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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



1. PASS information

Title	Trends in co-prescribing of renin-angiotensin system (RAS)-acting agents in France, Germany and the UK during 2000 - 2012
Protocol version identifier	1.3
Date of last version of the protocol	17 July 2013
EU PAS Register No:	Study not registered
Active substance	Angiotensin receptor blockers (ARBs); Angiotensin converting enzyme inhibitors (ACEis); Direct renin inhibitors (Aliskiren) ATC codes: C09A, C09B, C09C, C09D, C09X (except C09XA01)
Medicinal product(s):	Multiple
Product reference:	
Procedure number:	EMA/HA/31/1370
Study initiator	EMA
Research question and objectives	<p>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.</p> <p>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 2000-2012 including in patients with diabetes mellitus (DM) and chronic kidney disease (CKD). This will be done using the EMA's in-house IMS Health databases.</p> <p>It is anticipated that the results will support the PRAC in its decision-making in the current Article 31 referral.</p>

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Marketing authorisation holder

Marketing authorisation holder(s)	Multiple
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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

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

RAS: Renin-Angiotensin System

2. Responsible parties

Project lead: Gianmario Candore & Kristian Svendsen

Epidemiologist: Kevin Blake

Clinical lead: Francois Maignen

Statistical lead: Jim Slattery

Project sign off: Peter Arlett

3. Rationale and background

A previous EMA review of medicines containing aliskiren concluded in February 2012 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 in patients 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.

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. doi: 10.1136/bmj.f360.

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-prescription of medicinal products acting on the renin-angiotensin system in the EU.

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.²

At the EMA's regular internal 'best-evidence' meeting in May 2013 decided to conduct an in-house study using electronic health record databases from IMS Health. The primary objective of this study is to provide an estimate of the combined prescription of these agents in clinical practice separately in France, Germany and the UK, in the patients included in the datasets and in diabetes mellitus (DM) and chronic kidney disease (CKD) patients.

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 co-prescription of RAS-acting agents in the EU.

4. Research question and objectives

The PRAC 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 dual blockade of the RAS by describing the extent and the pattern of co-prescription of different RAS-acting agents prescribed on the same day and by the same physician in France, Germany and the UK. The study period will be from 1st January 2000 to 31 December 2012.

The PRAC List of Questions to MAHs³ makes explicit reference to sub-populations which may be at risk of harm such as patients with DM or CKD. Therefore sub-group analysis of these two populations will be conducted. Moreover, to provide additional background information, the extent of co-prescription will be presented in the population of patients with antihypertensive drug treatment.

Data provided in the study:

- Estimation of prevalence of RAS co-prescription in France, Germany and the UK;
- Description of the RAS co-prescription pattern in France, Germany and the UK over time (2000-2012);
- Estimation of RAS co-prescription prevalence and pattern in patients with DM or with CKD.

5. Research methods

5.1. Study design

Descriptive study based on an electronic health record (EHR) database.

² [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](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)

³ [http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Renin-angiotensin_system_\(RAS\)-acting_agents/Procedure_started/WC500143501.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Renin-angiotensin_system_(RAS)-acting_agents/Procedure_started/WC500143501.pdf)

5.2. Setting and data sources

This analysis includes all patients receiving a prescription of a drug acting on the RAS recorded in the IMS Disease Analyser in France, Germany and the UK.

The study period is restricted from 1st January 2000 to 31st December 2012.

The IMS Disease Analyser database includes anonymised patient medical records from France, Germany and the UK. In France and the UK data are collected through a representative panel of GPs; in Germany data are collected through a representative panel of internists (GPs) and specialist physicians working outside hospitals.⁴ For this analysis only internists will be considered.

In addition to prescription records, the IMS 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.

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

- IMS Health Germany database version March 2013 (internist only) containing 8,901,139 patients with data from 1992;
- IMS Health France database version December 2012 containing 4,172,700 patients with data from 1997;
- IMS Health UK database version March 2013 containing 5,686,400 patients with data from 1995.

This confirms the feasibility of the planned analyses throughout the study period (2000 – 2012) since all databases are active and have collected a significant number of prescription records.

5.3. Variables

The following classes of drugs acting on the RAS have been included: Angiotensin receptor blockers (ARBs); Angiotensin converting enzyme inhibitors (ACEis); Direct renin inhibitors (aliskiren)

Each of the class has been identified with the following WHO ATC codes:

ACEis: C09A Ace Inhibitors, Plain; C09B Ace Inhibitors, Combinations

ARBs: 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

Patients with DM or with CKD will be identified by searching the medical records using the International Classification of Disease (ICD) codes as recorded by the prescribers. ICD codes E10-E14 will be used to identify patients with DM. ICD code N18 will be used to identify patients with CKD.

Sub-group analyses of patients with 'renal impairment' will not be performed as this diagnosis is not routinely captured in the database with an ICD code and renal impairment based on laboratory values only can be transient. It is therefore difficult to determine whether drug use and the condition were concomitant.

⁴ 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

5.4. Study size

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

5.5. Data management

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

5.6. Data analysis

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

- Prevalence: number and percentage of patients prescribed any drug acting on RAS and with any co-prescription of these drugs in 2012:
 - In the general population included in the database;
 - In each of the following populations: patients treated with antihypertensive drugs, patients with diabetes and patients with chronic kidney disease.
- Prescription pattern: percentage of patients prescribed with any drug acting on RAS and with any co-prescription of these drugs between 2000 and 2012:
 - In the general population included in the database;
 - In each of the two populations: patients with diabetes and patients with chronic kidney disease.

Co-prescription will be defined as the prescription of different drug classes made on the same day and by the same physician: this approach has been adopted by Tobi et al.⁵ and used in the Wan et al.⁶ paper that describes the co-prescribing trend of ACEis and ARBs in Ireland. Co-prescribing as defined above has the advantage of high specificity in identifying patients with combined use of RAS-acting agents. Applying the same prescriber requirement also increases specificity and makes clear the intention of the treating physician to use more than one RAS-acting agent concurrently. 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 necessarily rely on assumptions about duration of therapy and might lead to misclassification of switching between medicines as co-medication or the other way around.

5.7. Strengths and limitations of the research methods

- The IMS Disease Analyser maintains data collected through a representative panel of physicians in each of the study countries, which allows population-based analyses;
- Prescription records represent the most complete set of data in IMS Disease Analyser, which strengthen the analyses at prescription level. However, prescriptions of drugs acting on the RAS in hospital or settings other than GP clinics in France, Germany and the UK will be missing;
- Missing information in the medical records may affect the selection of the sub-populations of patients with diabetes and chronic kidney disease;

⁵ Tobi, H., Faber, A., Van den Berg, P. B., Drane, J. W., & De Jong-van den Berg, L. Studying co-medication patterns: the impact of definitions. *Pharmacoepidemiol Drug Saf* 2007; 16(4):405–411.

⁶ Wan Md Adnan, W. A., Zaharan, N. L., Bennett, K., Wall, C. A. Trends in co-prescribing of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in Ireland. *Br J Clin Pharmacol*. 2011;71(3):458–66.

- 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 are outside the scope of the study.
- Variations in healthcare systems among individual countries
 - 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.
 - Registration of patients with a GP is not a requirement of the national healthcare system in France; however, 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.,
 - In Germany the national healthcare insurance system allow patients to visit a physician of choice whenever a medical need emerges, which results in possible information gaps in the patient's medical records maintained by any given physicians, including those contributing data to the German database of IMS Disease Analyser.

6. Plans for communicating study results

The study including the protocol will be registered in the ENCePP E-Register of Studies <http://www.encepp.eu/encepp/studiesDatabase.jsp> which currently serves as the EU PAS register referred in the Module VIII of the good pharmacovigilance practices (GVP) on post-authorisation studies.

The study results will be available in the ENCePP E-Register and will be forwarded to the PRAC (Co-) Rapporteurs and PRAC within the timeframe for the submission of responses from MAHs to the List of Questions for PRAC review i.e. 02 September 2013.⁷

⁷ [http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Renin-angiotensin_system_\(RAS\)-acting_agents/Procedure_started/WC500143502.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Renin-angiotensin_system_(RAS)-acting_agents/Procedure_started/WC500143502.pdf)