or backwards in time, suggesting a gradual and multifactorial impact over time rather than the single regulatory intervention's acute effect. Based on the risk difference between combination therapy and monotherapy,⁷ the change (-0.45 codispensing per million population per month) translate into a maximum of 2 or 3 adverse reactions, which is prevented yearly due to the regulatory intervention among the total adult Danish population. We believe that this is a minimal clinical impact of the regulatory intervention. Considering that coprescribing is low (162 patients in 2018) and warnings against coprescribing have been implemented throughout Europe including The Danish Hypertension Society,¹⁵⁻¹⁷ we find it unlikely that further interventions will reduce coprescribing even further. Also, the ARBs, candesartan and valsartan, are licensed as add-on therapy to ACEIs for people with symptomatic heart failure,² so clinicians may still coprescribe if considered absolutely necessary. It should be noted that continuous monitoring is vital to ensuring patient safety in view of the potential adverse clinical consequences of combined use of RAS blockers.

Our results are consistent with Allen and Donegan, who evaluated the regulatory intervention taken in 2014 on the coprescribing

of RAS blockers in the UK.⁸ That study showed a reduction in overall coprescribing in line with the recommendations from the PRAC, but according to the authors, the reduction was probably due to other factors than the PRAC recommendation, while acknowledging that the study period may not have been sufficiently long to observe the full potential reduction in coprescribing. Likewise, a possible explanation of the steadily declining trend starting in July 2009 in Denmark is that they were caused by the studies and clinical guidelines published before the PRAC recommendation in 2014.^{4-7,15,17,18} A study in the Irish population from 2000 to 2009, by contrast, observed an increase in coprescribing of ACEIs and ARBs,¹⁹ despite the publication of the ONTARGET trial in April 2008. This may indicate that changes in prescribing behaviour may lag behind the publication of significant studies. Considering that the UK study covered the period until July 2015, it may not have been sufficiently long to observe a further reduction in coprescribing following the regulatory intervention in April 2014. Our study shows that the decreasing trend in Denmark continues after July 2015.

A key strength of this study is the use of a national dataset, thereby making the findings representative for the wider Danish population. However, there are several limitations. First, since the data on codispensing covered same-day dispensing, we may have underestimated the overall extent of codispensing. Nonetheless, sensitivity analyses using a wider time window showed similar trends as the primary outcome and we observed increasing rates of codispensing with increasing time windows. As a wider time window leads to misclassification of switching as codispensing, higher rates are expected when increasing the time window. It is worth noting that the same-day approach has been adopted by Tobi et al.,²⁰ by Wan et al. who describe the coprescribing trend of ACEIs and ARBs in Ireland,¹⁹ by Allen and Donegan who investigated coprescribing of RAS blockers in the UK,⁸ and by the EMA.¹⁵

Second, although interrupted time series analysis is a robust quasiexperimental design to evaluate the effects of regulatory interventions,¹⁴ there is no comparator against which to adjust the results for changes that should not be attributed to the intervention itself. For ethical reasons, risk minimisation measures are implemented simultaneously to the entire target population. For this reason, it was

not feasible to use a comparator group in our study. To facilitate the discussion about whether other interventions influenced the outcome, we identified scientific publications and changes to clinical guidelines that may have contributed to the declining trend observed preintervention (see Table S4).

5 | CONCLUSION

From May 2009 to 2018, there has been a steady declining trend in codispensing RAS blockers. We observed an additional decline after the regulatory intervention in 2014, which is considered of minimal clinical impact. We believe that the marked reduction of codispensing is mainly attributable to other studies published before the regulatory intervention in 2014. However, it is reassuring that codispensing is low indicating prescribing is in accordance with regulatory guidelines. Hence, further interventions may not be required to restrict the combined use of RAS blockers.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019 a,b).²¹

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COMPETING INTERESTS

P.S., M.L.D.B., K.K., R.O.-A., C.E.H. and H.G. report no conflict of interest. At time of the project, R.O.-A., C.E.H. and M.L.D.W. were employed by Copenhagen Centre for Regulatory Sciences (CORS). CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring Pharmaceuticals, LEO Pharma) as well as patient organizations (Rare Diseases Denmark). The centre is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus and the research is not company-specific product or directly company related. In the last 5 years, CORS has received funding from Novo Nordisk, Lundbeck, Ferring Pharmaceuticals and LEO pharma for projects not related to this study. Currently, M.L.D.B. and H.G. are employed by Utrecht University and conduct research under the umbrella of the Utrecht-WHO Collaborating Centre for Pharmaceutical Policy and Regulation. This Centre receives no direct funding or donations from private parties, including pharma industry. Research funding from public-private partnerships, e.g. IMI, The Escher Project (<http://escher.lygature.org/>) is accepted under the condition that no company-specific product or company related study is conducted. The Centre has received unrestricted research funding from public

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None of the abovementioned companies had any involvement in the current study.

CONTRIBUTORS

All authors were involved in the study protocol design and interpretation of results and drafting of the manuscript. P.S. prepared the manuscript. P.S., R.O.-A., C.E.H. and M.L.D.B. were involved in data preparation, data checking and/or data analysis. All authors approved the final manuscript prior to submission

ETHICS APPROVAL

The study was approved by the Danish Data Protection Agency (514-0301/19-3000). Register-based studies do not require approval from an ethics review board.

DATA AVAILABILITY STATEMENT

No data are available for sharing. Data can be accessed according to the Danish National Prescription Registry's standard terms and conditions for conducting observational studies.

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SUPPORTING INFORMATION

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