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Trends in co-prescribing of renin-angiotensin system (RAS) - acting agents in France, Germany and the UK during 2001 – 2012

EMA drug utilisation study using IMS Health electronic health records

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1. PASS information

Title	Trends in co-prescribing of renin-angiotensin system (RAS)-acting agents in France, Germany and the UK during 2001 - 2012
Protocol version identifier	1.3
Date of last version of protocol	17 July 2013
EU PAS register number	Registered 31 July 2013 Reference No: ENCEPP/SDPP/4389
Active substance	Angiotensin receptor blockers (ARBs); Angiotensin converting enzyme inhibitors (ACEis); Direct renin inhibitors (Aliskiren) ATC code: C09A, C09B, C09C, C09D, C09X (except C09XA01)
Medicinal product(s)	Multiple
Procedure number	EMEA/HA/31/1370
Marketing authorisation holder(s)	Multiple
Joint PASS	No
Research question and objectives	At its meeting 13 – 16 May 2013 the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) started a review under Article 31 of Directive 2000/83/EC of the combined use of renin-angiotensin-system (RAS)-acting agents i.e. angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEis) and the direct renin inhibitor, aliskiren. This was due to concerns that combining RAS-acting agents could increase the risk of hyperkalaemia, hypotension, and renal failure compared with using one RAS-acting agent alone. In addition, using multiple RAS-acting agents may not be more beneficial than a single RAS-acting agent in terms of reducing overall mortality. These concerns are based on a number of published studies, including a meta-analysis published in the British Medical Journal in January 2013. The present study aims to describe the extent and the patterns of co-prescription of RAS-acting agents in three large EU countries in the period 2001-2012 including sub-group analyses in patients with diabetes mellitus (DM) and chronic kidney disease (CKD). This will be done using the EMA's in-house IMS Health databases. It is anticipated that the results of this drug utilisation study will support the PRAC in its decision-making in the current Article 31 referral by providing information on the extent of co-prescribing of RAS-acting agents in clinical practice in the European Union

	and thereby the potential public health impact of any regulatory action.
Country(-ies) of study	France, Germany, the UK
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2. List of abbreviations

ACEis: Angiotensin converting enzyme inhibitors

ARBs: Angiotensin receptor blockers

ATC: Anatomical Therapeutic Chemical, World Health Organisation classification system for drugs

CKD: Chronic kidney disease

CHMP: Committee for Medicinal Products for Human Use

DM: Diabetes mellitus

EMA: European Medicines Agency

EHR: Electronic Health Records

EPITT: European Pharmacovigilance Issues Tracking Tool

EU: European Union

GP: General Practitioner, Family Doctor

ICD: International Classification of Diagnosis

MAH: Marketing Authorisation Holder

PRAC: Pharmacovigilance Risk Assessment Committee

QOF: Quality and Outcomes Framework

RAS: Renin-Angiotensin System

3. Responsible parties

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Clinical lead: Francois Maignen

Statistical lead: Jim Slattery

Project sign off: Peter Arlett

4. Rationale and background

In February 2012 a previous EMA review of medicines containing aliskiren concluded that the combination of aliskiren with an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitors (ACEi) could increase the risk of side effects affecting the heart and blood vessels or the kidneys. The opinion of the EMA's Committee for Medicinal Products for Human Use (CHMP) was that the combination of aliskiren with an ACEi or ARB is not recommended and that the combination should be contraindicated in patients with diabetes or moderate to severe kidney impairment, since they are at greater risk.

On 1 February 2013, the EMA entered a new signal in the European Pharmacovigilance Issues Tracking Tool (EPITT reference no. 13359) arising from a recently published meta-analysis of randomised trials by Makani et al.[1] on dual renin-angiotensin system (RAS) blockade with ARBs, ACEis or aliskiren.

This meta-analysis compared the efficacy and safety of a dual blockade of the RAS to monotherapy. Compared to monotherapy, the combination of two medicines acting on the renin-angiotensin system failed to reduce the all-cause mortality and was associated with an excess risk of hyperkalaemia, hypotension, and renal failure. The public health impact of this risk is currently unclear in that to date no comprehensive drug utilisation study has been published to assess the extent of the co-medication of medicinal products acting on the renin-angiotensin system in more than one Member State in the EU. A 2011 study conducted in Ireland examined trends in co-prescribing of ACEi and ARBs.[2]

Having considered the new available evidence from the scientific literature and given the seriousness of the associated signals of harm, in May 2013 the EMA started a review of RAS-acting agents under Article 31 of Directive 2000/83/EC.[3]

At the EMA's regular internal 'best-evidence' meeting in May 2013 it was decided to conduct a study using electronic health record databases from IMS Health with the objective to estimate the combined prescription of these agents in France, Germany and the UK.

By reason of the large populations in the three study countries, which approximate to 40% of the total EU population, these population-based data may contribute to the assessment of the public health impact of any safety concern in relation to the combined use of RAS-acting agents in the EU.

5. Study objectives

The PRAC Article 31 review will evaluate the impact of new and existing information from available sources on the benefit risk balance of dual blockade of the RAS.

The primary objective of the present analysis is to provide drug utilisation data on RAS dual blockade by describing the extent and the pattern of co-prescription of different RAS-acting agents in France, Germany and the UK. The study period is from 1st January 2001 to 31st December 2012.

The PRAC List of Questions to MAHs[4] makes explicit reference to sub-populations which may benefit from dual blockade therapy as well as any sub-populations which may be at risk of harm, such as patients with diabetes mellitus (DM) or chronic kidney disease (CKD). Therefore sub-group analyses of these two populations are conducted. Moreover, to provide additional background information, the proportion of patients with any antihypertensive drug treatment is presented.

6. Research methods

6.1. Study design

Descriptive study based on electronic health record (EHR) databases.

[1] Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomized trials. BMJ 2013 Jan 28; 346: f360.
[2] Wan Md Adnan WAH, Zaharan NL, Bennett K, & Wall CA. Trends in co-prescribing of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in Ireland. Br J Clinical Pharmacol 2011; 71(3): 458–66.
[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Renin-angiotensin_system_(RAS)-acting_agents/human_referral_prac_000026.jsp&mid=WC0b01ac05805c516f
[4] http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Renin-angiotensin_system_(RAS)-acting_agents/Procedure_started/WC500143501.pdf

6.2. Study Population

This analysis included all patients with at least one consultation in the calendar year in question receiving a prescription of RAS-acting agents as recorded in the IMS Health databases in France, Germany and the UK.

The study period was restricted from 1st January 2001 to 31st December 2012.

6.3. Setting and data sources

The IMS Health databases of France, Germany and the UK include anonymised patient medical records. In addition to prescription records, the IMS Health databases include records of patients diagnoses, test results and demographic and lifestyle characteristics. Coding systems and extent of variables collected for medical terms and lab values differ across countries and completeness of longitudinal records is dictated by the national healthcare delivery system.

In France and the UK data are collected through a representative panel of GPs; in Germany there are no GPs and data are collected through a representative panel of internists and specialist physicians, all working outside hospitals[5]. For the present study of the German database, analysis was limited to internists as a preliminary analysis of the German data demonstrated that 99.6% of prescriptions of RAS-acting agents in the study period were done by this speciality and their position in the health care system closely resembles the GPs in the other countries studied.

Given patients are not required to register with an individual GP or internist in the French and German healthcare systems, patient registration records are absent in the corresponding databases. The patients included in the study were therefore those considered 'active' i.e. patients with at least one consultation in the calendar year in question. For consistency, the same approach is used to identify the active population in the UK database.

The IMS Health databases used for the analysis have the following characteristics:

- IMS Health UK (GP) database version March 2013 containing a total of 5,686,400 patients with at least one consultation in the study period (960,232 in 2012) and with data from 1990;
- IMS Health Germany database version March 2013 (internist only) containing a total of 8,901,139 patients with at least one consultation in the study period (2,902,195 in 2012) and with data from 1992;
- IMS Health France (GP) database version December 2012 containing a total of 4,172,700 patients with at least one consultation in the study period (1,297,596 in 2012) and with data from 1997.

The study period from 2001 was selected to ensure that all databases had a sufficiently large number of active patients in each calendar year.

6.4. Variables

Patients treated with drugs acting on the RAS were identified by having any prescription of the following pharmacological classes: angiotensin receptor blockers (ARBs); angiotensin converting enzyme inhibitors (ACEis); direct renin inhibitors (aliskiren).

Each of the class was identified with the following WHO ATC codes:

[5] A comprehensive bibliography of the studies conducted with IMS Disease Analyser databases, including validation studies in selected therapeutic areas is available at: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Researchers/IMS_bibliography.pdf

- ACEi: C09A "Ace Inhibitors, Plain"; C09B "Ace Inhibitors, Combinations"
- ARB: C09C "Angiotensin II Antagonists, Plain", C09D "Angiotensin II Antagonists, Combinations"
- Aliskiren: C09XA02 "aliskiren"; C09XA52 "aliskiren and hydrochlorothiazide"; C09XA53 "aliskiren and amlodipine"; C09XA54 "aliskiren, amlodipine and hydrochlorothiazide"

The combined use of RAS acting agents was explored through the use of co-prescription, defined as the prescription of at least two of the three pharmacological classes of agents acting on the RAS, made on the same day and by the same physician. This approach has been described by Tobi et al.[6] and was used in the study by Wan et al. describing the trends in co-prescribing of ACEis and ARBs in Ireland.[2] Anytime the term 'co-prescription' is mentioned in this report, it refers to any co-prescription of at least two different classes of RAS acting agents i.e. ARB, ACEi and the direct renin inhibitor, aliskiren.

Patients treated with antihypertensive drugs were identified by having one or more prescriptions of any drug as defined in annex I.

Patients with DM or with CKD were identified by searching the medical records using the International Classification of Disease (ICD) codes as recorded by the prescribers during or before each calendar year in the study period. ICD codes E10-E14 were used to identify patients with DM (includes both type I and II); ICD code N18 was used to identify patients with CKD.

In the DM and CKD populations, patients treated with drugs acting on the RAS were identified with having a relevant prescription after or at the same time the DM / CKD medical code was recorded.

Patients can belong to both sub-populations if both diagnoses are recorded. Also, a patient being prescribed RAS acting products is also in the group of patients being prescribed antihypertensives. Finally, a patient can be counted in more than one class of RAS acting agents and in more than one group of co-prescribing; this would happen if the same patient during a year used more than one class of RAS acting products or if the patient was co-prescribed with more than one of the three possible combinations of pharmacological classes.

6.5. Study size

This study is a descriptive analysis of EHR data from IMS Health. No sample size or statistical precision calculation was performed.

6.6. Data management

Data extraction and management was performed in IMS Disease Analyser; any additional analysis was performed in SAS Enterprise Guide 5.1.

6.7. Data analysis

This analysis is descriptive in nature. In each country the following was investigated:

- Prescription in 2012

  Number and percentage of patients prescribed with any antihypertensive, any drug acting on RAS and any co-prescription of RAS acting agents:

  - In the active population included in the database;

[6] Tobi H, Faber A, Van den Berg PB, Drane JW, De Jong-van den Berg L. Studying co-medication patterns: the impact of definitions. Pharmacoepidemiol Drug Saf 2007; 16(4): 405–411.

- In each of the following populations: patients with DM and patients with CKD.

- Prescription pattern between 2001 and 2012

  Proportion (expressed as a percentage) of patients prescribed with any antihypertensive, any drug acting on RAS and any co-prescription of RAS acting agents:

  - In the active population included in the database;
  - In each of the following populations: patients with DM and patients with CKD.

  The co-prescribing pattern is also shown as a proportion of the patients treated with RAS acting drugs to take into account the changing proportion of RAS-acting drugs prescriptions in the populations studied.

6.8. Strengths and limitations of the research methods

- The IMS database maintains data collected through a representative panel of physicians in each of the countries selected in the study, which allows population-based analyses. The panel is regularly updated to remain representative[7];
- The IMS database contains all prescriptions prescribed by the physician included; however, prescriptions of drugs acting on the RAS in hospital or settings other than GP or internist practices in France, Germany and the UK are not analysed in the study;
- Missing information in the medical records may affect the selection of the sub-populations of patients with DM and CKD;
- Sub-group analyses of patients with 'renal impairment' (mentioned in the PRAC list of question as a population that might be at risk) is not performed as this diagnosis is not routinely captured in the database with a specific ICD code and definition of renal impairment based only on laboratory values can be transient. It is therefore difficult to determine whether the prescription and the condition occurred concomitantly;
- The combined use of RAS acting agents was measured through the use of co-prescription, defined as the prescription of at least two classes of the three pharmacological classes of agents acting on the RAS, made on the same day and by the same physician. The use of co-prescribing in the present study has the advantage of high specificity in identifying patients with combined use of RAS-acting agents. Applying the same prescriber requirement ensures that the co-prescribing is intentional. However, the definition used might underestimate the overall extent of co-medication since it has the strict same day requirement. Using a wider definition to attempt to estimate the real extent of co-medication will necessary rely on assumptions about duration of therapy and might lead to misclassification of switching as co-medication or the other way around;
- This study is aimed at quantifying the co-prescription extent and patterns. As such, possible objectives like adherence to the prescription by patients, the duration of co-prescribing and the reasons for initiating or stopping treatments were outside its scope.
- Direct comparison of outcome measures from drug utilisation studies across individual countries is complicated by variations in national healthcare systems, national guidelines, regulatory intervention and market penetration e.g.:

[7] Becher H, & Kostev K, Schroder-Bernhardi D. Validity and representativeness of the "Disease Analyzer" patient database for use in pharmacoepidemiological and pharmacoeconomic studies. Int J Clin Pharmacol Ther 2009; 47(10): 617–626

- The role of gatekeeper that the GP plays in the national healthcare system in the UK, including registration of each patient with one GP, makes the UK database a reliable resource for longitudinal analyses. The patient's file maintained by the GPs in the UK includes also medical information from services provided outside of the GP clinic, such as referral to specialists or hospital discharge information and diagnoses;
- Registration of patients with a GP is not a requirement of the national healthcare system in France, unless full eligibility to reimbursement of health costs is required; even if GPs are increasingly regarded as the primary point of contact for patients and their records can provide substantial information on the patient's medical history managed at primary care level, diagnoses can be missed if only treated by specialists;
- In Germany the national healthcare insurance system allows patients to visit a physician of choice whenever a medical need emerges, which results in possible information gaps in the patient's medical records as is the case for the French database.

For these reasons most of the results of this study are presented separately for each of the Member States included and caution should be applied in interpreting these results across countries.

7. Plans for disseminating and communicating study results

The study is registered in the ENCePP E-Register of Studies, which currently serves as the EU PAS referred in the Module VIII of the good pharmacovigilance practices (GVP) on post-authorisation studies register http://www.encepp.eu/encepp/studiesDatabase.jsp (study reference no: ENCePP/SDPP/4389)

The study results will be forwarded to the PRAC (Co-) Rapporteurs and PRAC and will be uploaded into the ENCePP E-Register of studies within the timeframe for the submission of responses from MAHs to the List of Questions for PRAC review i.e. 2nd September 2013[8].

[8] http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Renin-angiotensin_system_(RAS)-acting_agents/Procedure_started/WC500143502.pdf

8. Study results

8.1. Study results in UK

8.1.1. Results observed in 2012

From the IMS Health UK database version March 2013 a total of 960,232 active patients (with at least one consultation) in 2012 were included in the analysis. Of these, 117,920 (12.3%) patients were treated with an RAS-acting drug and 1,129 (0.1%) were co-prescribed different drug classes acting on the RAS.

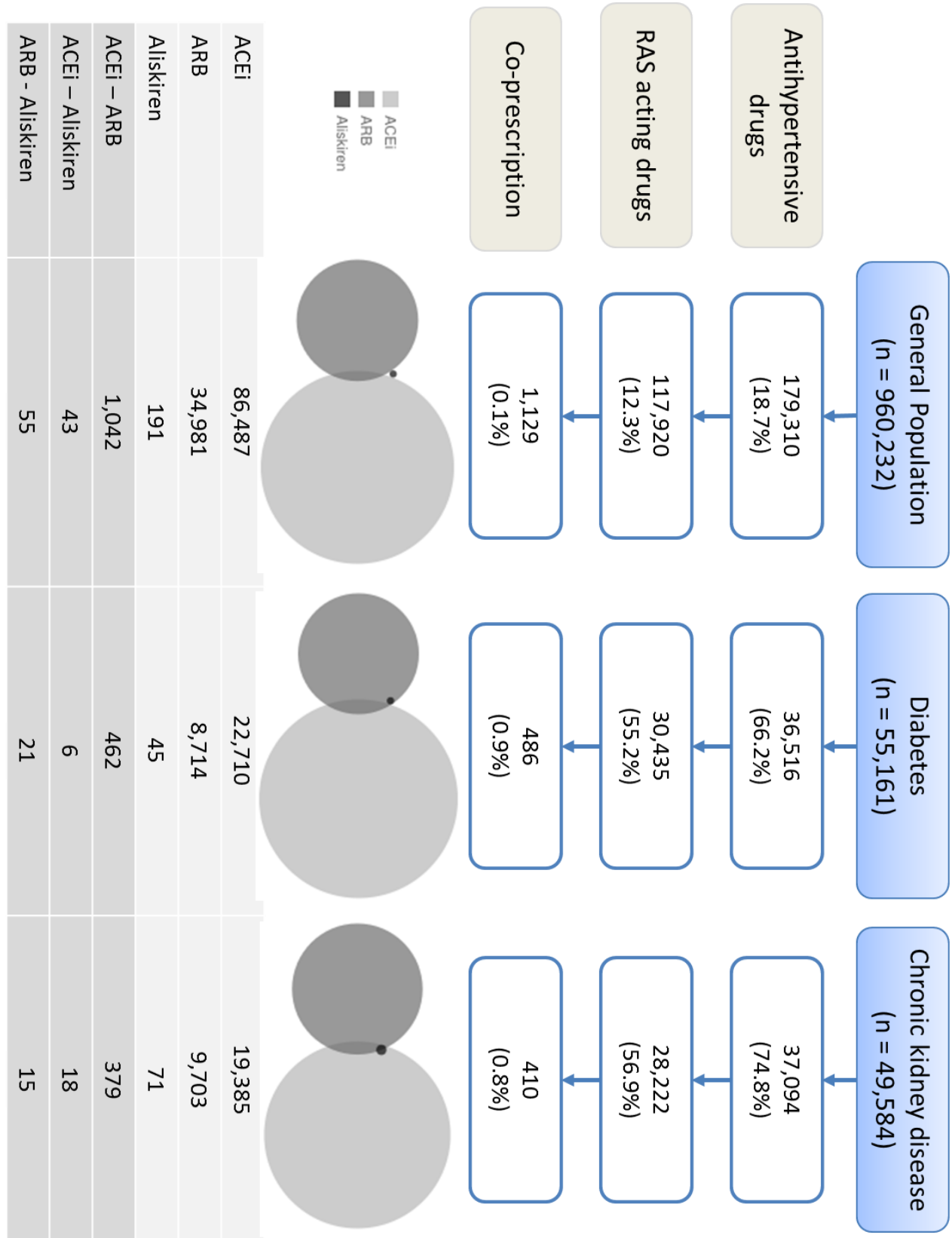
Of the total number of 960,232 active patients in 2012, 55,161 (5.7%) patients had diabetes mellitus. Of these, 30,435 (55.2%) were treated with an RAS-acting drug and 486 (0.9%) were co-prescribed different drug classes acting on the RAS.

Again of the total number of 960,232 active patients in 2012, 49,584 (5.2%) patients had chronic kidney disease. Of these, 28,222 (56.9%) were treated with an RAS-acting drug and 410 (0.8%) were co-prescribed different drug classes acting on the RAS.

These numbers are presented in tabular format in Figure 1 which also presents the numbers of patients prescribed an individual or a combination of RAS-acting agents.

Of 117,920 patients in the total active population prescribed an RAS-acting agent, 1,129 (1.0%) were co-prescribed two RAS-acting agents. By comparison, 486 (1.6%) of the 30,435 patients prescribed an RAS-acting agent who also had DM were co-prescribed two RAS-acting agents. The corresponding percentage of patients co-prescribed two RAS-acting agents in patients with CKD and treated with an RAS-acting agent was 1.5% (410/28,222). Therefore, in the sub-populations of patients with DM prescribed an RAS-acting agent and patients with CKD prescribed an RAS-acting agent, co-prescribing of two RAS-acting agents was more common compared to patients on an RAS-acting agent treatment without these diagnoses.

Figure 1. UK data for 2012. Number of patients and, in bracket, percentages based on the different populations; Venn diagram showing the three RAS acting drug classes and numbers below.[9]



ACEi	86,487	22,710	19,385			
ARB	34,981	8,714	9,703			
Aliskiren	191	45	71			
ACEi – ARB	1,042	462	379			
ACEi – Aliskiren	43	6	18			
ARB - Aliskiren	55	21	15			

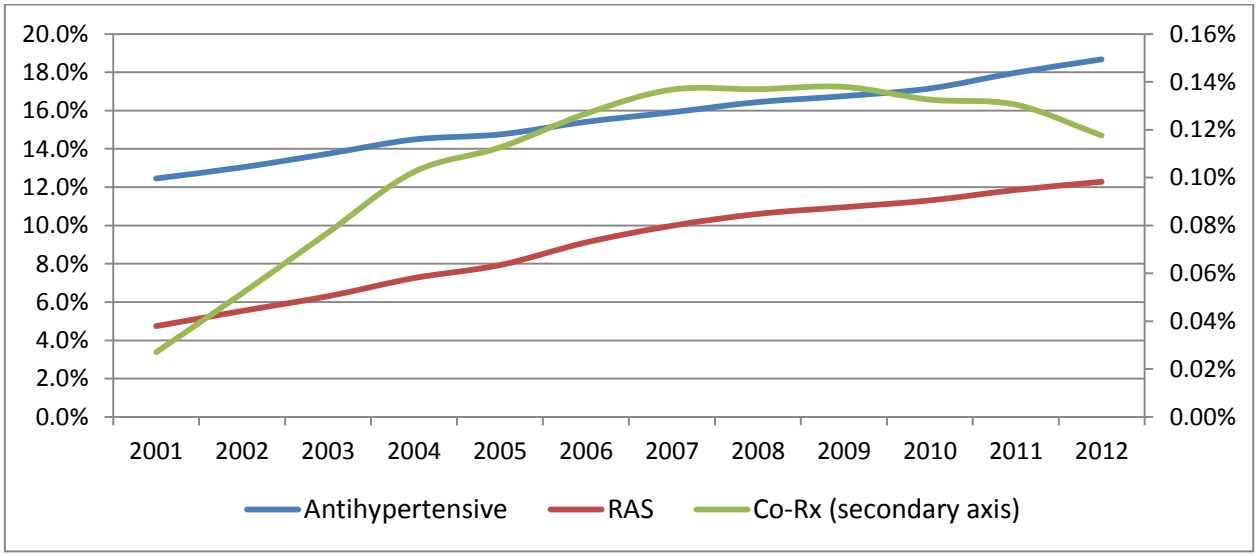
[9] For individual drugs and for combinations, the sum of the numbers of patients is higher than the broad categories as patients may have several drugs and several combinations in one year. This applies to all figures presented (see Variables paragraph 6.4).

8.1.2. Co-prescription patterns 2001-2012

8.1.2.1. In the total active population

As shown in figure 2, the proportions of patients treated with any antihypertensive and of patients treated with drugs acting on the RAS increased steadily between 2001 and 2012. The proportion of patients in the active population included in the analyses being co-prescribed RAS-acting agents increased from 0.03% in 2001 to 0.14% in 2007 and then decreased to 0.12% in 2012.

Figure 2. Proportion of patients prescribed i) an antihypertensive agent; ii) an RAS-acting agent; iii) at least two RAS-acting agents; in the active population (co-prescription on secondary axis to the right) - UK

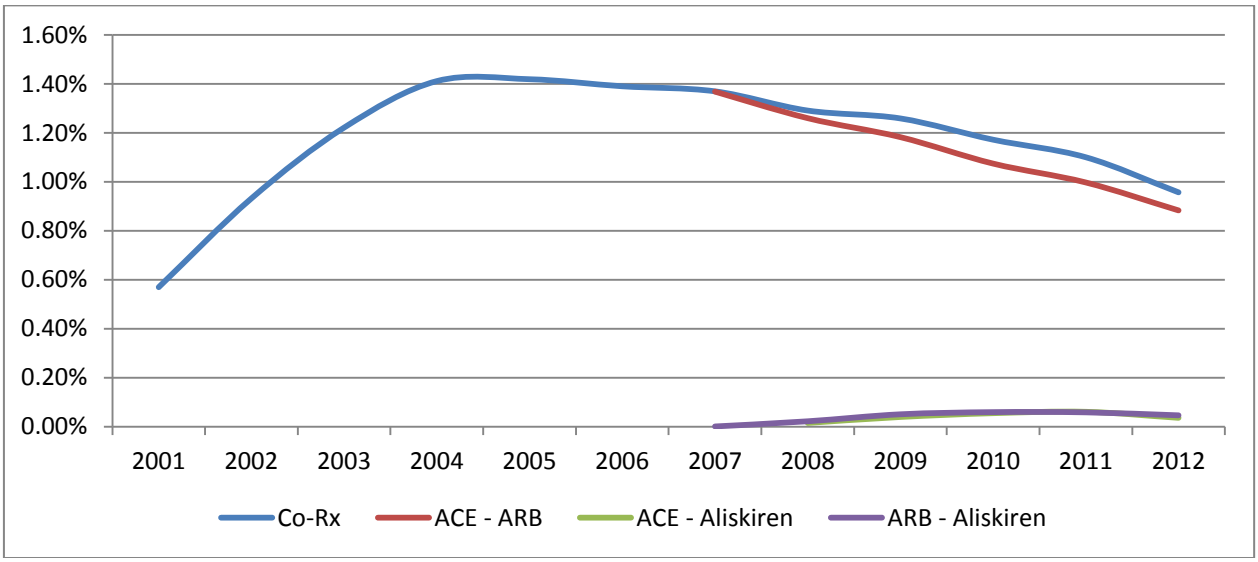


8.1.2.2. In the total active population treated with RAS-acting agents

As shown in figure 3, in the population of patients treated with RAS-acting agents a sharp increase in the rate of co-prescription of RAS-acting agents was recorded between 2001 and 2004 (from 0.57% to 1.41%) followed by a plateau and then a slower constant decrease from 2008 (down to 0.96% in 2012).

The proportion of patients co-prescribed another RAS-acting agent with aliskiren increased from its introduction in 2007 up to 2011, but decreased in 2012. While this proportion remained very low throughout the period, aliskiren had the highest rate of co-prescription with another RAS-agent e.g. in 2012, out of 191 patients treated with aliskiren 43 were co-prescribed an ACEi and 55 were co-prescribed an ARB (figure 1).

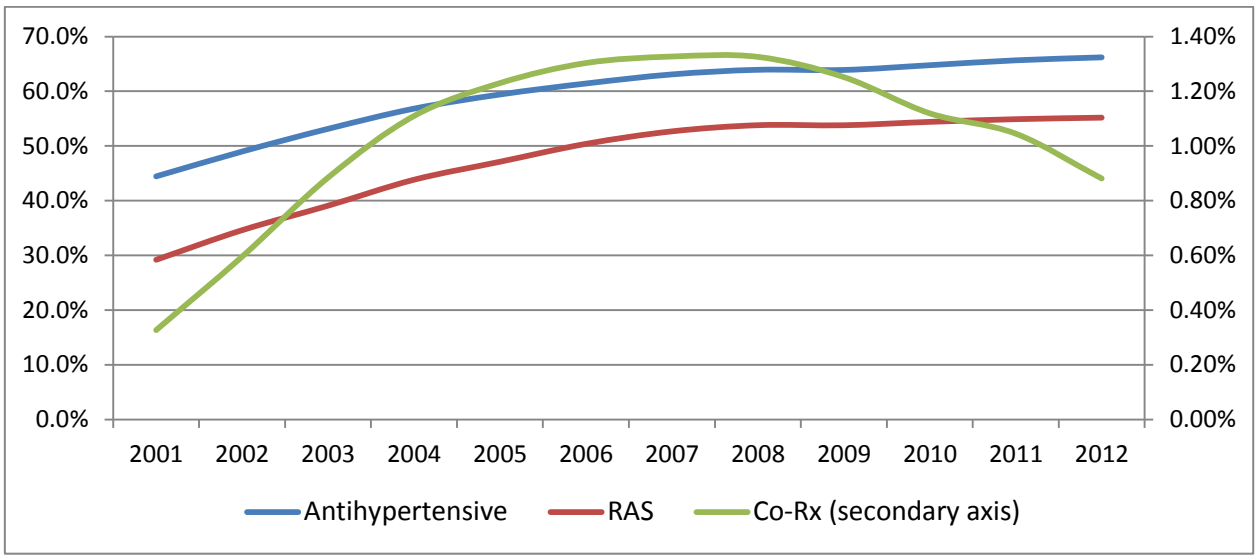
Figure 3. Proportion of patients co-prescribed RAS-acting agents in patients treated with any drug acting on RAS - UK



8.1.2.3. In patients with diabetes

The proportion of DM patients treated with any antihypertensive and treated with drugs acting on the RAS increased in the period 2001-2012 (figure 4). The pattern was different for DM patients with a co-prescription of RAS-acting agents, where growth until 2007 (from 0.33% to 1.30%) was followed by a plateau and a decrease from 2010 to 0.88% in 2012.

Figure 4. Proportion of patients prescribed i) an antihypertensive agents; ii) an RAS-acting agent; iii) at least two RAS-acting agents; in patients with diabetes (co-prescription on secondary axis to the right) - UK

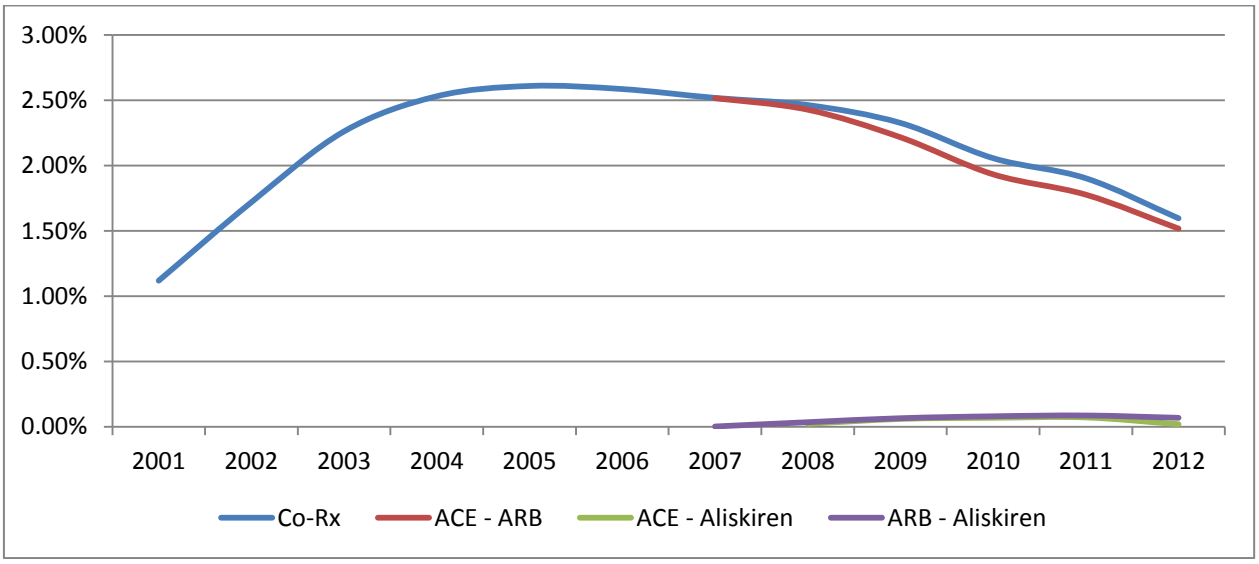


8.1.2.4. In patients with diabetes treated with RAS-acting agents

In DM patients treated with RAS-acting agents the rate of co-prescription had a similar pattern as in the general population (figure 5): sharp increase between 2001 and 2004 (from 1.12% to 2.53%) followed by a plateau and then a slower constant decrease from 2008 (down to 1.60% in 2012).

Even if the proportion of co-prescription with aliskiren was very low, the majority of patients with DM prescribed aliskiren were also prescribed another class of RAS-acting agents (e.g. 6 with an ACEi and 21 with an ARB out of 45 patients in 2012 – figure 1).

Figure 5. Proportion of patients co-prescribed RAS-acting agents in patients with diabetes treated with any drug acting on RAS - UK

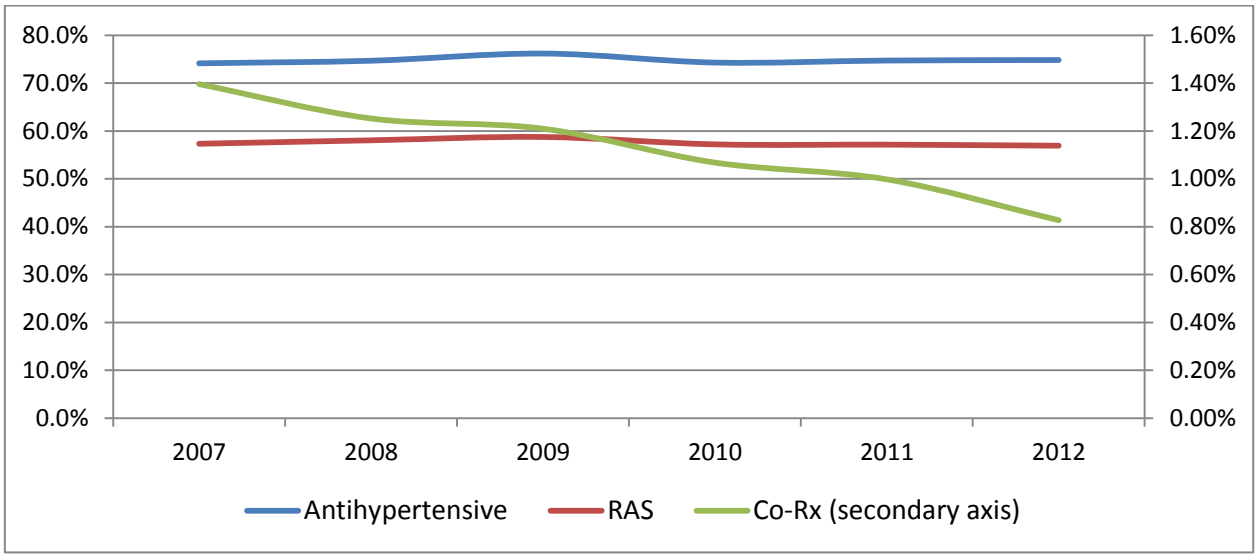


8.1.2.5. In patients with chronic kidney disease

For the UK data, the study period for the population of CKD patients is restricted to 2007 – 2012 due to the 2006 inclusion of measures relating to the recording of CKD in the Quality and Outcomes Framework (QOF) programme which led to a dramatic increase in the number of patients with CKD recorded; from 9,634 in 2005 to 64,849 in 2007.

Between 2007 and 2012 the proportion of CKD patients treated with any antihypertensive and CKD patients treated with drugs acting on RAS was stable; around 75% for the former and slightly below 60% for the latter. By contrast, the proportion of patients being co-prescribed RAS-acting agents decreased constantly over the whole period (from 1.4% to 0.8% - figure 6).

Figure 6. Proportion of patients prescribed i) an antihypertensive agents; ii) an RAS-acting agent; iii) at least two RAS-acting agents; in patients with chronic kidney disease (co-prescription on secondary axis to the right) - UK

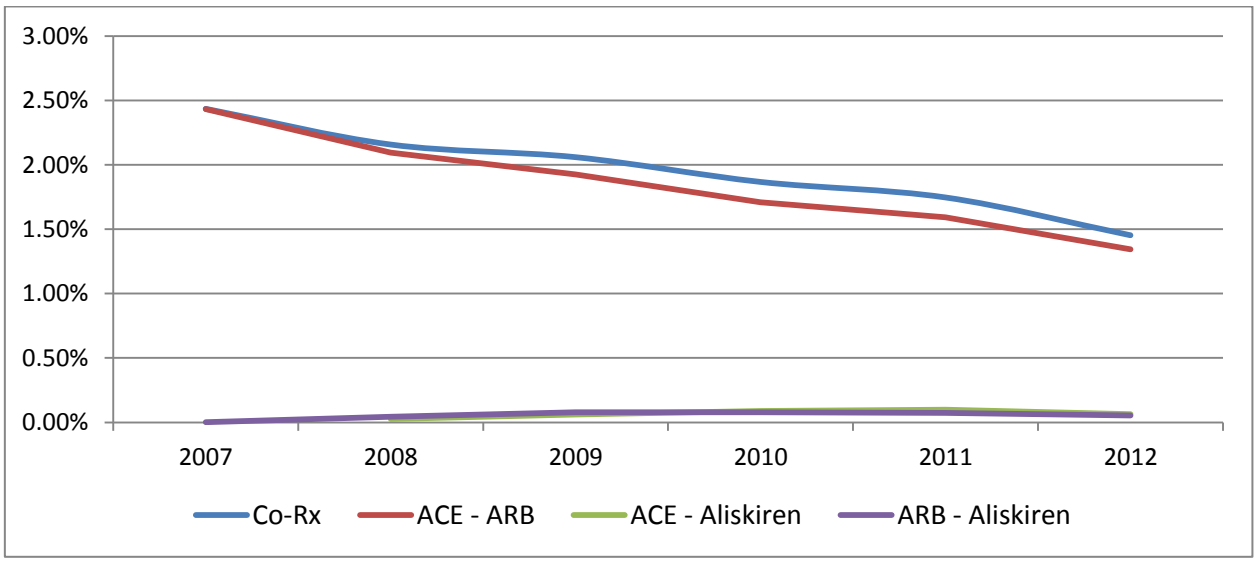


8.1.2.6. In patients with chronic kidney disease treated with RAS-acting agents

In CKD patients treated with any RAS acting drugs, the rate of co-prescription had a similar pattern as in the general population and in DM patients for the period 2007-2012: a steady decrease from 2.43% to 1.34% (figure 7).

Again, while the prevalence of co-prescription with aliskiren was very low, a high proportion of patients with CKD treated with aliskiren were also prescribed another class of RAS-acting agents (e.g. 18 with an ACEi and 15 with an ARB out of 71 patients in 2012 – figure 1).

Figure 7. Proportion of patients co-prescribed RAS-acting agents in patients with chronic kidney disease treated with any drug acting on RAS - UK



8.1.3. Comments on population data

In the UK, while the proportion of patients treated with any antihypertensive increased steadily in the general population and in patients with DM, the proportion of patients treated with any RAS-acting agent increased more sharply (see Annex III). At the end of the study period, patients treated with RAS-acting agents represented two third of patients prescribed any antihypertensive agent in the total active population and approximately 80% of patients prescribed any antihypertensive agent with DM or CKD.

ACEi were the most prescribed products with a greater than a 2:1 ratio compared to ARB. The first prescription of aliskiren was recorded in 2007 and its use remained extremely low (see Annex II).

The proportion of patients treated with at least two agents acting on the RAS increased at an even faster rate during the first part of the study period. However, it remained very low (approximately 0.12% in the total active population, and around 1% in patients with either DM or CKD) and decreased in the second part of the study period, from 2010 in the general population and earlier in DM patients and in CKD patients. Moreover, in patients treated with any drug acting on RAS, the proportion of patients co-prescribed decreased earlier.

Most of the patients receiving a co-prescription were treated with a combination of an ACEi and an ARB. Of note, no patients were co-prescribed a combination of all three different classes in any of the three countries.

In patients receiving a co-prescription of RAS-acting agents in 2012, more than 40% had DM and more than a third had CKD; moreover, co-prescribing of two RAS-acting agents was more common in patients with DM prescribed an RAS-acting agent and patients with CKD prescribed an RAS-acting agent compared to patients on an RAS-acting agent treatment without these diagnoses.

8.2. Study results in Germany

8.2.1. Results observed in 2012

From the IMS Health Germany database version March 2013 a total of 2,902,195 active patients (with at least one consultation) in 2012 were included in the analysis. Of these, 529,679 (18.3%) patients were treated with an RAS-acting drug and 8,723 (0.3%) were co-prescribed different drug classes acting on the RAS.

Of the total number of 2,902,195 active patients in 2012, 433,866 (14.9%) patients had diabetes mellitus. Of these, 193,626 (44.6%) were treated with an RAS-acting drug and 4,236 (1.0%) were co-prescribed different drug classes acting on the RAS.

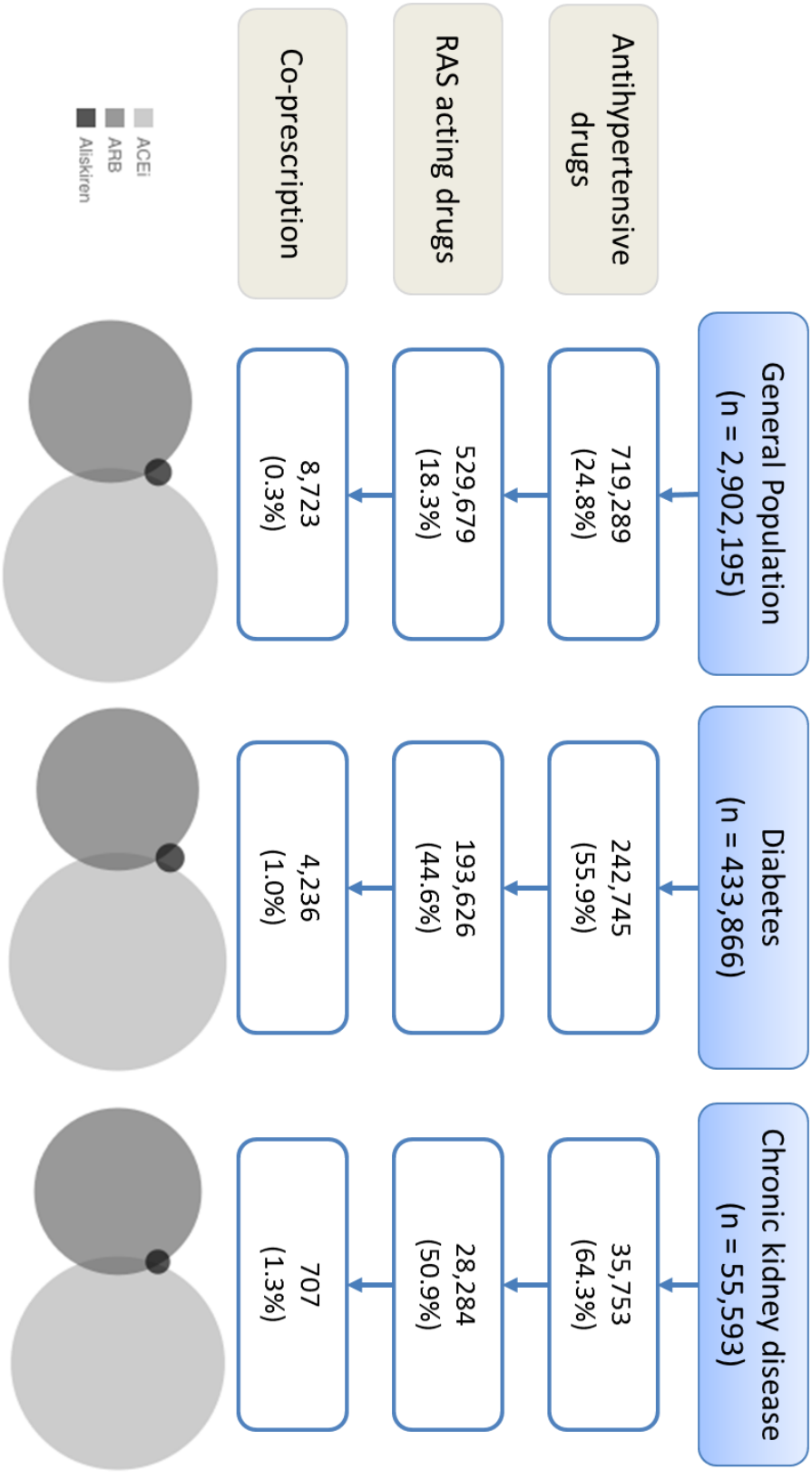
Again of the total number of 2,902,195 active patients in 2012, 55,593 (1.9%) patients had chronic kidney disease. Of these, 28,284 (50.9%) were treated with an RAS-acting drug and 707 (1.3%) were co-prescribed different drug classes acting on the RAS.

These numbers are presented in tabular format in Figure 1 which also presents the numbers of patients prescribed an individual or a combination of RAS-acting agents.

The prevalence of CKD in Germany as reflected in the IMS database may be biased by the national health care system with the possibility to visit a physician of choice meaning diagnosis and management of CKD is mainly done by nephrologists. Since mild to moderate CKD may not require active treatment, this diagnosis, if made by a nephrologist, may not always be made available to internists.

Of 529,679 patients in the total active population prescribed an RAS-acting agent, 8,723 (1.6%) were co-prescribed two RAS-acting agents. By comparison, 4,236 (2.2%) of the 193,626 patients prescribed an RAS-acting agent who also had DM were co-prescribed two RAS-acting agents. The corresponding percentage of patients co-prescribed two RAS-acting agents in patients with CKD and treated with an RAS-acting agent was 2.5% (707/28,284). Therefore, in the sub-populations of patients with DM prescribed an RAS-acting agent and patients with CKD prescribed an RAS-acting agent, co-prescribing of two RAS-acting agents was more common compared to patients on an RAS-acting agent treatment without these diagnoses.

Figure 8. German data in 2012. Number of patients and, in brackets, percentages based on the different populations; Venn diagram showing the three RAS acting drug classes and numbers below.[10]



ACEi	345,512	128,211	18,163
ARB	202,775	73,225	11,401
Aliskiren	6,862	2,908	374
ACEi – ARB	6,346	3,194	492
ACEi – Aliskiren	1,049	476	97
ARB - Aliskiren	1,530	668	134

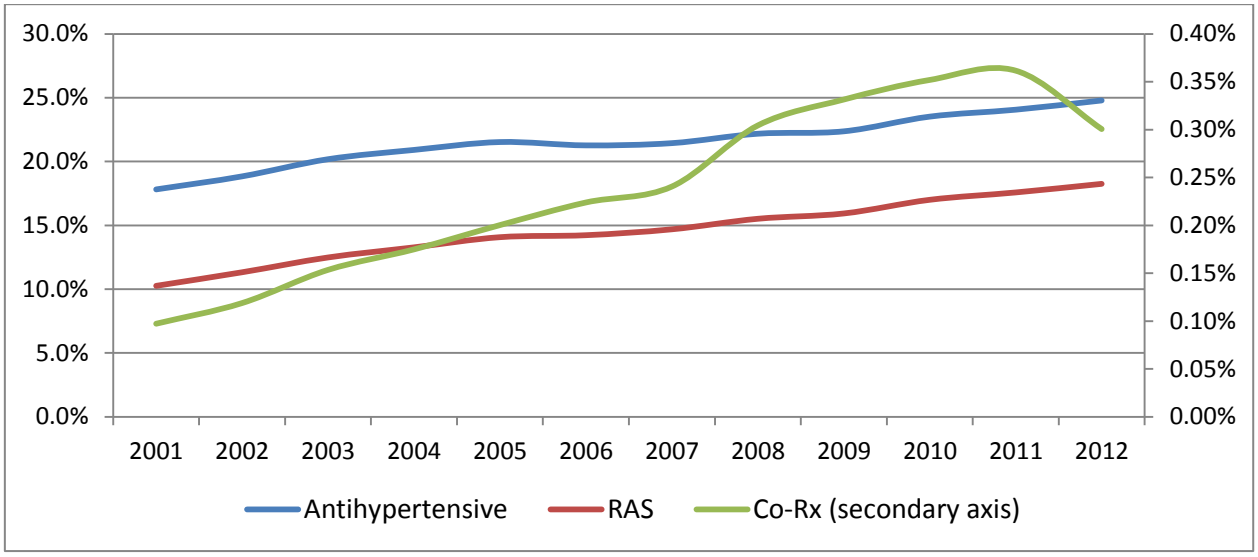
[10] For individual drugs and for combinations, the sum of the numbers of patients is higher than the broad categories as patients may have several drugs and several combinations in one year. This applies to all figures presented (see Variables paragraph 6.4).

8.2.2. Co-prescription patterns 2001-2012

8.2.2.1. In the total active population

As shown in figure 9, the proportion of patients treated with any antihypertensive and patients treated with drugs acting on RAS increased constantly in the period 2001-2012; while the proportion of co-prescribed patients increased at a faster rate reaching a peak in 2011 (from 0.10% to 0.36%) and with a marked decrease the following year (down to 0.30%).

Figure 9. Proportion of patients prescribed i) an antihypertensive agents; ii) an RAS-acting agent; iii) at least two RAS-acting agents; in the active population (co-prescription on secondary axis to the right) - Germany



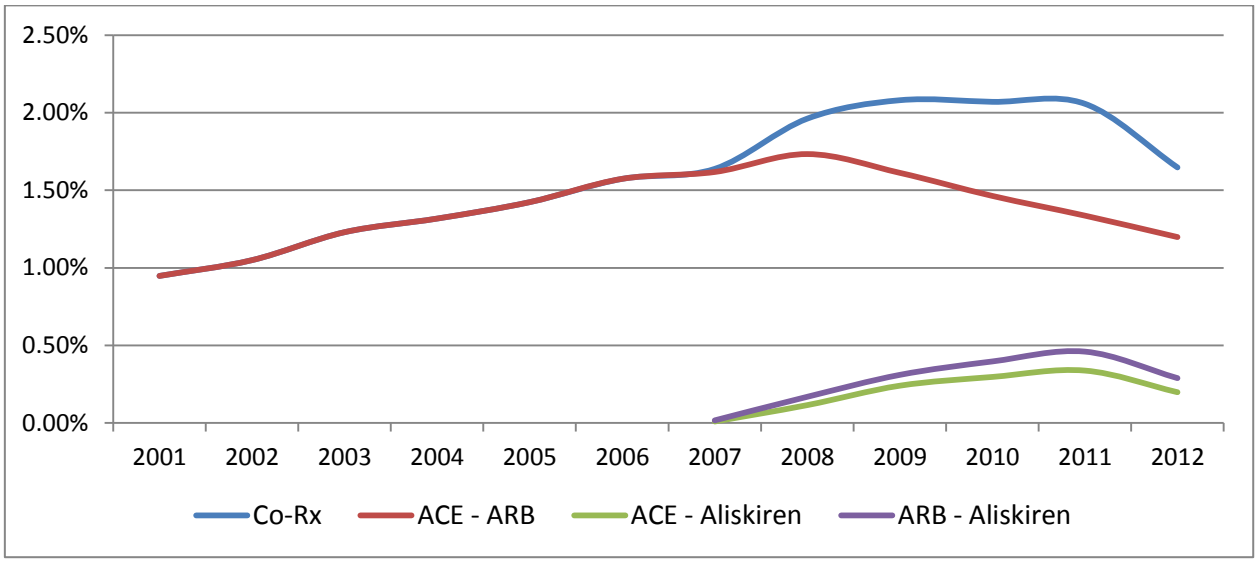
8.2.2.2. In the total active population treated with RAS-acting agents

In patients treated with RAS acting agents, a sharp increase in the rate of co-prescription was recorded between 2001 and 2008 (from 0.95% to 1.96%) followed by a plateau around 2% and then a decrease in 2012 down to 1.65% (figure 10).

The proportion of patients co-prescribed another RAS-acting agent with aliskiren increased steadily from its introduction up to 2011, but decreased in 2012. The year after aliskiren introduction, the proportion of co-prescription of ACEis and ARBs started decreasing suggesting a replacement of either ACEi or ARB with aliskiren.

While the proportion of patients co-prescribed with aliskiren remained low, almost 40% of patients treated with aliskiren were co-prescribed with ACEi or ARB e.g. in 2012 1,049 patients were co-prescribed with an ACEi and 1,530 with an ARB out of 6,862 patients treated with aliskiren (figure 8).

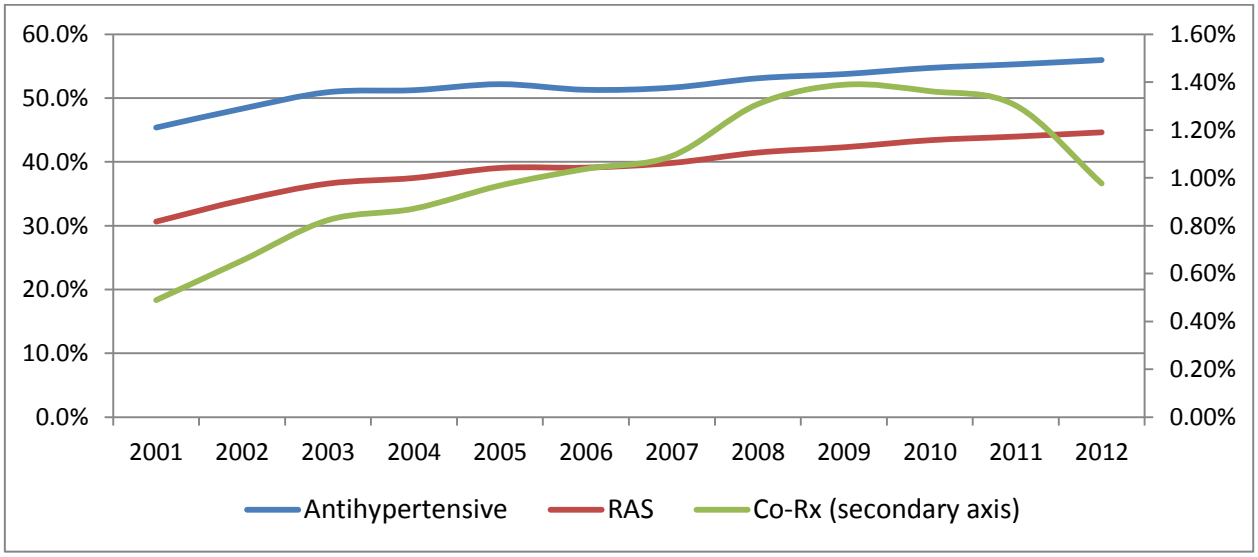
Figure 10. Proportion of patients co-prescribed RAS-acting agents in the patients treated with any drug acting on RAS - Germany



8.2.2.3. In patients with diabetes

The proportion of DM patients treated with any antihypertensive and treated with drugs acting on RAS increased constantly in the period 2001-2012, with the latter increased faster. The proportion of patients co-prescribed increased at a faster rate reaching a peak in 2009 (from 0.49% to 1.39%) and with a marked decrease to 0.98% in 2012 (figure 11).

Figure 11. Proportion of patients prescribed i) an antihypertensive agents; ii) an RAS-acting agent; iii) at least two RAS-acting agents; in the active population (co-prescription on secondary axis to the right) - Germany

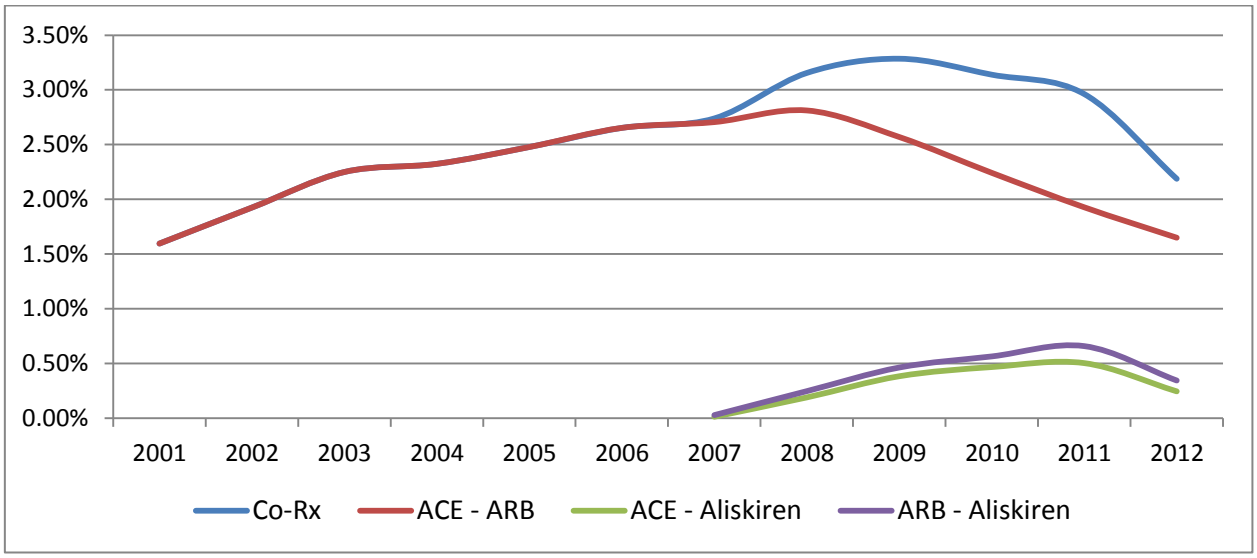


8.2.2.4. In patients with diabetes treated with RAS-acting agents

In DM patients treated with RAS acting agents, the rate of co-prescription has a similar pattern as in the general population (figure 12): marked increase between 2001 and 2008 (from 1.60% to 3.16%) followed by a plateau just above 3% and then a decrease down to 2.19% in 2012.

As for the general population, the ACEi – ARB co-prescription peak was in 2008 and the afterwards decrease was mirrored by the co-prescribing involving aliskiren. Finally, even if the proportion of co-prescription with aliskiren was low, around 40% of patients with DM treated with aliskiren were also prescribed another RAS-acting agent (e.g. 476 with an ACEi and 668 with an ARB out of 2,908 in 2012 - figure 8).

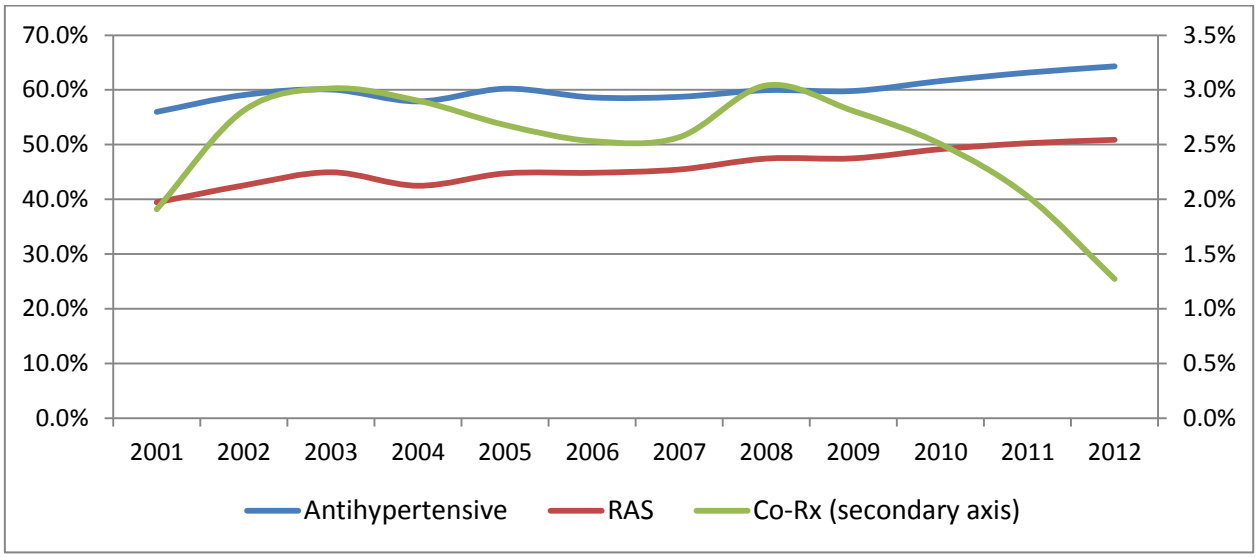
Figure 12. Proportion of patients co-prescribed RAS-acting agents in patients with diabetes treated with any drug acting on RAS - Germany



8.2.2.5. In patients with chronic kidney disease

Between 2001 and 2012 the proportions of CKD patients treated with any antihypertensive and of CKD patients treated with drugs acting on RAS increased constantly, with the latter increased faster. The proportion of co-prescribed patients instead oscillated between 2.0% and 3.0% until 2008 and decreased afterwards down to 1.3% (figure 13).

Figure 13. Proportion of patients prescribed i) an antihypertensive agents; ii) an RAS-acting agent; iii) at least two RAS-acting agents; in patients with chronic kidney disease (co-prescription on secondary axis to the right) - Germany

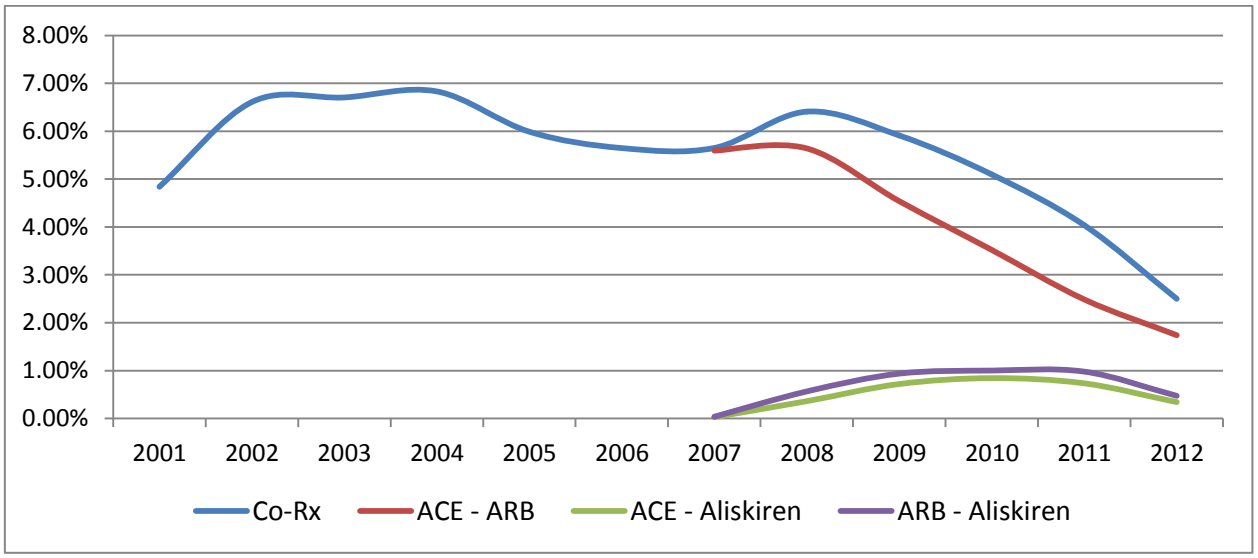


8.2.2.6. In patients with chronic kidney disease treated with RAS-acting agents

In CKD patients treated with any RAS acting agents, the proportion of co-prescription oscillated between 2001 and 2008, not showing the constant increase observed in the general population and DM patients (figure 14). The period 2009-2012 was characterised by a fast decrease, from 6.41% down to 2.50%.

To note, lastly, that more than 60% of patients treated with aliskiren were co-prescribed with another class of RAS-acting agents (e.g. 97 with an ACEi and 134 with an ARB out of 374 patients in 2012 – figure 8).

Figure 14. Proportion of patients co-prescribed in patients with chronic kidney disease treated with any drug acting on RAS - Germany



8.2.3. Comments on population data

In Germany, both the proportions of patients treated with any antihypertensive and of patients treated with any RAS-acting agent increased in the study period, with the latter showing a sharper growth (see Annex III). In 2012, patients treated with any RAS-acting agent represented three quarters of patients prescribed with any antihypertensive in the total active population and approximately 80% of patients prescribed any antihypertensive agent with DM or CKD.

ACEi were the products mostly prescribed, with almost a 2:1 ratio compared to ARB; however, ARB registered a much faster growth especially in the CKD population (see Annex II). Aliskiren first prescription was recorded in 2007 and its use remained low.

The proportion of patients treated with at least two classes acting on the RAS remained low, approximately 0.3% in the total active population, around 1% in patients with DM and between 1% and 3% in patients with CKD. In the active population, the proportion of patients co-prescribed reached a peak in 2011, showing a high rate of increase (almost four-fold, see Annex III). In the DM population, the trend and rate of increase was similar but the peak was reached earlier, in 2009; while in the CKD population the trend was oscillating before the decrease starting in 2008. Of note, in all three populations a sharp decrease was observed in 2012.

Most of the patients receiving a co-prescription were treated with an association of an ACEi with an ARB. Of note, no patients were co-prescribed a combination of all three different classes in any of the three countries.

In patients receiving a co-prescription of RAS-acting agents in 2012, a high percentage (about half) of patients was from the DM population; moreover, co-prescription of two RAS-acting agents was more common in patients with DM prescribed an RAS-acting agent and patients with CKD prescribed an RAS-acting agent compared to patients on an RAS-acting agent treatment without these diagnoses.

8.3. Study results in France

8.3.1. Results observed in 2012

In the IMS Health France database version December 2012 a total of 1,297,596 patients active (with at least one consultation) in 2012 were included in the analysis. Of these, 133,999 (10.3%) patients were treated with an RAS-acting drug and 1,767 (0.1%) were co-prescribed different drug classes acting on the RAS.

Of the total number of 1,297,596 active patients in 2012, 46,695 (3.6%) patients had diabetes mellitus. Of these, 24,118 (51.7%) were treated with an RAS-acting drug and 607 (1.3%) were co-prescribed different drug classes acting on the RAS.

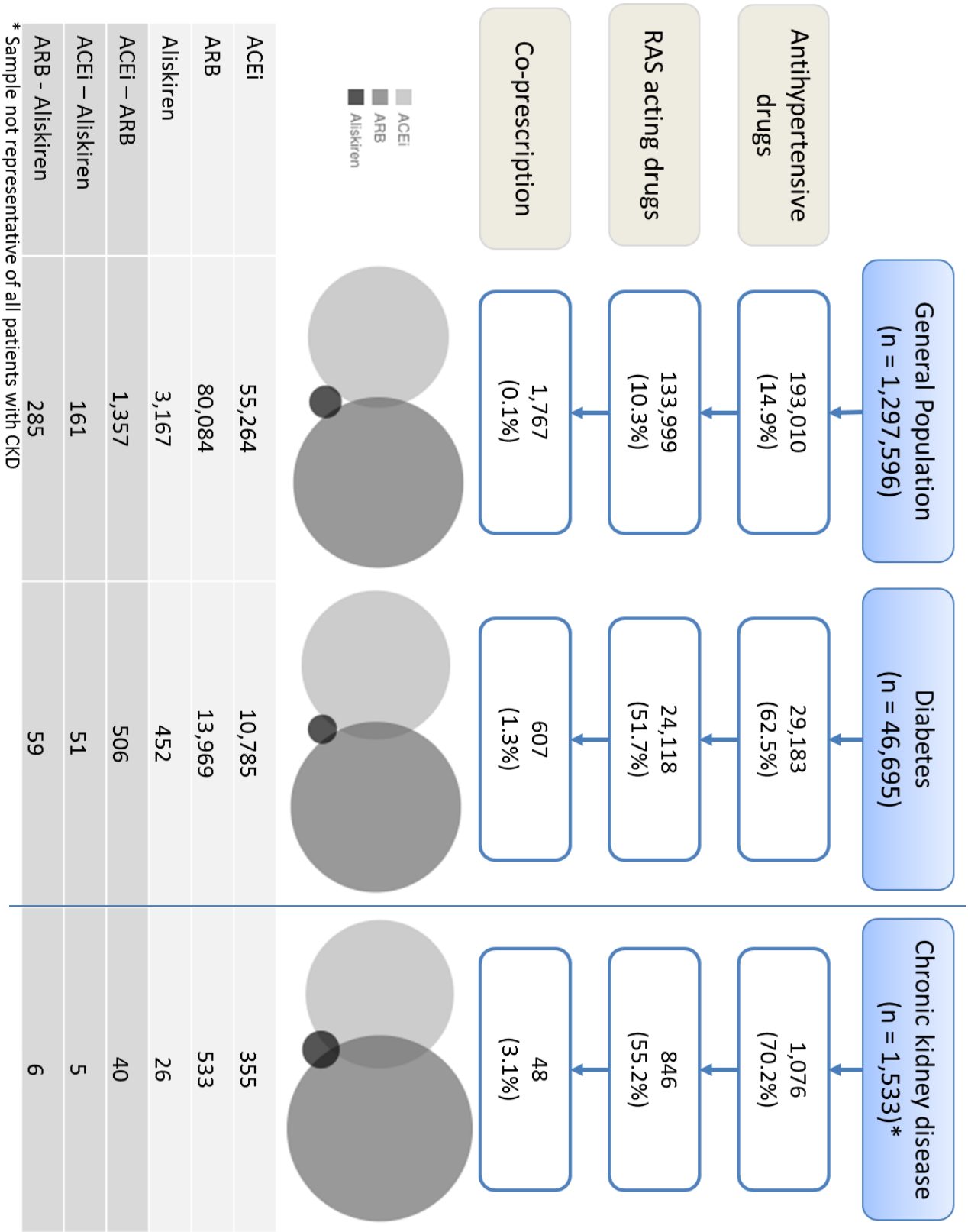
Again of the total number of 1,297,596 active patients in 2012, 1,533 (0.1%) patients had chronic kidney disease. Of these, 846 (55.2%) were treated with an RAS-acting drug and 48 (3.1%) were co-prescribed different drug classes acting on the RAS.

These numbers are presented in tabular format in Figure 15 which also presents the numbers of patients prescribed an individual or a combination of RAS-acting agents.

As mentioned, recording of diagnosis varies significantly across databases; in France this might help explain the lower than expected prevalence in DM and CKD. In particular, a smaller proportion of consultations will include a diagnosis code, since a repeated prescription will often be coded with "repeated prescription" ICD-10 code instead of the indication for the drug. This, together with having a shorter observation time starting in 1997 and the fact that mild to moderate CKD is treated only in some cases, renders the French database unable to capture more than a small proportion of the CKD patients. Therefore, results for this sub-population are shown for 2012 only for information (no over-time pattern is shown); caution should be used in the interpretation.

Of 133,999 patients in the total active population prescribed an RAS-acting agent, 1,767 (1.3%) were co-prescribed two RAS-acting agents. By comparison, 607 (2.5%) of the 24,118 patients prescribed an RAS-acting agent who also had DM were co-prescribed two RAS-acting agents. Therefore, in the sub-population of patients with DM prescribed an RAS-acting agent, co-prescribing of two RAS-acting agents was more common compared to patients on an RAS-acting agent treatment without this diagnosis.

Figure 15. French data in 2012. Number of patients and, in brackets, percentages based on the different populations; Venn diagram showing the three RAS acting drug classes and numbers below.[11]



ACEi	55,264	10,785	355
ARB	80,084	13,969	533
Aliskiren	3,167	452	26
ACEi – ARB	1,357	506	40
ACEi – Aliskiren	161	51	5
ARB - Aliskiren	285	59	6

* Sample not representative of all patients with CKD

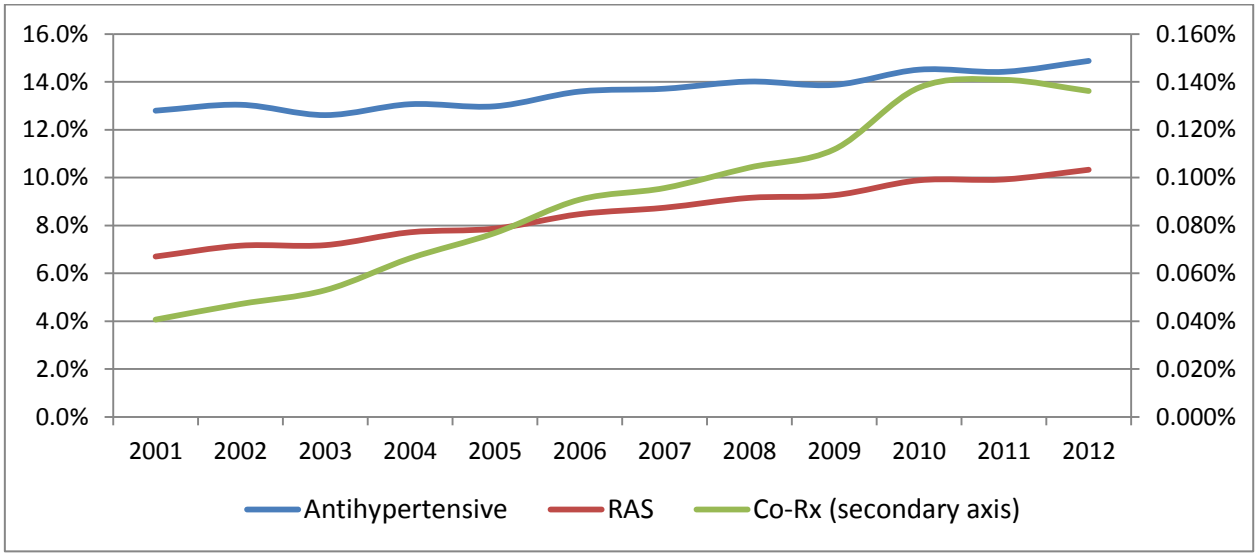
[11] For individual drugs and for combinations, the sum of the numbers of patients is higher than the broad categories as patients may have several drugs and several combinations in one year. This applies to all figures presented (see Variables paragraph 6.4).

8.3.2. Co-prescription patterns 2001-2012

8.3.2.1. In the total active population

As shown in figure 16, the proportions of patients treated with any antihypertensive and patients treated with drugs acting on RAS increased slowly in the period 2001-2012. The trend is different for co-prescription as the growth was faster (from 0.04% to 0.14%) and a very slight decrease was observed in 2012.

Figure 16. Proportion of patients prescribed i) an antihypertensive agents; ii) an RAS-acting agent; iii) at least two RAS-acting agents; in the active population (co-prescription on secondary axis to the right) - France

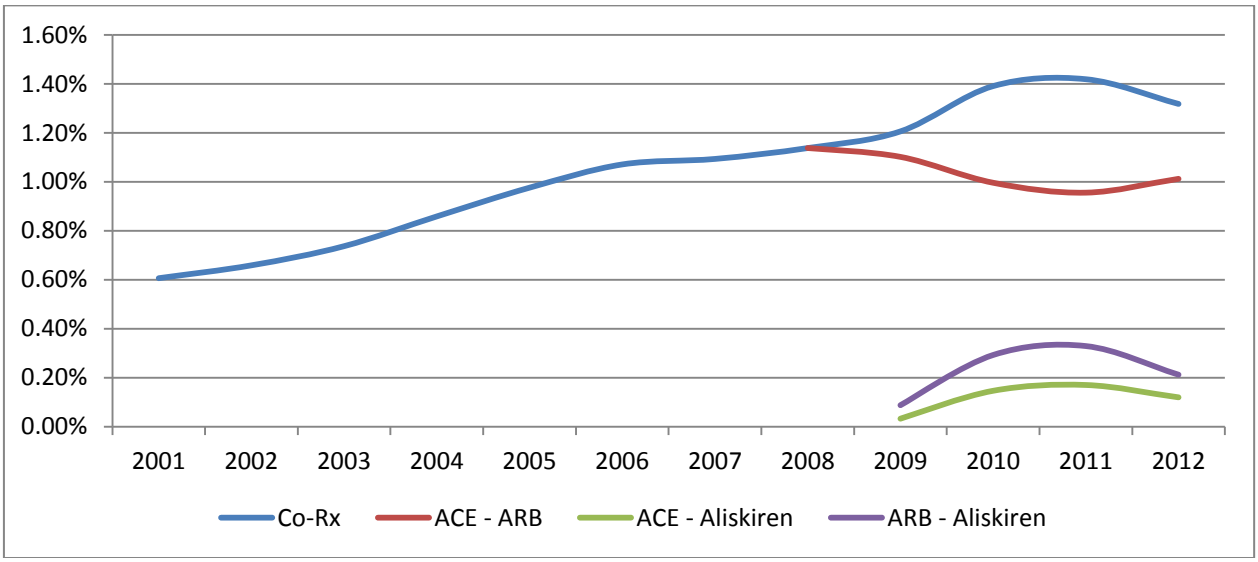


8.3.2.2. In the total active population treated with RAS-acting agents

In patients treated with RAS-acting agents, an increase in the proportion of patients co-prescribed was recorded between 2001 and 2011 (from 0.61% to 1.42%) followed by a decrease in 2012 (down to 1.32% - figure 17).

The proportion of patients co-prescribed another RAS-acting agent with aliskiren increased from its introduction up to 2011, but decreased in 2012. For the ACEi – ARB co-prescription the peak was seen in 2008, and the decrease is mirrored by the introduction of aliskiren co-prescribing. While the proportion of patients co-prescribed with aliskiren was relatively low, almost 20% of patients treated with aliskiren were also prescribed another class of RAS-acting agents (e.g. 161 with an ACEi and 285 with an ARB out of 3,167 patients in 2012 – figure 15).

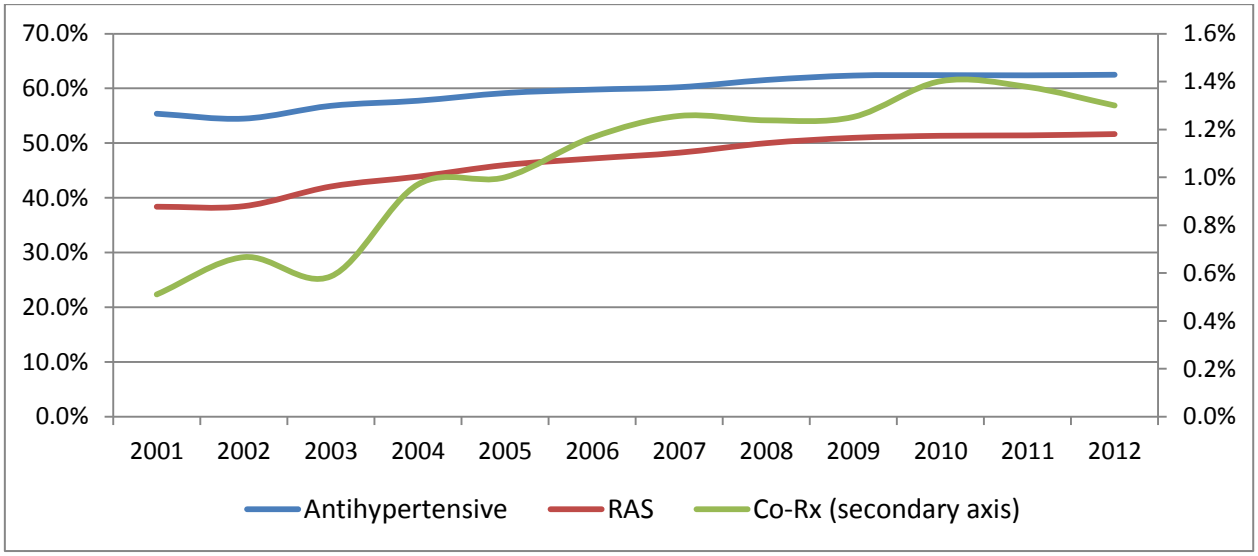
Figure 17. Proportion of patients co-prescribed RAS-acting agents in the patients treated with any drug acting on RAS - France



8.3.2.3. In patients with diabetes

The proportions of DM patients treated with any antihypertensive and treated with drugs acting on RAS increased in the period 2001-2012 (figure 18). The strongest increase was seen for DM patients with a co-prescription where the proportion of patients co-prescribed almost tripled from 0.5% in 2001 to 1.4% in 2011.

Figure 18. Proportion of patients prescribed i) an antihypertensive agents; ii) an RAS-acting agent; iii) at least two RAS-acting agents; in the active population (co-prescription on secondary axis to the right) - France

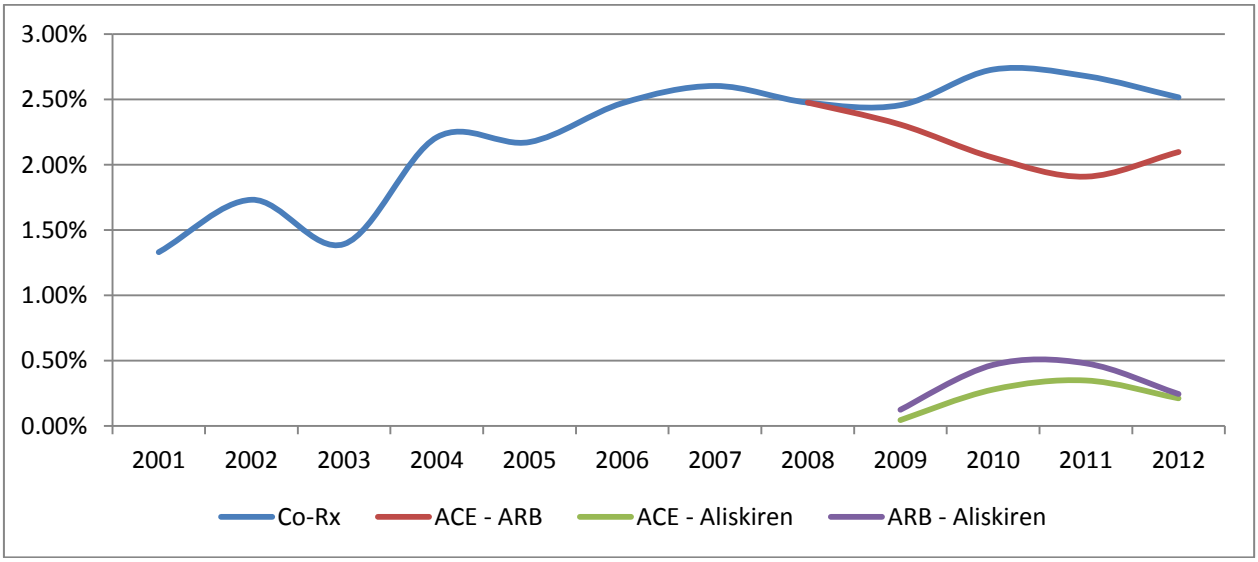


8.3.2.4. In patients with diabetes treated with RAS-acting agents

In DM patients treated with RAS acting agents the rate of co-prescription had a more variable pattern than in the general population (figure 19). However, an increasing trend was still observable from 2001 until the peak in 2010 (from 1.33% to 2.73%) followed by a decrease down to 2.52% in 2012.

To note that the numbers of patients were low especially in 2001-2003 with less than 100 patients co-prescribed. As in the total active population the proportion of patients co-prescribed with aliskiren was low, but around 20% of patients treated with aliskiren were also prescribed another class of RAS-acting agents (e.g. 51 with an ACEi and 59 with an ARB out of 452 patients in 2012 – figure 15).

Figure 19. Proportion of patients co-prescribed in diabetes patients treated with any drug acting on RAS - France



8.3.3. Comments on population data

In France, the proportion of patients treated with any antihypertensive slightly increased and the proportion of patients treated with any RAS acting drugs increased more sharply (see Annex III). In 2012, patients treated with RAS-acting agent represented approximately 70% of patients treated with any antihypertensive in the total active population and more than 80% of patients treated with any antihypertensive and with DM.
ACEi were the products mostly prescribed in 2001 and 2002; afterwards ARB took over as the RAS drug class used by the most patients. The first prescription of aliskiren was recorded in 2009 and its use remained low (see Annex II).

The proportion of patients treated with at least two agents acting on the RAS increased at a faster rate during the first part of the study period; however, it remained very low (approximately 0.14% in the total active population and around 1% in patients with diabetes) and decreased at the end of the study period.

Most of the patients receiving a co-prescription were treated with an association of an ACEi with an ARB. Of note, no patients were co-prescribed a combination of all three different classes in any of the three countries.

In patients receiving a co-prescription of RAS-acting agents in 2012, a high percentage (about a third) of patients was from the DM population; moreover, co-prescription of two RAS-acting agents was more common in patients with DM prescribed an RAS-acting agent compared to patients on an RAS-acting agent treatment without these diagnoses.

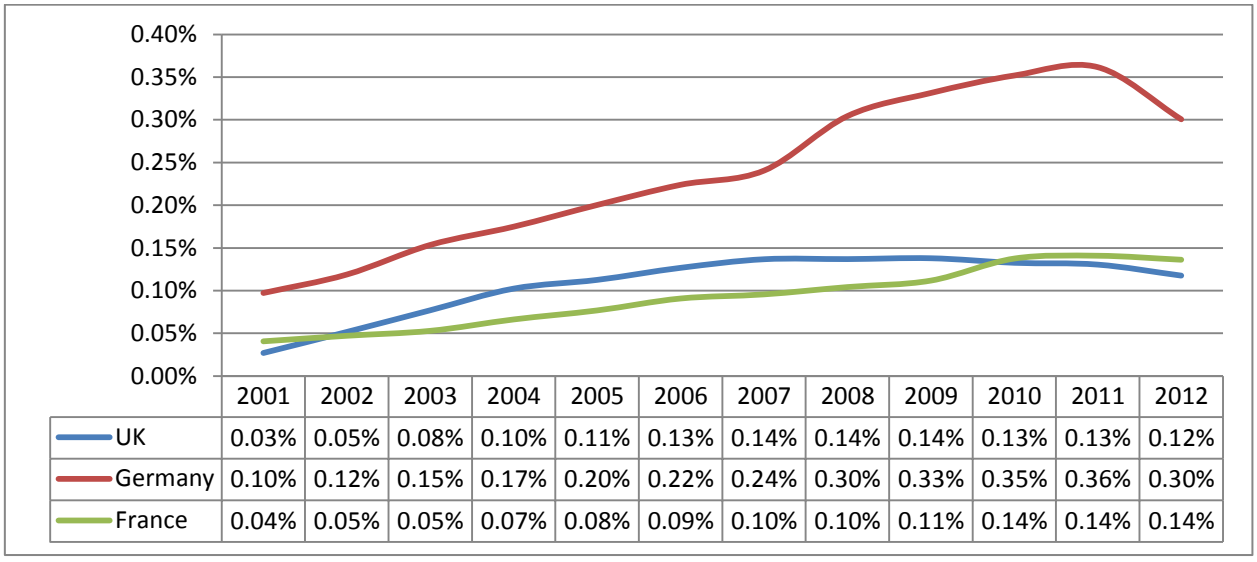
8.4. Co-prescription pattern across countries: summary of results

As mentioned, comparisons across countries would require a careful consideration of healthcare delivery systems, national guidelines, regulatory intervention and market penetration analyses, which are beyond the scope of this study. However, a summary of how the proportion of co-prescribed patients evolved in France, Germany, and the UK is useful in highlighting commonalities and differences.

In the total active population, the proportion of patients co-prescribed increased during the first years of the study period and decreased towards the end in all countries analysed (figure 20); however, the extent and timing of these changes were different across countries. In the UK, the peak was reached in 2007 (earlier than in the other countries) then the proportion of patients co-prescribed remained stable with a slow decrease from 2010. Germany, on the other hand, showed an increase until 2011 (with a stronger growth in 2008 which may be attributable to the introduction of aliskiren) and a sharp decrease in 2012. Finally, France had a constant but slower increase until 2009, a stronger growth in 2010 (the year after the introduction of aliskiren) and then a very small decrease in 2012.

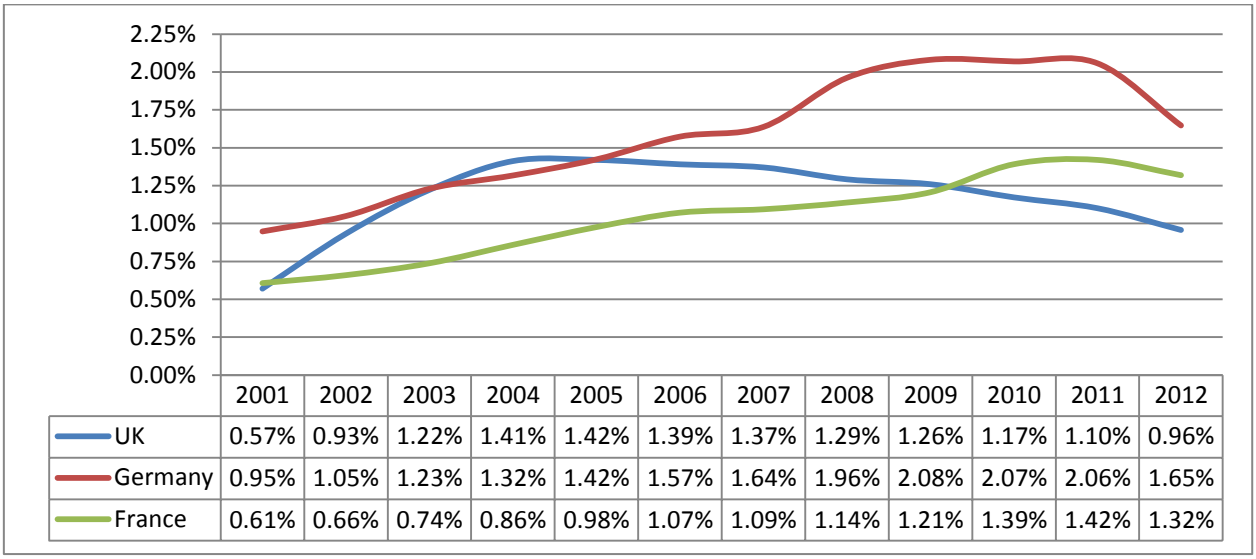
To take into account the increasing proportion of patients treated with any RAS acting agents observed in all the countries analysed, the co-prescribing pattern is shown in figure 21 as the proportion of the patients with any RAS acting agents prescription; the peak in the proportion of co-prescribed patients was reached earlier and the decrease that followed was more visible in all the three countries. In particular, in the UK the peak was in 2004 (compared to 2007) and the following decrease was stronger; in Germany the peak was also reached earlier (2009 vs. 2011) and in France, a visible decrease was observed in 2012 (while it was smaller in the general population).

Figure 20. Proportion of patients co-prescribed at least two RAS-acting agents in the total active population of UK, Germany and France



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
UK	0.03%	0.05%	0.08%	0.10%	0.11%	0.13%	0.14%	0.14%	0.14%	0.13%	0.13%	0.12%
Germany	0.10%	0.12%	0.15%	0.17%	0.20%	0.22%	0.24%	0.30%	0.33%	0.35%	0.36%	0.30%
France	0.04%	0.05%	0.05%	0.07%	0.08%	0.09%	0.10%	0.10%	0.11%	0.14%	0.14%	0.14%

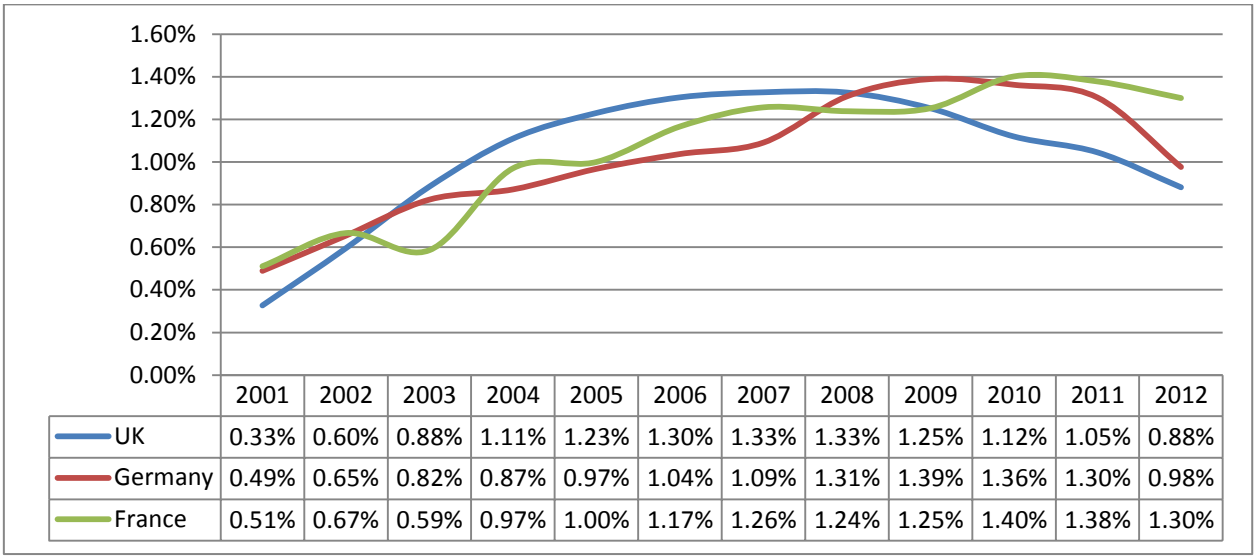
Figure 21. Proportion of patients co-prescribed at least two RAS-acting agents in the total active population treated with an RAS-acting agent in UK, Germany and France



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
UK	0.57%	0.93%	1.22%	1.41%	1.42%	1.39%	1.37%	1.29%	1.26%	1.17%	1.10%	0.96%
Germany	0.95%	1.05%	1.23%	1.32%	1.42%	1.57%	1.64%	1.96%	2.08%	2.07%	2.06%	1.65%
France	0.61%	0.66%	0.74%	0.86%	0.98%	1.07%	1.09%	1.14%	1.21%	1.39%	1.42%	1.32%

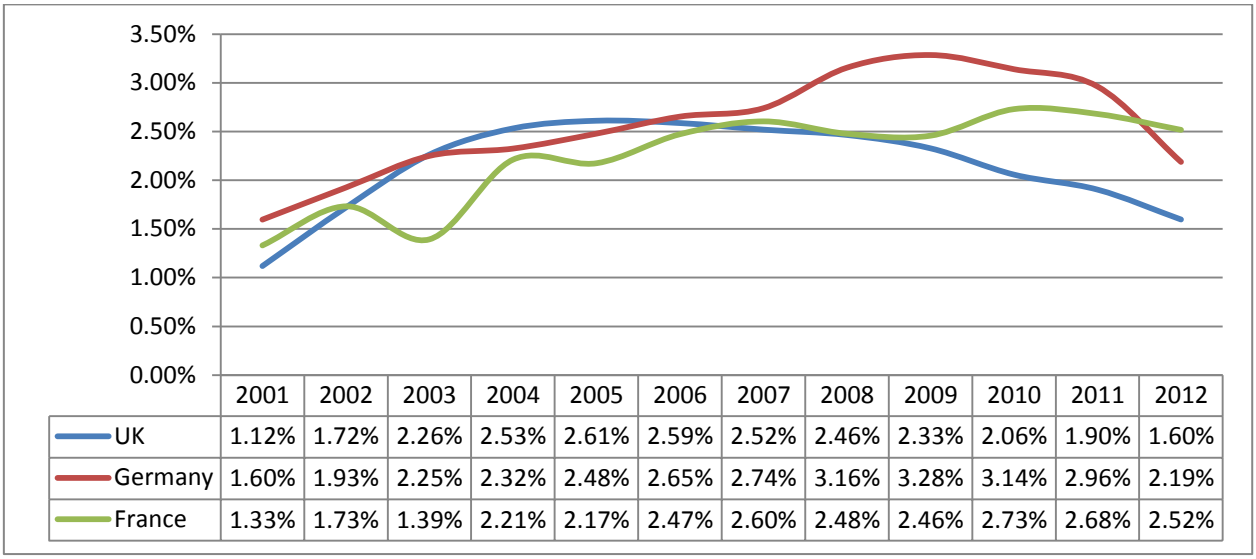
In the DM population, the pattern in the proportion of patients co-prescribed is very similar to the total active population with the only difference being that in Germany the decrease started earlier (figure 22). No significance difference is observed with the co-prescribing pattern in patients treated with an RAS-acting agent (figure 23).

Figure 22. Proportion of patients co-prescribed at least two RAS-acting agents in patients with diabetes in UK, Germany and France



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
UK	0.33%	0.60%	0.88%	1.11%	1.23%	1.30%	1.33%	1.33%	1.25%	1.12%	1.05%	0.88%
Germany	0.49%	0.65%	0.82%	0.87%	0.97%	1.04%	1.09%	1.31%	1.39%	1.36%	1.30%	0.98%
France	0.51%	0.67%	0.59%	0.97%	1.00%	1.17%	1.26%	1.24%	1.25%	1.40%	1.38%	1.30%

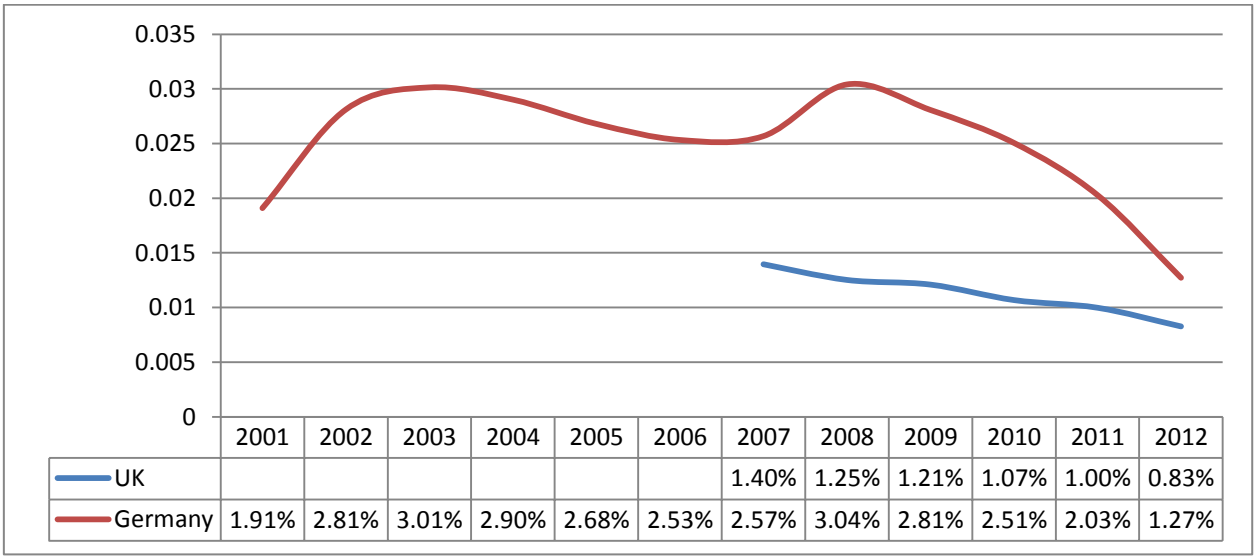
Figure 23. Proportion of patients co-prescribed at least two RAS-acting agents in patients with diabetes treated with an RAS-acting agent in UK, Germany and France



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
UK	1.12%	1.72%	2.26%	2.53%	2.61%	2.59%	2.52%	2.46%	2.33%	2.06%	1.90%	1.60%
Germany	1.60%	1.93%	2.25%	2.32%	2.48%	2.65%	2.74%	3.16%	3.28%	3.14%	2.96%	2.19%
France	1.33%	1.73%	1.39%	2.21%	2.17%	2.47%	2.60%	2.48%	2.46%	2.73%	2.68%	2.52%

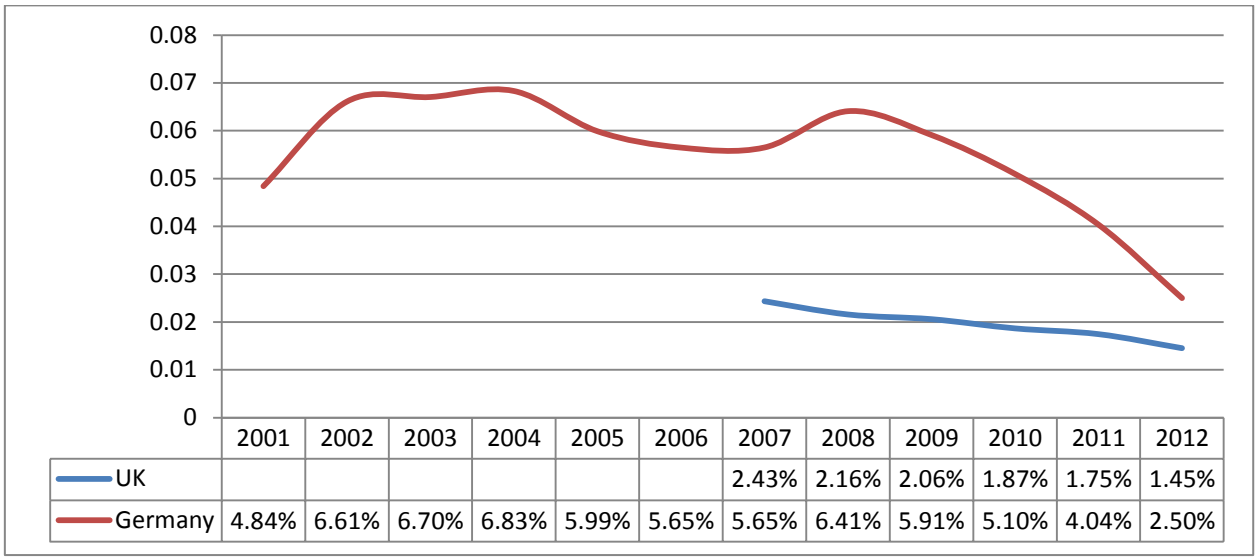
Finally, in the CKD population, the decreasing trend in co-prescription started even earlier in Germany (2009) compared to the total active population and patients with DM. Moreover, in Germany in the period 2002-2008 the proportion of co-prescribed patients oscillated and did not show the usual increase (figure 24). Even in this case, a comparison with the co-prescribing pattern as a proportion of the patients treated with an RAS-acting agent does not show any particular difference (figure 25).

Figure 24. Proportion of patients co-prescribed at least two RAS-acting agents in patients with chronic kidney disease in UK and Germany



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
UK							1.40%	1.25%	1.21%	1.07%	1.00%	0.83%
Germany	1.91%	2.81%	3.01%	2.90%	2.68%	2.53%	2.57%	3.04%	2.81%	2.51%	2.03%	1.27%

Figure 25. Proportion of patients co-prescribed at least two RAS-acting agents in patients with chronic kidney disease treated with an RAS-acting agent in UK and Germany



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
UK							2.43%	2.16%	2.06%	1.87%	1.75%	1.45%
Germany	4.84%	6.61%	6.70%	6.83%	5.99%	5.65%	5.65%	6.41%	5.91%	5.10%	4.04%	2.50%

8.5. Aliskiren containing-products: impact of SPC safety update

As mentioned previously, in February 2012, a review conducted by the European Medicines Agency on aliskiren-containing medicines concluded that these medicinal products should be contraindicated in patients with diabetes or moderate to severe renal impairment who take ACEis or ARBs. This contraindication was implemented in the SPC of aliskiren products; in addition, a warning that advised that the combination of aliskiren with an ACE inhibitor or ARB is not recommended in all other patients was also included.

A post-hoc exploratory analysis was performed to investigate whether the labelling changes in the SPC for aliskiren may have led to a different prescribing pattern in the three countries studied. Table 1 shows the rate of aliskiren co-prescription per 1,000 patients treated with any RAS acting agents in 2011 and 2012. There was a decrease in all three populations, sharper in the DM and CKD populations, as expected; while up to 2011 the trend was consistently increasing.

Table 1. Aliskiren co-prescription per 1,000 patients treated with RAS acting drug (number of patients in brackets)

Populations	UK		Germany		France	
	2011	2012	2011	2012	2011	2012
General	1.12 (147)	0.79 (93)	7.62 (3,912)	4.71 (2,496)	4.84 (669)	3.21 (430)
Diabetes	1.41 (47)	0.85 (26)	11.06 (2,023)	5.71 (1,106)	8.03 (196)	4.44 (107)
*Kidney**	1.68 (54)	1.13 (32)	16.39 (422)	7.96 (225)		

* Data not shown for France due to the sample not being representative of all patients with CKD (trend consistent with other data shown).

9. Conclusions

This study describes the extent and the patterns of co-prescription of RAS-acting agents in France, Germany, and the UK over a period of eleven years providing an overview of co-prescribing in the population of three large EU countries.

The results show that while the proportion of patients with a prescription of RAS acting agents was high (with ACEis being the most prescribed in the UK and Germany whereas ARBs being the most prescribed in France), only a small proportion of these patients were co-prescribed two different RAS drug classes. Moreover, the co-prescribing was more common in the diabetes and chronic kidney disease sub-populations than in the general population.

In the total active population, there was an increase in co-prescribing in all countries followed by a decrease in 2012 (earlier in the UK); a similar trend was observed in the diabetes sub-population while the decreasing trend in co-prescribing started earlier in the chronic kidney disease sup-population. In the total active population, the decrease in co-prescribing was sharper in all the countries analysed and in the UK and Germany started earlier when focusing in patients treated with any RAS-acting agents. This trend seems to reflect the current therapeutic guidelines in use in Europe[12] [13]where co-prescription is not recommended. In the current UK NICE guidelines, co-prescribing of ACE and ARB is contra-indicated.

Most of the patients receiving a co-prescription were treated with a combination of an ACEi with an ARB.

The use of aliskiren was low in Germany and France and minimal in the UK; however, a large percentage of these users were co-prescribed another class of RAS-acting agents. The decrease in 2012 seems to suggest that the recommendations from EMA in early 2012 to avoid co-prescription with aliskiren and contraindicating it in diabetes and chronic kidney disease patients may have been effective. However, other external factors and reasons influencing the observed trend cannot be excluded and further work, including 2013 data, would be needed in order to investigate the possible reasons for the decreasing trend.

In conclusion, the results show that while the prevalence of RAS acting agents was high, only a small proportion of these patients were co-prescribed two different RAS drug classes (0.1% - 0.3% of the active population). The study also shows a decreasing trend in the proportion of patients co-prescribed at least two RAS-acting agents in France, Germany and the UK in the last year(s). Finally, co-prescribing was more common in the diabetes and chronic kidney disease sub-populations than in the general population.

[12] NICE clinical guideline 127 Hypertension: clinical management of primary hypertension in adults (2011). www.nice.org.uk/guidance/CG127

[13] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Dominiczak A. 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). European Heart Journal 2013; 34(28): 2159–219.

10. Annex

10.1. Annex I: Selection of antihypertensive drugs

10.1.1. UK

ATC code*	Excluded substance
C02A1	CLONIDINE
C02A2	DOXAZOSIN
C02D0	
C03A3	
C03A5	
C07A0	SOTALOL
C07B1	
C08A0	
C08B1	
C08B2	
C09A	
C09B	
C09C	
C09D	
C09X	REMISKIREN

*Ephmra codes, 3/4th level

10.1.2. Germany

ATC code*	Excluded ATC codes
C02 ANTIHYPERTENSIVES	
C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING	C02AC01
C02C ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING	C02CA04, C02CA07, C02CA08
C02D ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON	
C02L ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	
C03 DIURETICS	
C03A LOW-CEILING DIURETICS, THIAZIDES	
C03B LOW-CEILING DIURETICS, EXCL. THIAZIDES	
C03C HIGH-CEILING DIURETICS	
C03D POTASSIUM-SPARING AGENTS	
C03E DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION	C03EA15, C03EA16, C03EB01, C03EB21, C03ED01
C03X OTHER DIURETICS	
C07 BETA BLOCKING AGENTS	
C07A BETA BLOCKING AGENTS	C07AA07
C07B BETA BLOCKING AGENTS AND THIAZIDES	
C07C BETA BLOCKING AGENTS AND OTHER DIURETICS	
C07D BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS	
C07E BETA BLOCKING AGENTS AND VASODILATORS	
C07F BETA BLOCKING AGENTS AND OTHER ANTIHYPERTENSIVES	
C08 CALCIUM CHANNEL BLOCKERS	
C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	C08CA06
C08D SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS	
C08E NON-SELECTIVE CALCIUM CHANNEL BLOCKERS	
C08G CALCIUM CHANNEL BLOCKERS AND DIURETICS	
C09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	
C09A ACE INHIBITORS, PLAIN	
C09B ACE INHIBITORS, COMBINATIONS	
C09C ANGIOTENSIN II ANTAGONISTS, PLAIN	
C09D ANGIOTENSIN II ANTAGONISTS, COMBINATIONS	
C09X OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09XA01

*WHO codes, 2/3rd level

In addition products where substance contains: “album”, “multi substanz”, “keine zuordnung” were removed

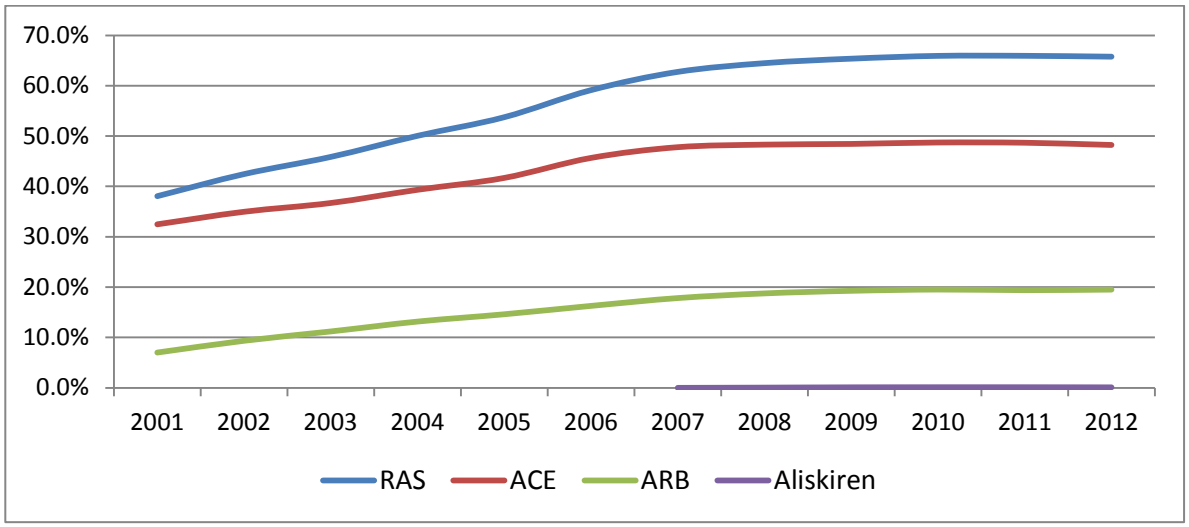
10.1.3. France

ATC code*	Excluded substance
C02A1	CLONIDINE
C02A2	
C02D0	
C03A3	
C03A5	
C07A0	SOTALOL
C07B1	
C08A0	
C08B2	
C09A	
C09B	
C09C	
C09D	
C09X	REMISKIREN

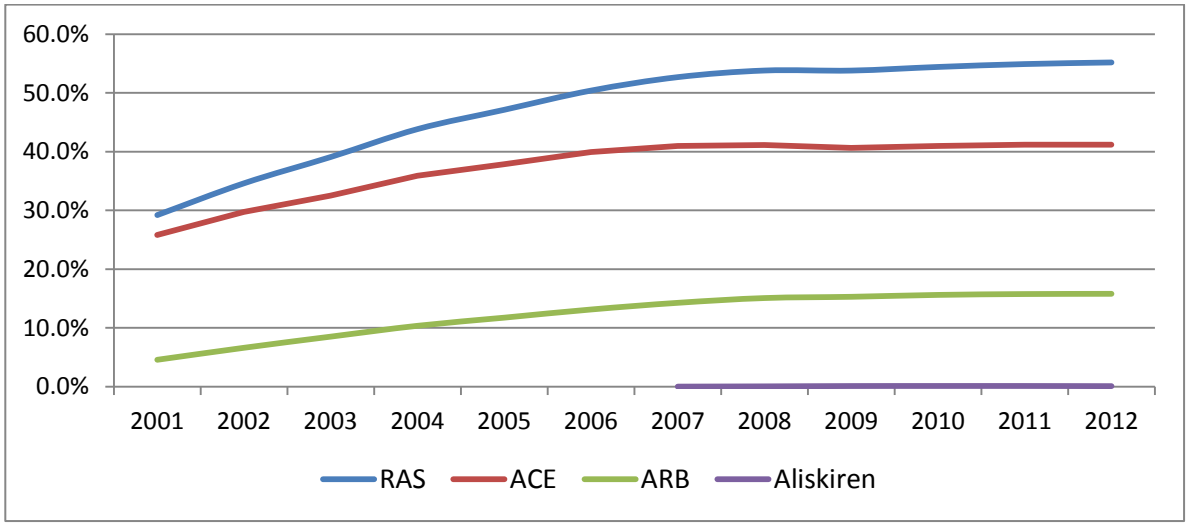
*Ephmra codes, 3/4th level

10.2. Annex II: Proportion of patients prescribed any RAS acting agents

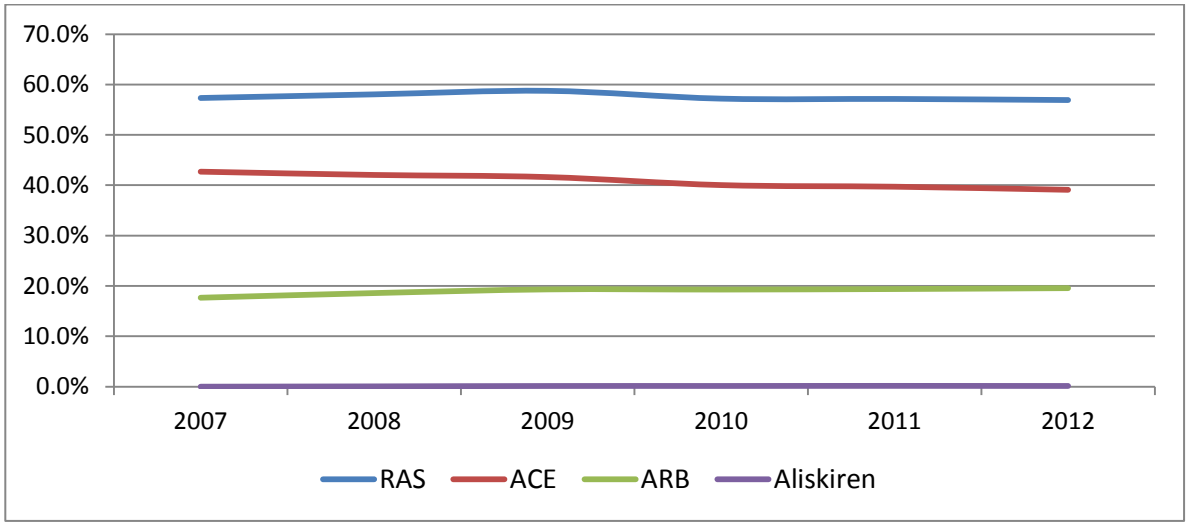
10.2.1. UK – General population



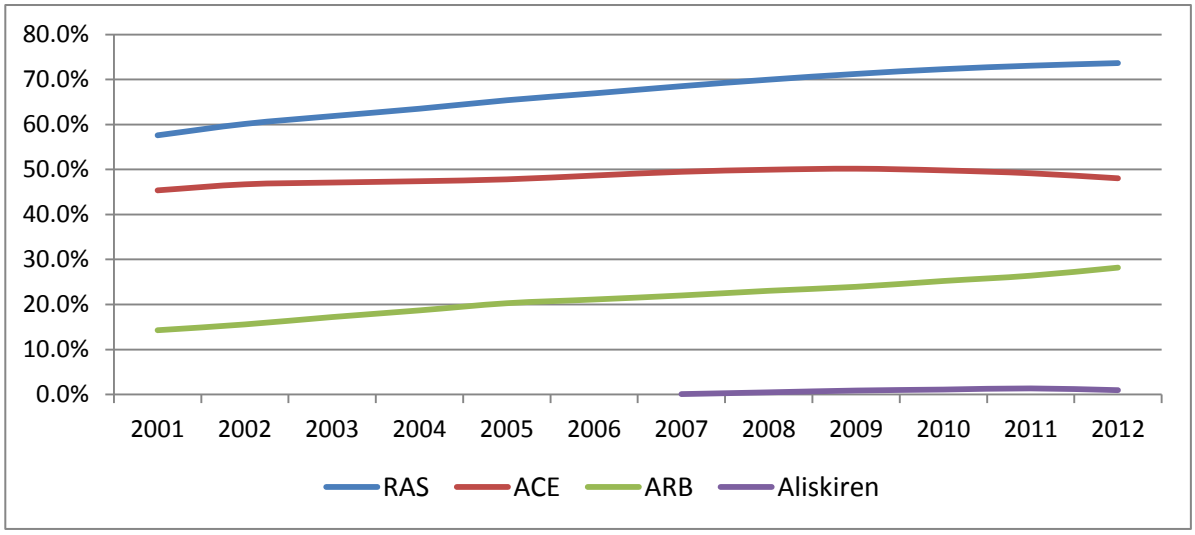
10.2.2. UK – Diabetes population



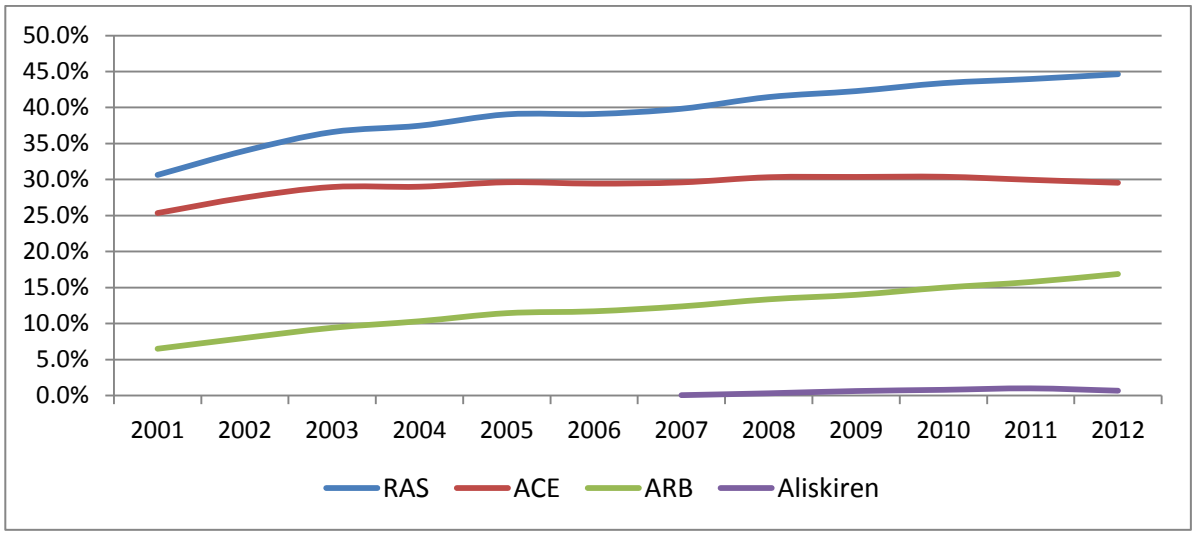
10.2.3. UK – Chronic kidney disease population



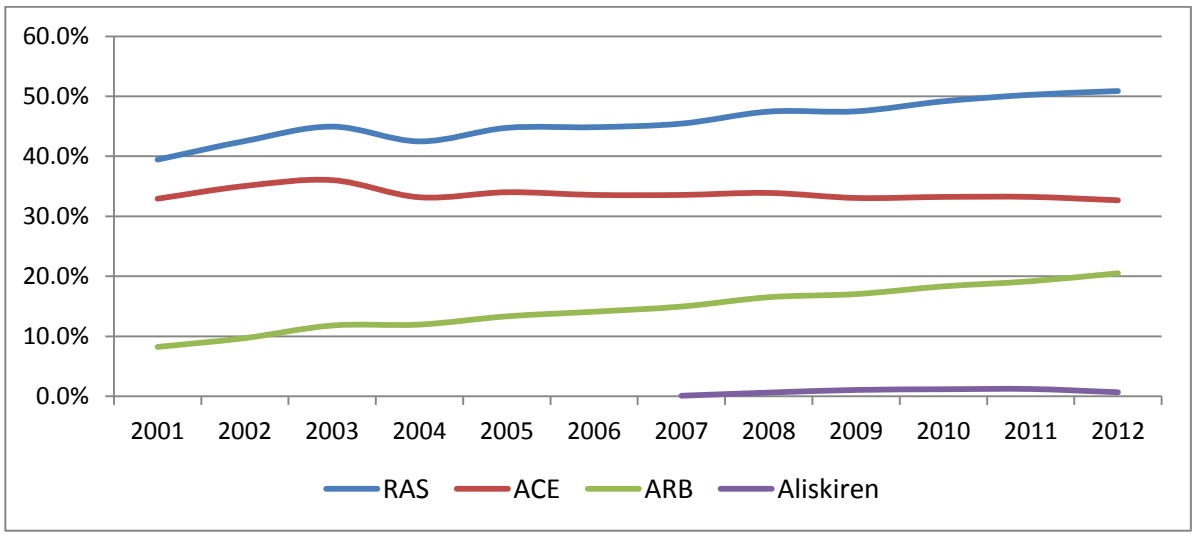
10.2.4. Germany – General population



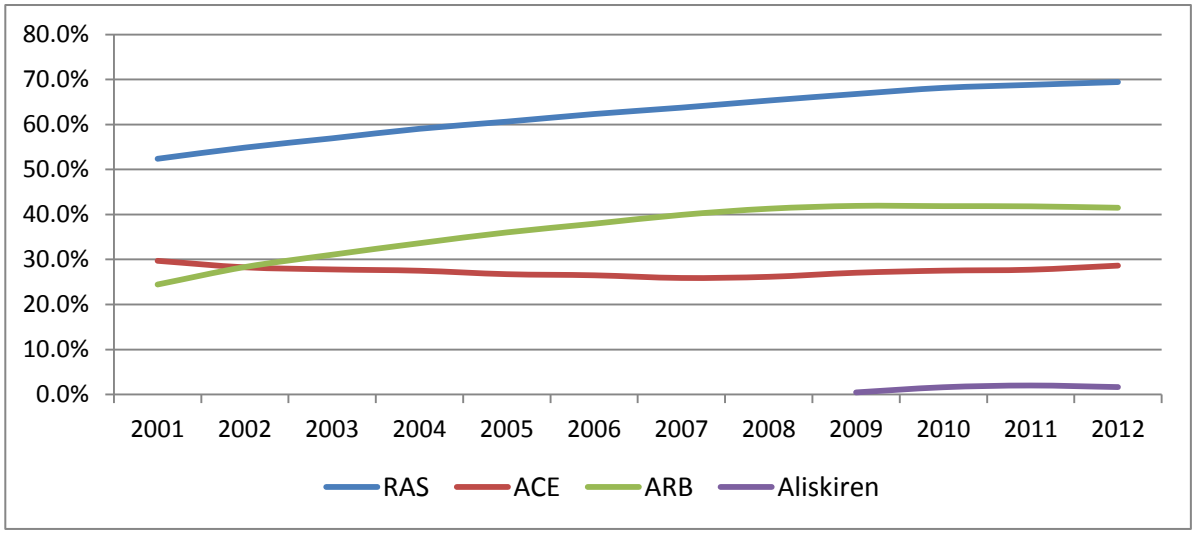
10.2.5. Germany – Diabetes population



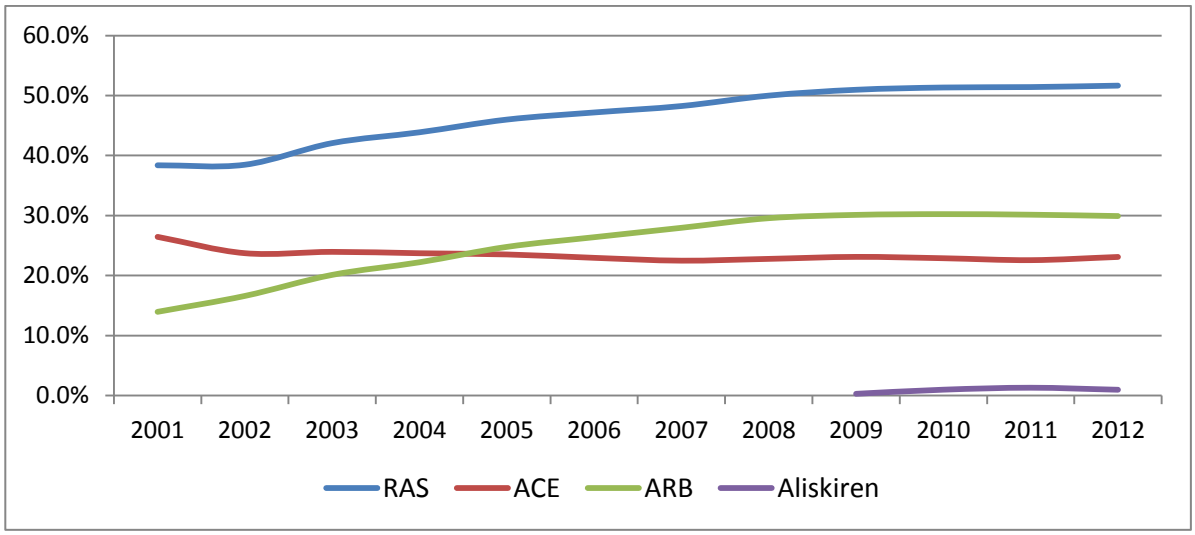
10.2.6. Germany – Chronic kidney disease population



10.2.7. France – General population

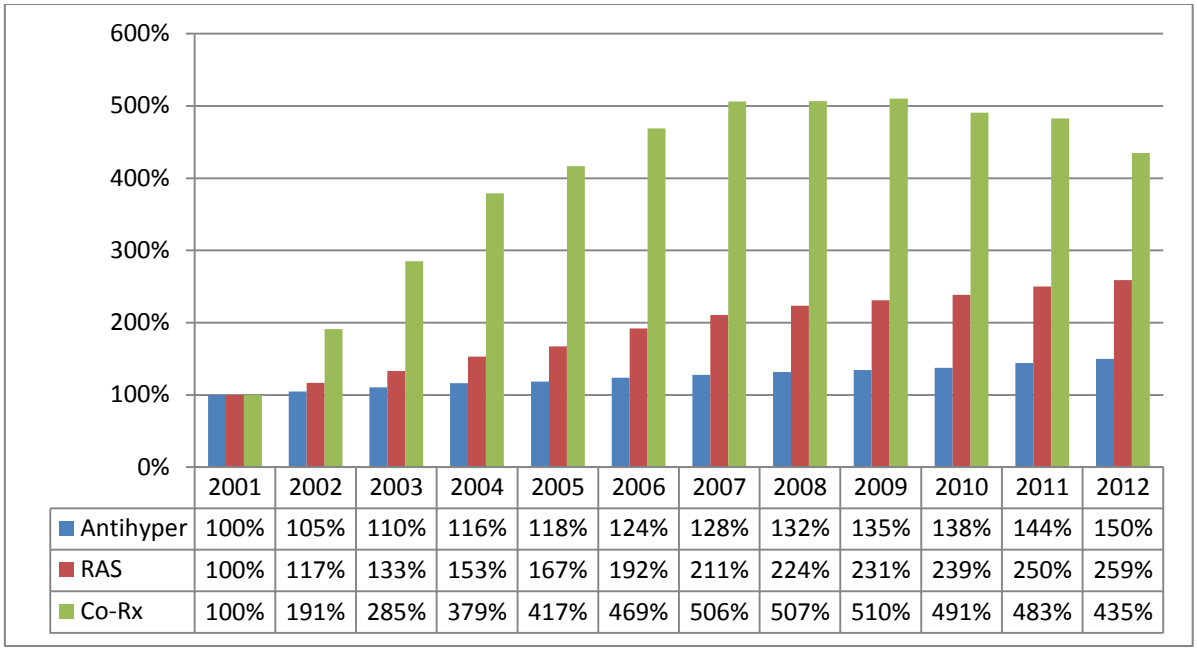


10.2.8. France – Diabetes population



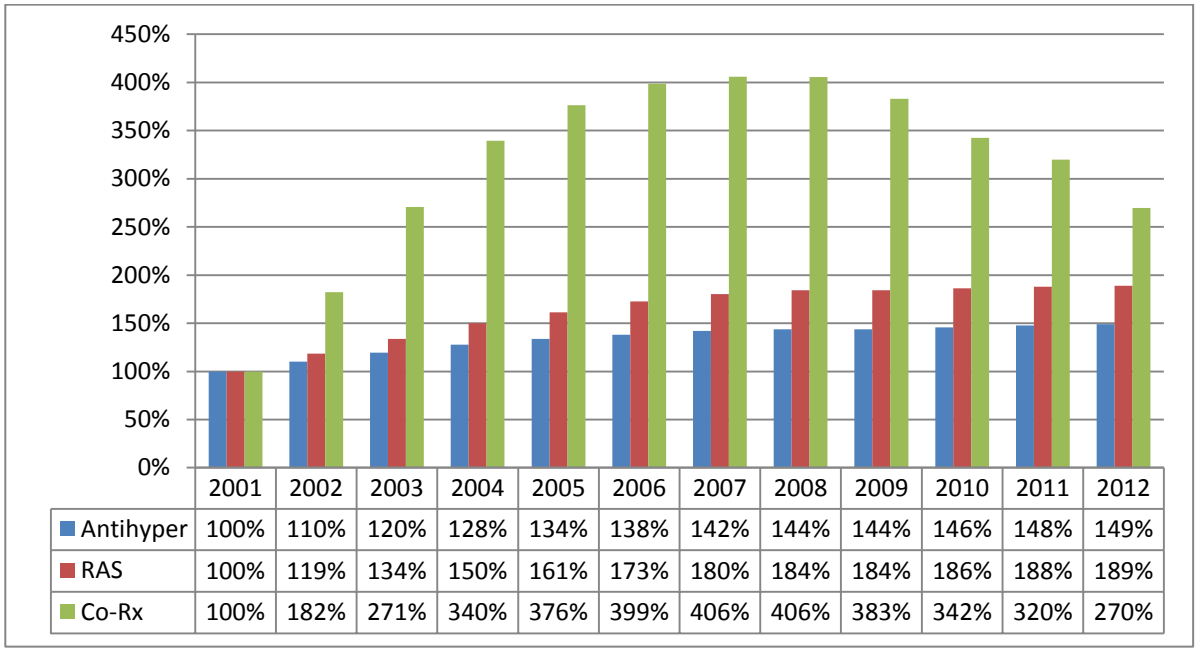
10.3. Annex III: Percentage change in prevalence (baseline = 2001)

10.3.1. UK – General population



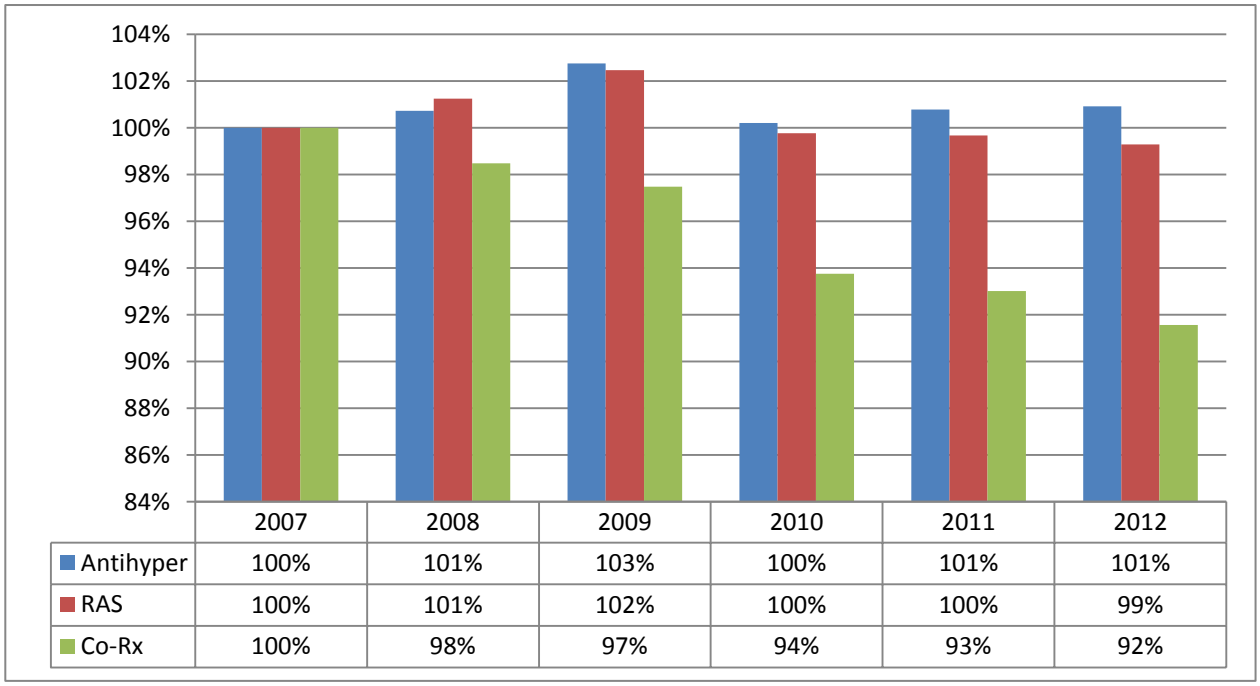
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Antihyper	100%	105%	110%	116%	118%	124%	128%	132%	135%	138%	144%	150%
RAS	100%	117%	133%	153%	167%	192%	211%	224%	231%	239%	250%	259%
Co-Rx	100%	191%	285%	379%	417%	469%	506%	507%	510%	491%	483%	435%

10.3.2. UK – Diabetes population



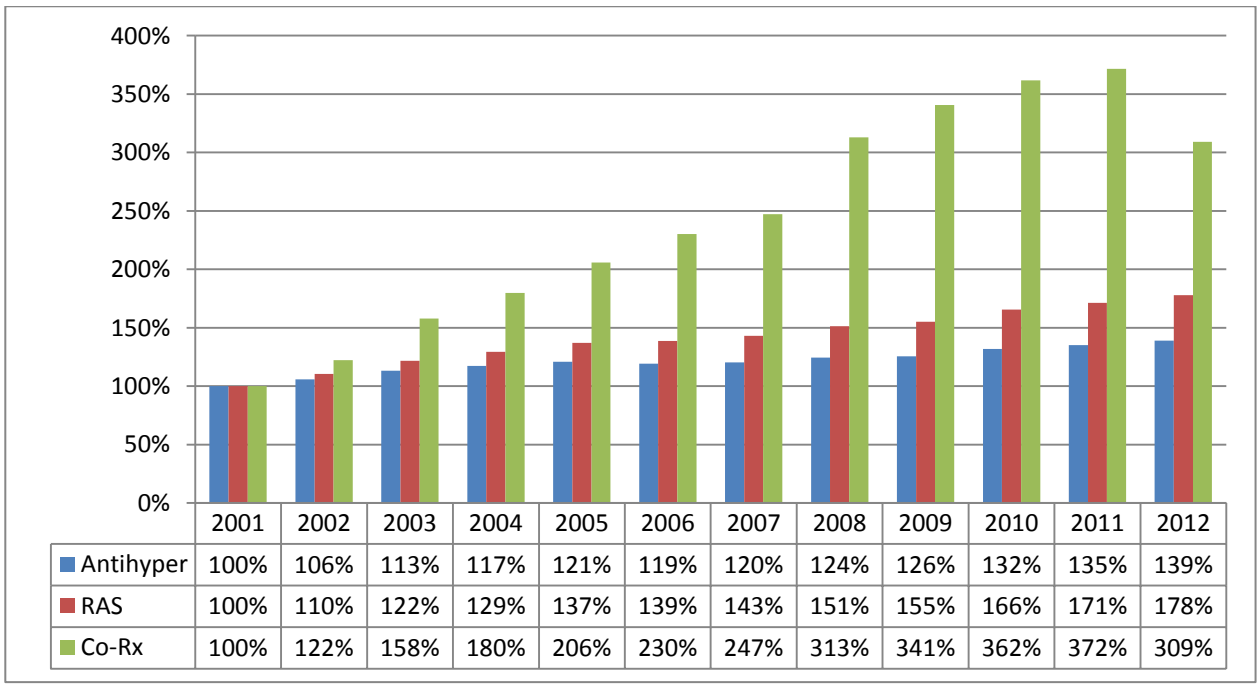
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Antihyper	100%	110%	120%	128%	134%	138%	142%	144%	144%	146%	148%	149%
RAS	100%	119%	134%	150%	161%	173%	180%	184%	184%	186%	188%	189%
Co-Rx	100%	182%	271%	340%	376%	399%	406%	406%	383%	342%	320%	270%

10.3.3. UK - Chronic kidney disease population (baseline = 2007)



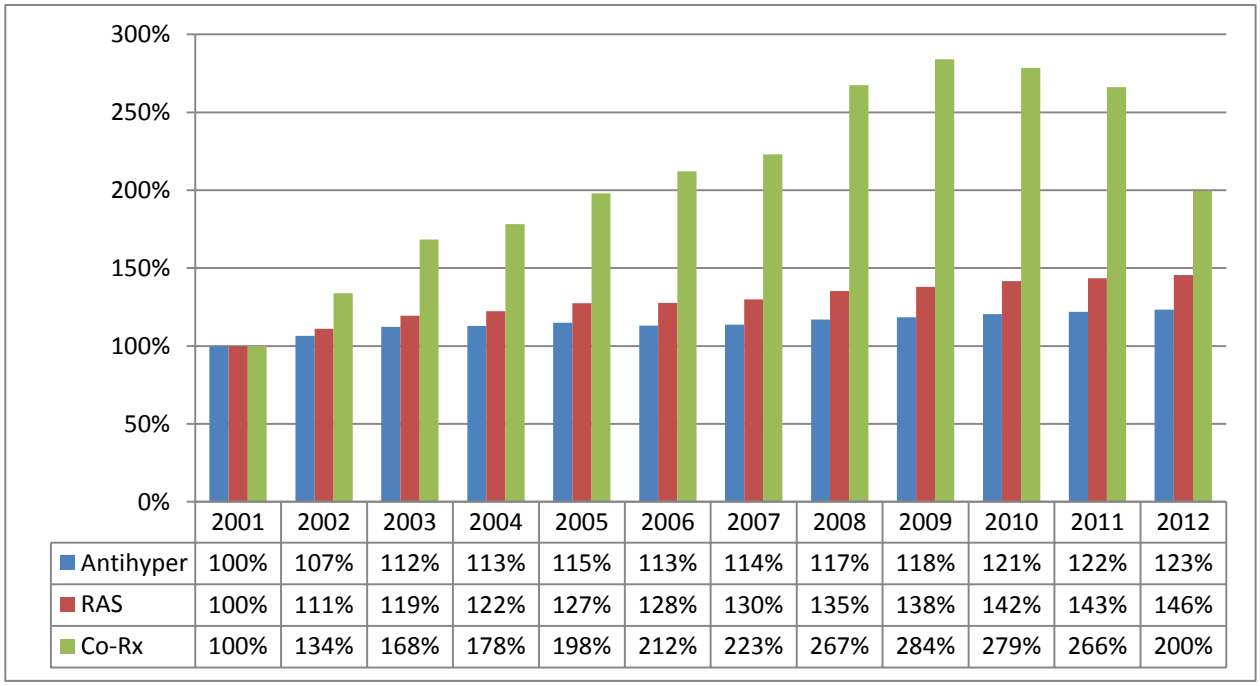
	2007	2008	2009	2010	2011	2012
Antihyper	100%	101%	103%	100%	101%	101%
RAS	100%	101%	102%	100%	100%	99%
Co-Rx	100%	98%	97%	94%	93%	92%

10.3.4. Germany – General population



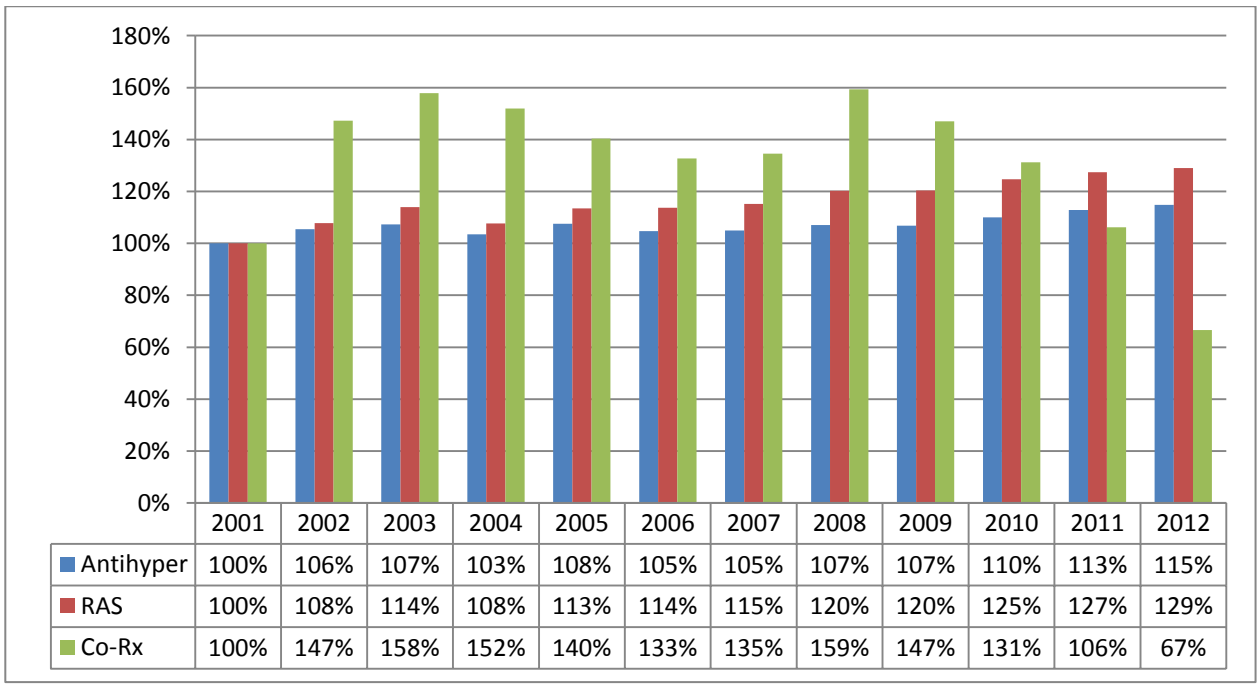
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Antihyper	100%	106%	113%	117%	121%	119%	120%	124%	126%	132%	135%	139%
RAS	100%	110%	122%	129%	137%	139%	143%	151%	155%	166%	171%	178%
Co-Rx	100%	122%	158%	180%	206%	230%	247%	313%	341%	362%	372%	309%

10.3.5. Germany - Diabetes population



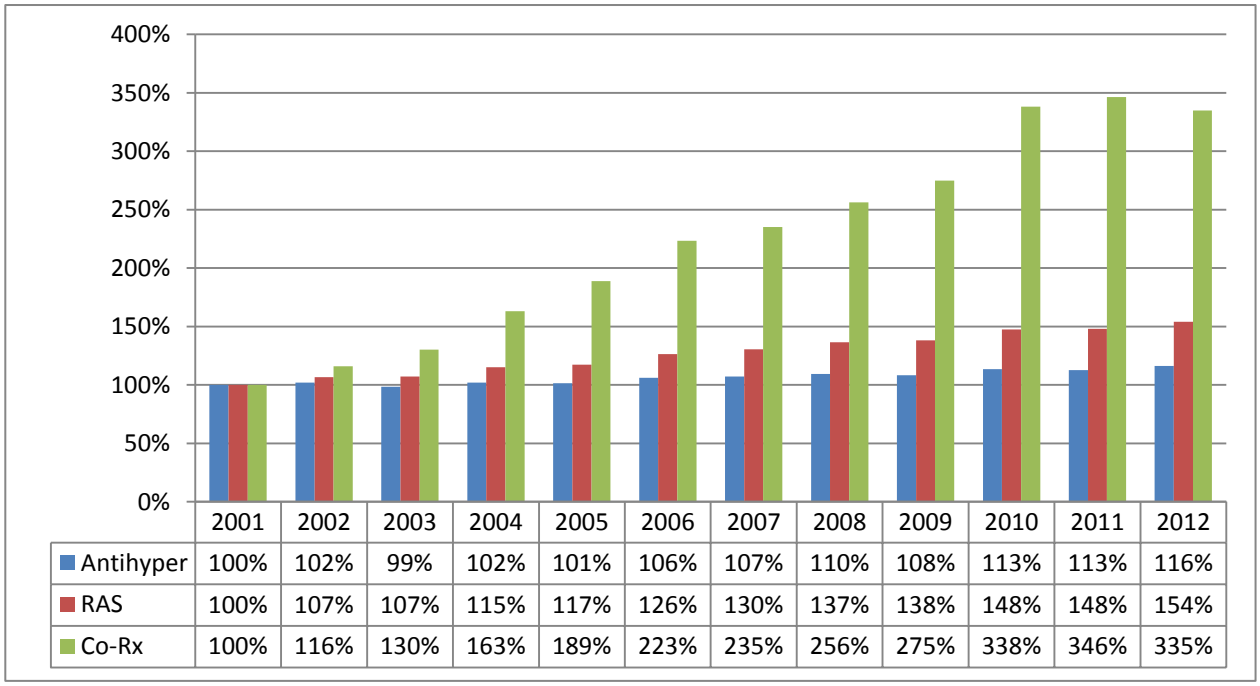
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Antihyper	100%	107%	112%	113%	115%	113%	114%	117%	118%	121%	122%	123%
RAS	100%	111%	119%	122%	127%	128%	130%	135%	138%	142%	143%	146%
Co-Rx	100%	134%	168%	178%	198%	212%	223%	267%	284%	279%	266%	200%

10.3.6. Germany - Chronic kidney disease



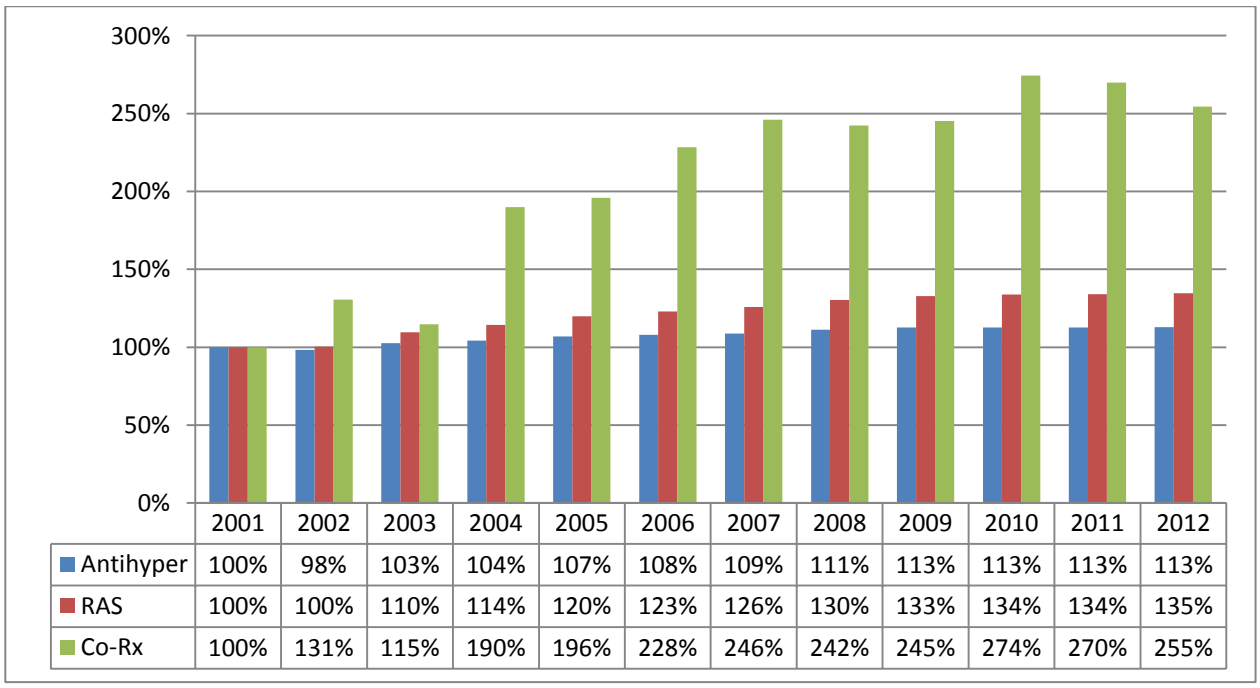
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Antihyper	100%	106%	107%	103%	108%	105%	105%	107%	107%	110%	113%	115%
RAS	100%	108%	114%	108%	113%	114%	115%	120%	120%	125%	127%	129%
Co-Rx	100%	147%	158%	152%	140%	133%	135%	159%	147%	131%	106%	67%

10.3.7. France – General population



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Antihyper	100%	102%	99%	102%	101%	106%	107%	110%	108%	113%	113%	116%
RAS	100%	107%	107%	115%	117%	126%	130%	137%	138%	148%	148%	154%
Co-Rx	100%	116%	130%	163%	189%	223%	235%	256%	275%	338%	346%	335%

10.3.8. France - Diabetes population



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Antihyper	100%	98%	103%	104%	107%	108%	109%	111%	113%	113%	113%	113%
RAS	100%	100%	110%	114%	120%	123%	126%	130%	133%	134%	134%	135%
Co-Rx	100%	131%	115%	190%	196%	228%	246%	242%	245%	274%	270%	255%