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ORIGINAL REPORT

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Dual renin-angiotensin-aldosterone blockade: Implementation of published research and Dear Doctor letters in ambulatory care: A retrospective observational study using prescription data

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Abstract

Purpose: This study aims to assess the implementation of published research, contraindications, and warnings on the prescription of dual renin-angiotensin-hormone system (RAS) blockade in ambulatory care in Germany.

Methods: Cohort study based on health claims data of 6.7 million subjects from 2008 to 2015. Yearly prevalence and incidence for dual RAS blockade with (a) angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ACEI + ARB) and (b) aliskiren and ACEI or ARB (aliskiren + ACEI/ARB) were calculated. We assessed prescriber specialty and associations between discontinuing dual RAS blockade with specialist (internal medicine, cardiology, nephrology) visits and hospital discharge in the previous year.

Results: A total of 2 984 517 patients were included (age 51.4 ± SD 18.4 y, 48.5% male). Prescription rates for ACEI + ARB decreased from 0.6% (n = 17 907) to 0.4% (n = 12 237) and for aliskiren + ACEI/ARB from 0.23% (n = 6634) to 0.03% (n = 818). Incident prescriptions decreased from 0.23% (n = 6705) to 0.19% (n = 5055) (ACE + ARB) and from 0.1% (n = 2796) to 0.005% (n = 142) (aliskiren + ACE/ARB); 59% of ACEI + ARB and 48% of aliskiren + ACE/ARB combinations were prescribed only by one physician. Of those, 73% (ACEI + ARB) and 58% (aliskiren + ACE/ARB) were primary care providers (PCPs). Discontinuing dual RAS blockade was associated with specialist care and hospital discharge in the previous year (specialist care: RR 1.4, 95% CI, 1.3-1.6; hospital visit: RR 1.5, 95% CI, 1.3-1.6).

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Conclusions: Our results suggest a delayed uptake of treatment recommendation for ACEI + ARB and a higher impact of Dear Doctor letters addressing PCPs directly compared with published research, contraindications, and warnings. Targeted continuous medical education, practice software alerts, and stronger involvement of pharmacists might improve the implementation of medication safety recommendations in ambulatory care.

KEYWORDS

ACE inhibitors, ARB, Dear Doctor letter, dual RAS blockade, pharmacoepidemiology

1 | INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEI) and, for patients with side effects of ACEI, angiotensin-receptor blockers (ARB) are recommended first-line drugs for hypertension in patients with and without nephropathy and widely used.[1] ACEI, ARB, and renin inhibitors are blockers of the renin angiotensin (RAS) hormone system at different levels. In 2007, the direct renin inhibitor aliskiren was approved in the United States and the European Union. A combination of ACEI with ARB results in a more complete blockade of the RAS system. A combination compared with monotherapy was found to result in a greater reduction of blood pressure in some patient groups including patients with type 1 diabetes, and positive effects of lowering proteinuria in diabetic and nondiabetic nephropathy were reported.[2-6] However, in 2008, the ONTARGET trial showed a higher rate of hypotensive symptoms, syncope, and renal dysfunction in patients treated with ACE inhibitors and ARB, compared with monotherapy.[7] For people at high vascular risk, a combination therapy was found to worsen renal outcomes despite a better reduction of proteinuria than monotherapy.[8] The VA NEPHRON-D study and several large clinical trials and meta-analyses confirmed an increased risk of hyperkalaemia, hypotension, and impaired renal function for a dual RAS blockade with ACEI and ARB or a direct renin inhibitor (aliskiren) with ACEI or ARB compared with monotherapy with RAS blocking agents.[9-14]

In 2012, in Germany, two Dear Doctor letters (DDLs) informed physicians about risks of combining aliskiren with another RAS blocker and new contraindications and warnings for aliskiren-containing medicines by the European Medicines Agency (EMA). The EMA recommended (a) physicians to stop prescribing aliskiren-containing medicines to patients with diabetes or kidney impairment treated with ACEI or ARB and (b) the inclusion of a warning about possible adverse outcomes of a combination of aliskiren with ACEI or ARB in all other patients.[15-17] In 2014, the European Medicines Agency (EMA) issued a statement on restrictions of combining any two RAS blocker classes in any patient and, in particular, of ACEI with ARB in patients with diabetes-related kidney problems (diabetic nephropathy).[18] Since this did not affect a single substance, no DDL was issued. The combined use of ACEI with ARB (candesartan or valsartan licensed as add-on therapy to ACEI) remained restricted to supervised specialist use under close monitoring in individual cases of heart failure patients intolerant to mineralocorticoid antagonists with persistent symptoms despite optimal treatment.

Previous observational studies have investigated the effects of regulatory action on prescribing and shown that DDL or Direct Healthcare Professional Communication letters are only weakly perceived by physicians, differ in format and wording, and do not communicate reliable and effective information to health care providers.[19-26]

Our study aims to assess the implementation of published research, published contraindications, and warnings on the prescription of a dual RAS blockade in ambulatory care in Germany.

2 | METHODS

2.1 | Study design and population

This is a cohort study based on anonymised health claims data of 6.7 million Germans with statutory health care insurance (InGef database).[27] The database was shown to correspond to general hospitalisation rates, overall mortality, and prescription rates for the 20 most often reimbursed drug classes and had a slightly lower overall morbidity burden compared with German reference data. For this study, a sample of 4 million patients from January 2008 to December 2015 was drawn and adjusted for age and sex based on official national statistics (Destatis, 31 December 2014). All patients aged 18 years or older who could be followed for a period of at least 270 days for each year of the study period or until the date of death during the study period were identified. A patient observation was censored, if for an index year the patient could be followed for less than 270 days. Patients could only be enrolled in one insurance policy at one time.

For each patient, the following data were available: an anonymised identification number, birthdate, sex, date of death, periods of coverage for the health insurance, diagnoses according to ICD-10-GM (German modification of the 10th revision of the International Classification of Diseases) for ambulatory care and hospital discharge diagnoses and prescription data, including all prescriptions by GPs and specialists from ambulatory care handed in to the pharmacy. Prescription data comprise a central pharmaceutical number for each prescribed drug (an identification number providing every detail of the

finished drug, including an ATC classification for the active substance and the number of units [tablets, capsules] and DDDs), prescription dates, ID number, and specialty of the prescribing physician.

2.2 | Data Analysis

Patients with at least one RAS blocker prescription were identified using ATC code (ACEI: C09A- - C09B-, ARB: C09C- - C09D-, aliskiren: C09XA-). The yearly prevalence of a dual RAS blockade was calculated by dividing the number of patients receiving prescriptions for two different classes of RAS blockers within 184 days (6 mo) at least once during the index year by the total number of patients under observation during the index year. An incident dual RAS blockade was defined in patients with no dual RAS blockade in the previous year but dual RAS blockade in the index year. Hypertension (I10-I15), cardiovascular disease (I20-I25 and I70-I74, I77), diabetes mellitus (E10-E14), chronic kidney disease (CKD) (N17-N19), and electrolyte disturbances (E87.0, E87.5, E87.6) were defined to be present, if at least one ICD-10-GM code was documented during the study period in ambulatory care or at hospital discharge. Only diagnoses coded as "confirmed" were included.

We investigated prescription rates and rates of an incident dual RAS blockade for (a) ACEI with ARB and (b) aliskiren with an ACEI, an ARB, or both per year. Prescription rates for combinations of aliskiren with ACEI/ARB were calculated for the total study cohort and for the subgroup of patients with diabetes or CKD. Based on the anonymised physician ID and specialty, we categorised prescribers of dual RAS blockade. Trends and seasonality of observed changes in prescription rates over the study period were assessed using time series analysis (autoregressive integrated moving average [ARIMA] modelling using augmented Dickey-Fuller test for stationarity).

For a subgroup of patients with diabetes, hypertension, cardiovascular disease, vascular disease, or CKD, where the primary care provider (PCP, including general practitioners [GPs] and specialists internal medicine working as GPs) was the sole prescriber of a dual RAS blockade, the association between terminating a dual RAS blockade (index year 2015) with (a) at least one visit to a specialist (internal medicine, cardiology, nephrology) during the (previous) year 2014 and (b) at least one hospital discharge during the year 2014, was investigated using a Poisson regression model. Hospital discharges or admissions were not restricted to specific diagnoses.

Analyses were performed with R, version 3.2.3.

3 | RESULTS

3.1 | Population

A total of 2 984 517 patients were included in the analysis (mean age 51.4 ± SD 18.4 y, 48.5% male). During the study period, n = 337 735 patients died (overall mortality rate 1.47%). At study begin, 34.3% of patients had hypertension (ICD-10-GM I10-I15), 10.2% diabetes mellitus (ICD-10-GM E10-E14), and 2.8% CKD (ICD-10-GM N18-N19).

KEY POINTS

- Prescription rates of a dual RAS blockade in Germany declined from 2008 to 2015 but incident prescriptions for ACE inhibitors with ARB were unchanged.
- The decline for combinations of aliskiren with ACE inhibitor and/or ARB was greater.
- Our results suggest a higher impact of Dear Doctor Letters and contraindications addressing primary care providers directly, compared with publications of study results or EMA warnings.
- Factors as medication budgets might be important for discontinuation of potentially inappropriate medication.
- Targeted continuous medical education, alerts from practice software, better access to medication plans and stronger involvement of pharmacists might improve the implementation of medication safety recommendations in ambulatory care.

3.2 | Prescription rates for combinations of ACE inhibitors with ARB

During the study period, 38.4% (n = 1 146 055) of included patients were prescribed an ACE inhibitor or ARB and 1.9% (n = 56 435) an ACE inhibitor and ARB (Figure 1). From 2008 to 2015, the prescription rates for either an ACE inhibitor or ARB increased from 22.2% (n = 662 563) to 29.6% (n = 883 417) and decreased for combinations of ACE inhibitors with ARB from 0.6% (n = 17 907) to 0.4% (n = 12 237) (Dickey-Fuller −2.3, P = .5). The rate of incident combinations of ACE inhibitor with ARB decreased from 0.23% (n = 6705) in 2009 to 0.19% (n = 5055) in 2015.

Time trend analysis indicates a true decrease in prescription rates for combinations of ACE inhibitors with ARB in the total cohort.

3.3 | Prescription rates for combinations of aliskiren with ACEI, ARB, or ACEI and ARB

During the study period, 0.37% (n = 11 025) of included patients were prescribed aliskiren with ACE inhibitor or ARB. Prescription rates for a dual RAS blockade with aliskiren and either ACE inhibitor or ARB in the total study population increased from 0.07% (n = 2116) in 2008 to 0.23% (n = 6634) in 2011 and decreased subsequently to 0.03% (n = 818) in 2015 (Dickey-Fuller −2.3, P = .4). The rate for incident prescriptions was 0.1% (n = 2796) in 2009 and 2011 (n = 2927) and decreased to 0.005% (n = 142) in 2015. Correspondingly, in patients with diabetes (ICD-10-GM E10-E14) or CKD (ICD-10-GM N18-N19) prescription rates for a dual RAS blockade with aliskiren and either ACE inhibitor or ARB increased from 0.05% (n = 1575) in 2008 to 0.16% (n = 4713) in 2011 and decreased subsequently to 0.01%

(n = 375) in 2015 (Dickey-Fuller −2.3, P = .5). The rate for incident prescriptions increased from 0.05% (n = 1528) in 2009 to 0.06% (n = 1695) in 2011 and decreased to 0.003% (n = 72) in 2015.

Time trend analysis indicates a true decrease in prescription rates for a dual RAS blockade with aliskiren and either ACE inhibitor or ARB in the total cohort and in the subgroup of patients with diabetes or CKD.

3.4 | Dual RAS blockade prescriptions, specialty of prescribers, and association with specialty care/ hospital admissions

In 59% (n = 30 377) of cases, combinations of ACE inhibitors with ARB were continuously prescribed only by one physician (Figure 2). Of those, 73% (n = 22 045) were PCPs. Correspondingly, aliskiren combinations with ACE inhibitors or ARB were continuously prescribed only by one physician in 48% (n = 5311) of cases; 58% (n = 3066) of those were PCPs.

After adjusting for age and sex, a discontinuation of a dual RAS blockade was associated with specialist care and hospital visits in the previous year for patients with diabetes or CKD where the PCP was the sole prescriber of dual RAS blockade (specialist care: RR 1.4, 95% CI, 1.3-1.6; hospital visit: RR 1.5, 95% CI, 1.3-1.6) (Table 1). A discontinuation of a combined treatment of aliskiren with ACE inhibitor or ARB was only weakly associated with specialist care and hospital visits in the previous year for patients where the PCP was the sole prescriber of dual RAS blockade (specialist care: 1.7, 95% CI, 1.0-3.0; hospital visit: RR 1.8, 95% CI, 1.1-3.1) (Table 1).

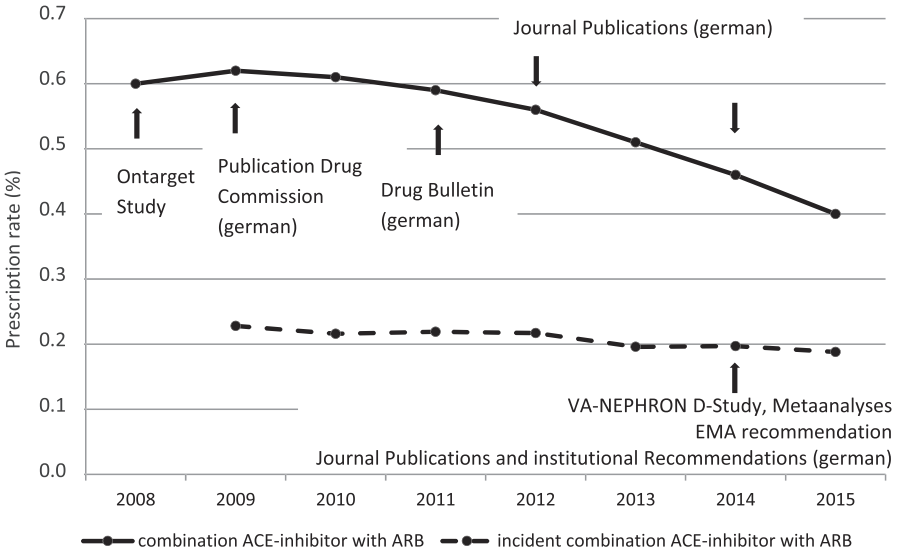

FIGURE 1 Prescription rates and incident prescriptions for a dual RAS blockade with ACEI and ARB in the total study population

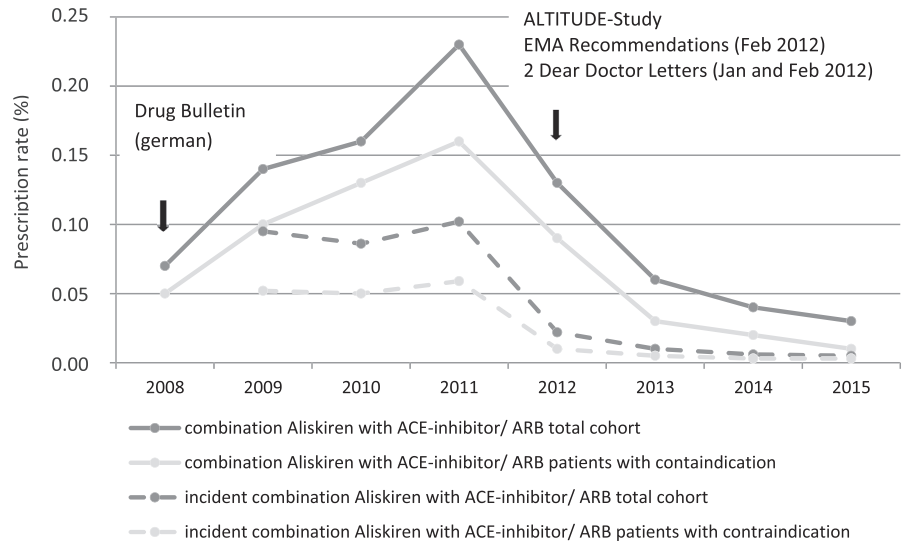

FIGURE 2 Prescription rates and incident prescriptions for a dual RAS blockade with aliskiren and ACEI and/or ARB in the total study population and in patients with contraindications

Contraindications: diabetes or chronic renal insufficiency

TABLE 1 Association of specialist visit and hospital admission with discontinuation of dual RAS blockade for patients with dual RAS blockade prescriptions from only one primary care provider

	RR	95% CI	*P*		RR	95% CI	*P*
Discontinuation of combined ACEI with ARB treatment[a]							
Specialist visit[b]	1.44	1.28-1.60	.000	Hospital admission[c]	1.47	1.31-1.64	.000
Age	1.00	1.00-1.01	.37	Age	1.00	1.00-1.01	.48
Male	0.87	0.78-0.98	.02	Male	0.90	0.80-1.01	.06
Discontinuation of combined aliskiren with ACEI or ARB treatment[a]							
Specialist visit[b]	1.72	1.00-3.02	.05	Hospital admission[c]	1.83	1.05-3.14	.03
Age	1.02	0.99-1.05	.19	Age	1.02	0.99-1.05	.18
Male	1.11	0.63-1.99	.71	Male	1.22	0.68-2.21	.51

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers.
[a]Discontinuation of a dual RAS blockade in 2015 in the subgroup of patients with diabetes, hypertension, cardiovascular disease, vascular disease or chronic renal insufficiency, where the primary care provider was the sole prescriber of a dual RAS blockade.
[b]Defined as at least one visit to a specialist (internal medicine, cardiology, nephrology) in 2014.
[c]Defined as at least one hospital admission in 2014.

4 | DISCUSSION

4.1 | Summary of the main results

From 2008 to 2015, prescription rates for combinations of ACE inhibitors with ARB declined slowly and rates of incident prescriptions remained stable, suggesting a delayed uptake of treatment recommendations. For combinations of aliskiren with ACE inhibitors or ARB, treatment rates declined markedly. Despite the publication of study results, DDLs, and recommendations by authorities, in 2015, still a significant proportion of patients continued treatment or was started on a dual RAS blockade. A high rate of dual RAS blockade was continuously prescribed by the same physician, the largest proportion of those being PCPs. In patients where the PCP was the sole prescriber of a dual RAS blockade, discontinuing treatment was associated with visits to a specialist and hospital discharge.

4.2 | Prescription rates for combinations of ACEI with ARB and aliskiren with ACEI or ARB

Our results show marked differences in the decline of prescription rates both for continuous and incident prescriptions between combinations of ACEI with ARB and aliskiren with ACEI or ARB. For both treatment combinations, a range of study results and institutional recommendations including DDLs were published. In Germany, following international publications, information about risks of a dual RAS blockade with ACEI and ARB was published starting in 2009 in the freely available journal of the Drug Commission of the German Medical Association along with journals and drug bulletins available on subscription.[28-31] Information on restrictions of the combined use of RAS blockers in 2014 by the EMA at European level were published in the journal of the German Medical Association and National Association of Statutory Health Insurance Physicians, journals of regional associations of Statutory Health Insurance Physicians, and followed by an official recommendation of the Federal Institute for Drugs and Medical Devices (BfArM) in October 2014.[18,32-34]

Prescriptions of aliskiren increased rapidly starting with market release in Germany in 2007.[35] In Germany, information on the rationale use of aliskiren and an increased risk of hyperkalaemia when combined with ACEI or ARB was published in 2008 in the drug bulletin of the Drug Commission of the German Medical Association/National Association of Statutory Health Insurance Physicians (freely available) and in the yearly report on medication prescriptions following international publications of study results.[9,35,36] Two DDLs in 2012 followed recommendations of the EMA and publications of adverse effects of a combined treatment with aliskiren and ACEI or ARB in patients with type 2 diabetes and CKD including the ALTITUDE study.[10] According to our results, after the DDLs in 2012, continuous treatment prescriptions declined markedly and rapidly by 87% from the peak value in the total cohort and by 94% in patients with contraindication (decline new prescriptions in both groups: 95%). However, numbers amount to a still significant proportion of patients at the population level who are at increased risk of potentially life threatening side effects including renal failure, especially in the presence of multimorbidity (diabetes, chronic renal insufficiency).

We assume several factors to have affected the different uptake of recommendations on the use of (a) a combined therapy of ACEI and ARB and (b) aliskiren with ACEI or ARB. First, compared with aliskiren, there was no DDL for combinations of ACEI with ARB. Because of the time scope of our study, we cannot directly investigate differences between implementing national DDL recommendations and recommendations published by EMA, BfArM, and medical journals. However, despite we observed a certain decline in combinations of ACEI with ARB before regulatory actions, our findings suggest that international and national publications in subscription journals are only weakly perceived by PCPs compared with DDLs, addressing

physicians directly. This might be due to limited access to international publications or subscription journals, insufficient language skills, or lack of time. In an Irish study on co-prescribing of ACEI and ARB for 2000 to 2008, the authors reported an increase of co-prescribing and conclude that published trials with negative results did not affect co-prescribing, although the study period after ONTARGET was too short.[37]

Secondly, while ACEI and ARB were established first-line antihypertensives available as low cost generics (mean DDD-cost 2008: ACEI: 0.06-0.22 Euro, ARB: 0.58 Euro, aliskiren: 0.91 Euro), aliskiren was an expensive treatment option with limited data on long-term results and side effects. Due to budgets on prescription medications and accountability and liability of prescribers, it is assumed that drug costs have a substantial impact on the uptake of prescribing recommendations. Similar impact of cost on prescription rates of two SSRI (citalopram, escitalopram) following DDLs was suggested by a German study, where the authors attributed the more pronounced decline with escitalopram to concurrent measures leading to increased costs for treated patients.[24] In a study by Hanatani et al, comparing the effect of a DDL on the prescription of oseltamivir with effects of a label change for omeprazole regarding comedication with clopidogrel, authors suggest, that it might be more difficult to change prescribing with drugs commonly used or long term users.[23]

Because of aliskiren market release in 2007, the proportion of aliskiren prescriptions compared with ACEI or ARB prescriptions was initially lower, resulting in a lower number of prescribers. Furthermore, while a combination of aliskiren with ACEI/ARB was contraindicated, combinations of ACEI with ARB remained a treatment option for selected cases of heart failure patients without improvement despite optimal medication. Similar declining trends for prevalence (2009-2014) and incidence of RAS blocker co-prescribing were reported by Allen et al for the United Kingdom in 2017. In line with our findings, the authors report a relatively constant incidence after publication of 2014 EMA warnings and suggest a prescription of valsartan/candesartan licensed for an add-on therapy in selected patients with heart failure to be a possible cause.[26] A German study based on claims data assessing the prevalence of dual RAS blockade in nursing home residents from 2010 to 2014 observed a similar decline in dual RAS blockade prevalence from 9.6 per 1000 to 4.7 per 1000 RAS-inhibiting drug users.[38]

4.3 | Association with number of prescribers

In Germany, a current and accurate medication plan is frequently not available.[39] Treating physicians are depending on patients recall and referral documents to assess medication. Therefore, we investigated if prescriptions on dual RAS blockade were associated with visits to different prescribers. Our analysis shows that the majority of prescriptions of dual RAS blockade were issued by the same prescriber. For patients with multiple prescribers, storing of prescriptions on an accessible central data base or patient insurance card might be a solution to avoid inadvertent dual RAS blockade. Among those patients with only one prescriber, the highest proportion of prescribers were PCPs. Physicians could have been aware of prescribed co-medications. Possible solutions to overcome unawareness of drug warnings or inertia to adjust medication could be automated warning alerts from the practice software. Such tools exist but have to be purchased and are not mandatory. Another helpful source could be the pharmacist alerting prescribing physicians. This is sometimes done by pharmacists but has so far no formal role in medication review in Germany. Because of high prescription cost and the existing prescription budget, we assume that especially combinations of aliskiren with ACEI or ARB were initiated on hospital discharge. However, our data does not allow concluding where the treatment was initiated.

4.4 | Association of visits to specialists/hospital admissions with discontinuation of dual RAS blockade

Our results suggest that especially in patients with a combined treatment of ACEI with ARB, where the PCP is the sole prescriber, visits to specialists and hospital admission are associated with a discontinuation of treatment. The association was stronger for a combined treatment of ACEI with ARB and weak for a combined treatment of aliskiren and ACEI or ARB. Since no specific admission diagnoses were considered, it is possible that rates of discontinuation might have been even higher, if only patients with cardiovascular primary admission diagnoses were analysed. These results might reflect higher levels of awareness of research results including international publications of specialist and hospital doctors and highlight the importance of continuous medical education (CME). However, current mandatory CME activities in Germany are not oriented to patient or public health needs. Physicians can freely choose topics and content according to their preferences.

4.5 | Strengths and limitations

This is the largest study of prescription rates for a dual RAS blockade in Germany. Due to our definition of a dual RAS blockade with a period of up to 184 days between subsequent prescriptions, we might overestimate the rate of dual RAS blockade because we could not account for patients switching between two monotherapies. Not every dual RAS blockade we observed necessarily reflects an inappropriate continuation or initiation of drug therapy. Few patients might have been started purposefully on dual RAS blockade by a specialist, which we cannot exclude. We analysed only data on prescriptions from primary care handed in to the pharmacy and are not able to account for patient compliance. No data on patients on private health insurance were available. Due to patients switching between statutory health insurances or patient death, the denominator in our analysis varied between years. We did not analyse the duration of RAS blockade. Patients with a combined prescription of ACEI with ARB and aliskiren were included in both analysis groups (ACEI with ARB and aliskiren with ACEI and/or ARB).

5 | CONCLUSIONS

Our study shows a slow decline in prescription rates for combinations of ACEI with ARB and unchanged incident prescriptions, suggesting a delayed uptake of treatment recommendation, while prescription rates and incident prescriptions of aliskiren with ACEI and/or ARB declined markedly from 2008 to 2015. A high proportion of dual RAS blockade was issued by the same prescriber, mostly PCPs. Our results suggest a higher impact of DDLs and contraindications addressing PCPs directly compared with publications of study results or EMA warnings. Additionally, factors as medication budgets might be important, favouring the discontinuation of potentially dangerous medication. Targeted continuous medical education, alerts from practice software, better access to medication plans, and stronger involvement of pharmacists might improve the implementation of medication safety recommendations in ambulatory care.

ETHICS STATEMENT

No informed consent has to be obtained and no formal approval by an ethic review board is needed for the anonymised analysis of health claims data according to German Social Code (SGB X).

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