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Final protocol of a signal strengthening study

for service contract

EMA/2011/39/CN - BIPHOSPHONATES

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DEFINITIONS

- Participants in this tender are referred to herein according to the following codes:

  - **EMC**. Erasmus University Medical Center (Netherlands). Contractor
  - **PHARMO.** PHARMO Coöperation UA (Netherlands). Subcontractor
  - **UNIMIB.** Università di Milano-Bicocca (Italy). Subcontractor
  - **ARS.** Agenzia regionale di sanità della Toscana (Italy). Subcontractor
  - **SIMG.** Società Italiana di Medicina Generale (Italy). Subcontractor
  - **SYNAPSE.** Synapse Research Management Partners S.L. (Spain). Subcontractor

- **Contract**: Legal document signed between the Contractors and the European Medicines Agency for the undertaking of the tender.
- **Contractor**: A tenderer to which a framework contract has been awarded and signed with the EMA. It is responsible before the EMA of the right execution of the tender and of the delivery of the results in due time and form according to the Contract.
- **EMA.** European Medicines Agency.
- **Subcontractor**: Organisation supporting the Contractor in the fulfilment of the tender objectives and technical execution.
- **Technical specifications**. Official document generated by the EMA for the tender that includes a detailed description of all technical requirements, contractual arrangements, and price, that enables the EMA to specify and acquire services provided by resources not employed directly by the EMA.
- **Tender**: Public (or restrictive) offer made by the EMA to specific providers to enter into the contract of transaction of services at certain specified cost.
- **Work plan**: Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in the Contract.

SYNOPSIS

A signal of disproportionate reporting concerning the risk of cardiac valve calcification leading to cardiac valve insufficiency associated with the use of bisphosphonates was found in EudraVigilance. A similar association between bisphosphonate use and valvular and vascular calcification in women has also been previously described in a cohort study conducted in the United States (MESA study).[1]

The primary objective of this signal strengthening study is to confirm or refute the presence of a possible risk of cardiac valve disorders (all types of disorders, confirmed by cardiac imaging) in patients treated with bisphosphonates using EU longitudinal healthcare data from the EU-ADR Alliance. This signal strengthening study will determine the need for, and feasibility of conducting a traditional hypothesis testing study.

Signal strengthening will be performed using the most recently updated demographic, clinical, and prescription data from six databases in three EU member states (Italy, Netherlands, the United Kingdom), pooled using a distributed network approach by generation of common input data followed by local aggregation through custom-built software, Jerboa©. Potential cases of cardiac valve disorders in the database network will be identified using database-specific coding algorithms. Exposure to bisphosphonates will be assessed with drug prescription/dispensing data using the World Health Organisation's (WHO) Anatomical Therapeutic Chemical (ATC) classification system. Several signal detection/strengthening methods will be employed to assess the association of cardiac valve disorder and use of bisphosphonates.

1. BACKGROUND

Bisphosphonates are important medicines which are widely used to treat and prevent bone-related conditions. They are called bisphosphonates because they have two phosphonate (PO_4^{3-}) groups and are similar in structure to pyrophosphate. Bone undergoes constant turnover and is kept in balance (homeostasis) by osteoblasts creating bone and osteoclasts destroying bone. Bisphosphonates inhibit the digestion of bone by encouraging osteoclasts to undergo apoptosis, or cell death, thereby slowing bone loss.[2] There are two classes of bisphosphonates: the N-containing and non-N-containing bisphosphonates. The two types of bisphosphonates have different mechanisms of action.

The **non-nitrogenous (non-N-containing) bisphosphonates** are metabolised in the cell to compounds that replace the terminal pyrophosphate moiety of ATP, forming a nonfunctional molecule that competes with adenosine triphosphate (ATP) in the cellular energy metabolism. The osteoclast initiates apoptosis and dies, leading to an overall decrease in the breakdown of bone.[3] Etidronate, Clodronate and Tiludronate belong to this group.

Nitrogenous (N-containing) bisphosphonates bind and block the enzyme farnesyl diphosphate synthase (FPPS) in the HMG-CoA reductase pathway (also known as the mevalonate pathway), and exhibit their effect on bone metabolism in this way.[4] Disruption of the HMG CoA-reductase pathway at the level of FPPS prevents the formation of two metabolites (farnesol and geranylgeraniol) that are essential for connecting some small proteins to the cell membrane. This phenomenon is known as prenylation and is important for proper sub-cellular protein trafficking.[5] Pamidronate, Neridronate, Olpadronate, Alendronate, Ibandronate, Risedronate, Zoledronate belong to this group of bisphosphonates.

Individual bisphosphonates have different indications and are used:

1. for prevention and treatment of osteoporosis (weakness and thinning of bones) in postmenopausal women;
2. for treatment of Paget's disease of bone (where bones become weak and deformed);
3. as anticancer treatment regimens, particularly for metastatic bone cancer and multiple myeloma.

OVERVIEW OF SAFETY PROFILE

Oral dosage forms. One of the most common side effects of oral bisphosphonates is irritation of the oesophagus. Other common side effects of oral bisphosphonates are: heartburn; difficulty swallowing; pain upon swallowing; bone, muscle or joint pain; stomach pain; feelings of fullness or bloating; feeling sick; constipation; diarrhoea; flatulence; indigestion; headache; rash.

Intravenous dosage forms. The most common side effects of intravenous bisphosphonates are: flu-like symptoms; tiredness; lack of interest; weakness; diarrhoea; indigestion; vomiting; dizziness; gastrointestinal pain; sore throat; swelling of the lower limbs; skin

reactions such as redness, swelling and/or pain at the injection site. These symptoms usually disappear within a couple of hours or days.

SPECIFIC SAFETY ISSUES

In recent years several safety issues have been raised regarding the use of bisphosphonates.

- **Osteonecrosis of the jaw.** Bisphosphonate may cause a condition called osteonecrosis of the jaw (ONJ; death of jaw bone tissue).[6] The risk of this is greater in cancer patients receiving intravenous bisphosphonates than in patients receiving oral bisphosphonates for osteoporosis or Paget's disease of bone.

- **Atrial fibrillation**. Recent studies have reported bisphosphonate use (especially oledronate and alendronate) as a risk factor for atrial fibrillation in women.[7] A recent European review concluded that at the present time, atrial fibrillation does not need to be added to the list of possible side effects of alendronate in the product information; however, the safety issue of atrial fibrillation and all bisphosphonates should continue to be kept under close review.[8]

- **Atypical femoral fractures.** Such fractures may occur with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis. Pain, weakness or discomfort in the thigh, hip or groin may be an early indication of a possible fracture of the thigh bone.[9]

- **Cardiac valve calcification**. A signal of heart valve calcification leading to heart valve incompetence associated with the use of bisphosphonates has been found in the post-authorisation module of EudraVigilance, which contains mostly spontaneous reports. This signal (a statistical signal of disproportionate reporting) involves both mitral and tricuspid, as well as pulmonary, valves and involved four products of the class (alendronate, ibandronate, pamidronate and zoledronate), which probably reflects the actual use of these products, in particular in osteoporosis. An association between the use of bisphosphonates and the presence of heart calcification in women younger than 65 was observed in a study conducted on the Multi-Ethnic Study of Atherosclerosis (MESA) cohort and published in November 2010 in the Journal of the American College of Cardiology.[1] The primary objective of this study was to determine whether bisphosphonate therapy was associated with an increased risk of cardiovascular calcification (compared to non-users). In this cohort, bisphosphonates were mostly used by women. The relationship of bisphosphonates use to the prevalence of aortic valve, aortic valve ring, mitral annulus, thoracic aorta, and coronary artery calcification detected by computed tomography was assessed in 3,710 women within the MESA cohort. Analyses were age-stratified, because of a significant interaction between age and bisphosphonates use (interaction p values: AVC $p < 0.0001$; AVRC $p < 0.0001$; MAC $p = 0.002$; TAC $p < 0.0001$; CAC $p = 0.046$). After adjusting for age, body mass index, demographic data, diabetes, smoking, blood pressure, cholesterol levels and statin, hormone replacement, and renin-angiotensin inhibitor therapy, bisphosphonates use was associated with a lower prevalence of cardiovascular calcification in women 65 years of age (prevalence ratio: AVC 0.68 [95% confidence interval (CI): 0.41 to 1.13]; AVRC 0.65 [95% CI: 0.51 to 0.84]; MAC

0.54 [95% CI: 0.33 to 0.93]; TAC 0.69 [95% CI: 0.54 to 0.88]; CAC 0.89 [95% CI: 0.78 to 1.02]), whereas calcification was more prevalent in bisphosphonates users among the 2,181 women <65 years of age (AVC 4.00 [95% CI: 2.33 to 6.89]; AVRC 1.92 [95% CI: 1.42 to 2.61]; MAC 2.35 [95% CI: 1.12 to 4.84]; TAC 2.17 [95% CI: 1.49 to 3.15]; CAC 1.23 [95% CI: 0.97 to 1.57]). The study concluded that among women in the diverse MESA cohort, bisphosphonates were associated with decreased prevalence of cardiovascular calcification in older subjects (women older than 65) but more prevalent cardiovascular calcification in younger ones. No clear explanation (clinical or mechanistic) was given or found to explain this difference. There is conflicting evidence suggesting a causal association. The results of the MESA study must be considered in the light of previous studies suggesting that cardiovascular calcification correlates with atherosclerotic disease burden. However, experimental data has suggested that bisphosphonates might limit cardiovascular calcification. For these reasons, the signal of cardiac valve disorders associated with the use of bisphosphonates needs to be confirmed (or refuted) and further characterised. Considering the exposure to bisphosphonates (in particular among relatively healthy women suffering from osteoporosis) and the serious clinical consequences of the heart valve disorders (leading to heart valve incompetence), should the signal be confirmed, it would represent an important and significant risk to public health. The benefit/risk balance of the use of bisphosphonates in osteoporosis could be affected by this new risk.

2. OBJECTIVES

The primary objective of this study is to confirm, or refute, the existence of a statistical association of cardiac valve disorders (all types of disorders, confirmed by echocardiography, cardiac catheterisation, or other imaging modality) and use of bisphosphonate (for all indications), and eventually to identify effect modifiers. The secondary objective would be to investigate specifically the risk of cardiac valve calcification in users of bisphosphonate.

Finally, we will estimate the statistical power of the EU-ADR Alliance database network for the investigation of the relationship between cardiac valve disorders (overall and disorder-specific) and use of bisphosphonate through a subsequent traditional hypothesis testing study.

3. METHODOLOGY

3.1. STUDY DESIGN

Hypothesis-generating/strengthening study through data mining of electronic healthcare records

3.2. DATA SOURCES

The database platform that will be used for this study is based on the EU-ADR Alliance which combines anonymised healthcare data from established European databases located in three Member States. Health Search/CSD Patient (HSD, Italy), Interdisciplinary Processing of Clinical Information (IPCI, formerly known as Integrated Primary Care Information, the Netherlands), and The Health Improvement Network (THIN, United Kingdom) are general practice (GP) databases, where both clinical information and drug prescriptions are recorded. The PHARMO Network (the Netherlands), and the regional Italian databases of Lombardy (SSRI Lombardia) and Tuscany (SSRI Toscana) are all comprehensive record-linkage systems in which drug dispensing data of a well-defined population are linked to a registry of hospital discharge diagnoses and various other registries. Most healthcare services, including pharmaceutical services, are provided for, or subsidised by, the state in Italy and the UK and covered by obligatory health insurance in the Netherlands (NL) and turnover is low. In all of the countries with GP databases, GPs function as ‘‘gatekeepers’’ of the healthcare system.

All these databases have been previously used together for signal detection[10] and confirmation studies.[11] Overall, these databases cover approximately 27 million European citizens during an observation period ranging from 1996 to 2011 (Table 1). All database holders obtained ethical approval from their respective ethics committees and ensured that use of patient data for this study complies with European directives and national regulations, as well as local database governance rules regarding ethical and legal conduct.

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
IPCI	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
PHARMO			•	•	•	•	•	•	•	•	•	•	•	•	•	
THIN	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
HSD					•	•	•	•	•	•	•	•	•	•	•	•
Tuscany								•	•	•	•	•	•	•	•	•
Lombardy					•	•	•	•	•	•	•	•	•			

Table 1. *Availability of follow-up years in different healthcare databases (at 28/02/2012)*

All the main characteristics of the databases are summarised in **Table 2**.

CHARACTERISTICS	**HSD** (IT)	**Lombardia** (IT)	**Toscana** (IT)	**IPCI** (NL)	**PHARMO** (NL)	**THIN** (UK)
Current source population	1 500 000	9 000 000	3 500 000	1 100 000	4 000 000	9 000 000
Type of database	Medical records	Administrative	Administrative	Medical records	Hybrid (administrative and medical record/registries)	Medical records
Age range	From 15 onwards	All ages	All ages	All ages	All ages	All ages
% Males	47.2	48.8	48.1	49.6	45.8	47.8
DEMOGRAPHIC INFORMATION AVAILABLE						
Date of registration	Yes	Yes	Yes	Yes	Yes	Yes
Date of transferring out	Yes	Yes	Yes	Yes	Yes	Yes
Date of birth	MM-YY	DD-MM-YY	DD-MM-YY	MM-YY	YYYY	
Sex	Yes	Yes	Yes	Yes	Yes	Yes
DRUG INFORMATION AVAILABLE						
Date of prescription/dispensing	Yes	Yes	Yes	Yes	Yes	Yes
Dosing regimen and quantity	Yes	No	No	Yes	Yes	Yes
Indication of use	Yes	No	No	Yes	No	Yes
OUTCOME INFORMATION AVAILABLE						
Outpatient primary care diagnoses	Yes Free text/codes	No	No	Yes, as free text/codes	No	Yes
Outpatient specialist care diagnoses	Yes	No	No	Yes	No	Yes
Hospital discharge diagnoses	Yes, as free text /codes	Yes	Yes	Yes, as free text /codes	Yes	Yes
Diagnosis coding scheme	ICD-9CM	ICD-9CM	ICD-9CM	ICPC	ICD-9CM	READ
Diagnostic or laboratory procedures	Yes, some	Yes, some	Yes, some	Yes, some	Yes, some, mainly surgical and if occurring during hospital admission	Yes, some

***Table 2**. Characteristics of the databases participating in the project*

3.3. DISTRIBUTED NETWORK

A distributed network approach will be adopted for this signal strengthening study. To ensure homogeneous data extraction before data pooling we will use custom-built software Jerboa©. Jerboa© uses flat text files as input and is written entirely in Java™ to ensure that it will run in all operating systems. This software was developed within the EU-ADR project (www.euadr-project.org) and has been used in other EU-funded projects (i.e., SOS: www.sos-nsaids-project.org; and VAESCO: www.vaesco.net). In these projects the Jerboa© software has been evaluated by comparing the Jerboa© outputs for drug utilisation and case control study with the output generated by expert epidemiologists using SAS. The results obtained through Jerboa© were consistent with the results generated through the use of SAS software for data management and analyses.

Using the distributed network approach, standardised input files are created locally by each database. These common input files (patient, drug, and event files) are subsequently managed by Jerboa©, which aggregates, de-identifies and sends the results in encrypted format to a central repository for evaluation and further analysis. This repository is managed by the Department of Medical Informatics at Erasmus Medical Center in the Netherlands, the database network's coordinating centre. A detailed description of the distributed data processing can be found in an earlier publication.[10] The adaptation of this software to the needs of this project will be described in detail in the following deliverables.

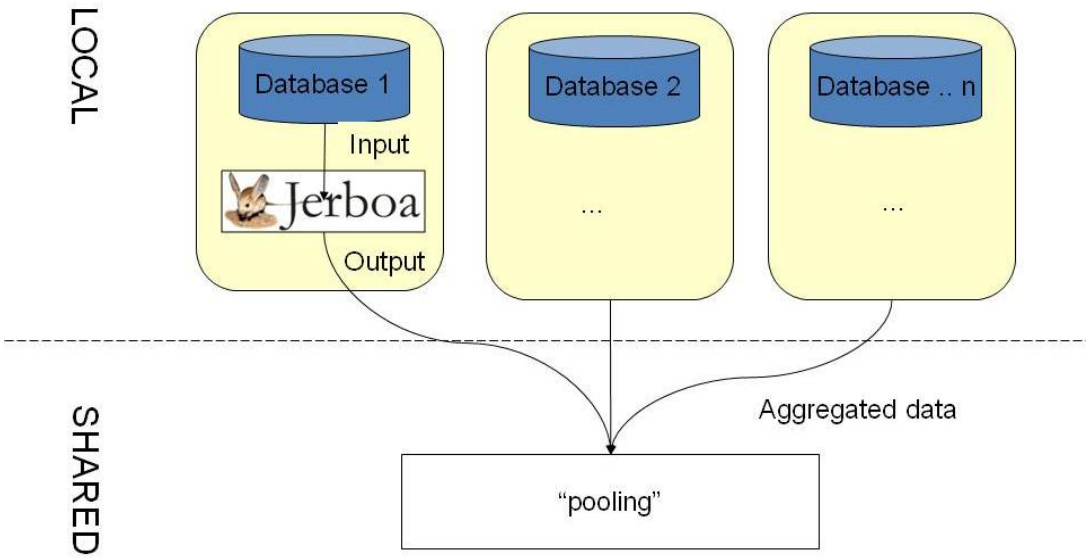

Figure 1. *Jerboa model for distributed computing on databases*

3.4. COHORT DEFINITION AND FOLLOW-UP TIME

The source population of this study will be represented by all the subjects who are registered in the databases participating in the study. All the subjects of any age with at least one year of data available in the database will be included in the study. All the subjects who received any time prior or during the study period at least one prescription of drugs, which may cause fibrosis (pergolide, cabergoline, amiodarone, fenfluramine, dexfenfluramine, and phentermine), as well as those patients with history of cardiac valve replacement, valvulopathy, rheumatic heart disease, carcinoid syndrome, endocarditis, and acromegaly prior to the study entry will be excluded from the study.

All the subjects will be followed starting from one year after the date of registration in the database (to characterise the subjects) until one of the following dates, whichever is earlier: a) date the patient transfers out of the system: b) the last supply of data; c) the patient's death. The follow-up for each patient will be also automatically censored upon the occurrence of the study outcome, as defined below.

3.5. CASE IDENTIFICATION

Potential cases of cardiac valve disorders in the database network will be identified using database-specific coding algorithms that utilise different disease coding terminologies: (1) International Classification of Primary Care (ICPC) for IPCI (2) International Classification of Diseases 9th revision-Clinical Modification (ICD-9CM for diagnosis and procedures) for SISR Lombardia, SISR Toscana, HSD, and PHARMO; and (3) READ CODE Classification (RCD) for THIN. The process of mapping of event data extraction from the different databases will be based on medical concepts derived from the Unified Medical Language System (UMLS)[12] and will be adopted from the process previously described in other publications.[13-14] Only incident events will be considered. Due to possible delay in hospitalisation after the first onset of symptoms, in claims databases, the first inpatient diagnosis or relevant inpatient procedure will be considered to be an event, but date of event will be assigned to a previous moment in time, according to specific outpatient healthcare services.

Three different case definitions will be developed and analysed, as listed below, from the most sensitive to the most specific:

a. Any cardiac valve disorder
b. Cardiac valve regurgitation (i.e. insufficiency, backflow, incompetence), of any valve
c. Cardiac valve calcification, of any valve

Whenever possible, valve-specific disorders will be investigated.

The final mapping results for all these different definitions will be provided in the deliverable of the final protocol for the strengthening study.

In Table 3, the mapping results for cardiac valve disorder as a whole (from SOS study), cardiac valve regurgitation (from the EU-ADR project) and cardiac valve calcification are reported.

Outcome	UMLS CUI	Preferred term	ICD9CM	ICPC	RCDv3
CARDIAC VALVE DISORDERS	C0340400	Functional pulmonary regurgitation			X201N
	C0340395	Pulmonary stenosis, non-rheumatic		K83010	G5431
	C0344408	Pulmonary valve stenosis with doming			X778D
	C0344409	Pulmonary valve stenosis with narrow jet			X778E
	C0348604	Other pulmonary valve disorders			Gyu58
	C0349076	Pulmonary valve stenosis with insufficiency			G5434
	C0344979	Acquired atresia of pulmonary valve			X77zb
	C0344980	Muscular pulmonary atresia			X77zc
	C0344973	Commissural fusion of pulmonary valve			X77zT
	C0344974	Pulmonary valve dysplasia, Mucoid thickening of pulmonary valve			X77zU
	C0344981	Pulmonary valve prolapsed			X77ze
	C0340383	Tricuspid stenosis, non-rheumatic			G5421
	C0340384	Tricuspid stenosis, cause unspecified			G1403
	C0003502	Nonrheumatic aortic valve disorders			
	C0003507	Aortic valve stenosis		K83006	X2011
	C0238669	Aortic root dilatation			X778h
	C0340377	Aortic incompetence, non-rheumatic			G5410
	C0344404	Aortic cusp regurgitation			X777a
	C0345003	Aortic valve cusp prolapsed			X7801
	C0340371	Aortic stenosis alone, cause unspecified			G5413
	C0340372	Aortic stenosis, non-rheumatic			G5411
	C0340375	Subaortic stenosis			P6y0.
	C0344401	Aortic stenosis with doming			X777W
	C0349516	Isolated aortic stenosis			Xa0Ct
	C0345044	Localised supravalvar aortic stenosis			X780Z
	C0345045	Diffuse supravalvar aortic stenosis			X780a
	C0348602	Other aortic valve disorders			Gyu56
	C0344991	Commissural fusion of aortic valve			X77zn
	C0344993	Aortic valve dysplasia, Mucoid thickening of aortic valve			X77zp
	C0348606	Aortic valve disorders in diseases classified elsewhere			Gyu5A

Outcome	UMLS CUI	Preferred term	ICD9CM	ICPC	RCDv3
	C0428792	Aortic valve fibrosis			X777d
	C0428794	Commissural fusion of aortic cusp			X777g
	C0428795	Bicuspid doming of aortic cusp			X777h
	C0428796	Senile sclerosis of aortic cusp			X777i
	C0264880	Chronic valvulitis			G54z2
	C0494590	Nonrheumatic mitral valve disorder, unspecified			
	C0264885	Myxoid transformation of mitral valve			X200z
	C0340362	Non-rheumatic mitral regurgitation			G5400
	C0340363	Mitral incompetence, cause unspecified			G5401
	C0238414	Mitral papillary muscle rupture			XE0VC
	C0340366	Mitral chordae rupture			XE2bE
	C0340367	Mitral papillary muscle dysfunction			XE0VE
	C0264667	Papillary muscle disorder			G5yy4
	C0264669	Papillary muscle atrophy	429.81		G5yy0
	C0264670	Papillary muscle degeneration	429.81		G5yy1
	C0264671	Scarring of papillary muscle	429.81		G5yy3
	C0340369	Functional mitral regurgitation			X200y
	C0344407	Mitral cusp prolapsed, Mitral leaf prolapse			X777q
	C0349521	Mitral valve anterior leaflet prolapsed			Xa0D0
	C0348601	Other non-rheumatic mitral valve disorders			Gyu55
	C0349075	Non-rheumatic mitral valve stenosis			G113.
	C0428809	Mitral sub-valve apparatus fibrosis			X7784
	C0265850	Fused commissures of mitral valve	746.5		P651.
	C0340361	Mitral restenosis			X200s
	C0349075	Non-rheumatic mitral valve stenosis		K83007	G113.
	C0348579	Other mitral valve diseases	394.9		Gyu10
	C0340383	Tricuspid stenosis, non-rheumatic			G5421
	C0340384	Tricuspid stenosis, cause unspecified			G1403
	C0348581	Other tricuspid valve diseases			Gyu12
	C0348582	Other multiple valve diseases			Gyu13
	C0348871	Disorders of both aortic and tricuspid valves			G5440
	C0348872	Disorders of both mitral and tricuspid valves			G5441
	C0348873	Combined disorders of mitral, aortic and tricuspid valves			G5442

Outcome	UMLS CUI	Preferred term	ICD9CM	ICPC	RCDv3
	C0340335	Mitral and aortic stenosis			G130.
	C0155572	Stenosis of mitral valve and aortic valve	396.0		
	C0003504	Aortic Valve Insufficiency		K83001, K83002	X2017
	C0026266	Mitral Valve Insufficiency		K83004	XE0Ux
	C0040961	Tricuspid Valve Insufficiency	397.0	K83012	XM00K
	C0034088	Pulmonary Valve Insufficiency	424.3		X201L, G5430
	C0026265	Diseases of mitral valve	394.9, 424.0		XE0UY, G11z., G540z
	C1260873	Aortic valve disorder	424.1, 395		G541z
	C0264774	Mitral and aortic incompetence	396.3		G133.
	C0264772	Mitral valve stenosis and aortic valve insufficiency	396.1		G131.
	C0865655	Aortic valve insufficiency NOS of specified cause, except rheumatic	424.1		
	C0340341	Incompetence of unspecified heart valve			G54z0
	C0375259	Mitral and aortic valve disease	396, 396.9		G13.., G13z.
	C0155576	Multiple mitral and aortic valve involvement	396.8		G13y.
	C1306822	Mitral valve insufficiency and aortic valve stenosis	396.2		G132.
	C0865572	Mitral valve stenosis with incompetence or regurgitation	394.2		
	C0340373	Senile aortic stenosis , aortic stenosis with tricuspid calcification			X2015
	C0349523	Calcific aortic stenosis - bicuspid valve			X2013
	C0428791	Aortic valve calcification			X777c
	C0428810	Mitral sub-valve apparatus calcification			X7785
	C0428811	Mitral valve annular calcification			X7786
CARDIAC VALVE REGURGITATION	C0003504	Aortic Valve Insufficiency		K83001, K83002	X2017
	C0026266	Mitral Valve Insufficiency		K83004	XE0Ux
	C0040961	Tricuspid Valve Insufficiency	397.0	K83012	XM00K
	C0034088	Pulmonary Valve Insufficiency	424.3		X201L, G5430
	C0026265	Diseases of mitral valve	394.9, 424.0		XE0UY, G11z., G540z
	C1260873	Aortic valve disorder	424.1, 395		G541z

Outcome	UMLS CUI	Preferred term	ICD9CM	ICPC	RCDv3
	C0264774	Mitral and aortic incompetence	396.3		G133.
	C0264772	Mitral valve stenosis and aortic valve insufficiency	396.1		G131.
	C0865655	Aortic valve insufficiency NOS of specified cause, except rheumatic	424.1		
	C0340341	Incompetence of unspecified heart valve			G54z0
	C0375259	Mitral and aortic valve disease	396, 396.9		G13.., G13z.
	C0155576	Multiple mitral and aortic valve involvement	396.8		G13y.
	C1306822	Mitral valve insufficiency and aortic valve stenosis	396.2		G132.
	C0865572	Mitral valve stenosis with incompetence or regurgitation	394.2		
CARDIAC VALVE CALCIFICATION	C0340373	Senile aortic stenosis , aortic stenosis with tricuspid calcification			X2015
	C0349523	Calcific aortic stenosis - bicuspid valve			X2013
	C0428791	Aortic valve calcification			X777c
	C0428810	Mitral sub-valve apparatus calcification			X7785
	C0428811	Mitral valve annular calcification			X7786

Table 3. *Mapping of cardiac valve regurgitation in the EU-ADR project*

LEGEND

CUI= Concept Unique Identifier; **UMLS**=Unified Medical language System; **ICD9CM**= International Classification of Diseases 9th revision-Clinical Modification; **ICPC**= International Classification of Primary Care; **RCDv3**=Read code version 3

Case validation using manual review of hospitalisation charts and medical records will be done, if possible, in all databases only for the subsequent hypothesis testing study.

3.6. DRUG EXPOSURE

The exposure of interest concerns the bisphosphonates. The following bisphosphonates, as monotherapy or combinations, will be considered in the study: a) etidronic acid (ATC: M05BA01); b) clodronic acid (ATC: M05BA02); c) pamidronic acid (M05BA03); d) alendronic acid (M05BA04); d) tiludronic acid (M05BA05); e) ibandronic acid (M05BA06); f) risedronic acid (M05BA07); g) zoledronic acid (M05BA08); h) etidronic acid and calcium (M05BB01); i) risedronic acid and calcium (M05BB02); l) alendronic acid and colecalciferol (M05BB03); and m) alendronic acid, calcium and colecalciferol. Other bisphosphonates for which an ATC code is not available will be explored as well (incadronate, medronate, minodronate, neridronate, olpadronate, oxidronate). These drugs have been identified as possibly associated with cardiac valve disorder in EudraVigilance and can be captured in EU-ADR Alliance database network.

Drug prescription and/or dispensing data will be used to evaluate the drug exposure to bisphosphonates. Drug prescriptions and dispensings in the databases are locally coded using the national product codes, which differ among countries but these product codes are linked to the World Health Organisation's (WHO) Anatomical Therapeutic Chemical (ATC) classification system.[15] Only THIN uses different coding scheme for drugs (British National Formulary/Multilex codes) which may be mapped to ATC however.

Using national product codes, it will be possible to distinguish between oral and intravenous formulations of bisphosphonates. In some databases intravenous administration might not be recorded; an estimate of exposure misclassification will be provided and possible impact on signal detection will be estimated through a sensitivity analysis.

Each database will estimate the duration covered by each prescription/ dispensing according to the legend duration (if dosing regimen is available), or will otherwise be based on the defined daily dose (DDD).[16] Overlapping treatment episodes with the same drug (same ATC code) are combined into a single episode of drug use that starts when the first prescription begins and stops when the last prescription ends. When a patient uses more than one drug at a time, the corresponding person-time is labelled accordingly. Using individual data on start date and end date of prescription or dispensing, Jerboa© determines and marks as unexposed those periods during which an individual is included in the study but is not using any drug. In line with previous publications that investigated drug-induced valve disorders using databases,[11, 17] a carry-over period of six (6) months will be included for each prescription due to possible induction time of the adverse event and the delay in the registration of the event.

Exposure definition and classification will be more into detail described in the following deliverables.

3.7. PRIMARY STATISTICAL ANALYSIS

3.7.1. Main analysis

Through data mining techniques any association of individual bisphosphonates and each outcome definition will be explored, quantified and characterised in the EU-ADR Alliance

database network. Various statistical methods have previously been evaluated in EU-ADR project for this purpose and in this study a combination of the best performing methods, as listed below, will be applied to data pooled from all six databases. Any divergent result from different analyses will be explored in depth.

a. **Incidence Rate Ratio (IRR)** is calculated as the ratio between the incidence rate during exposure to the drug compared to a background incidence rate. A Mantel-Haenszel test is used to test the differences between the incidence rates, typically correcting for age and sex. Events are assigned to exposure if they occur during the exposure duration.
b. **Longitudinal Gamma Poisson Shrinker (LGPS)**. LGPS is an adaptation of the GPS method (developed for use in spontaneous reporting databases) to longitudinal data. It applies Bayesian shrinkage to the incidence rate ratio (ratio between the incidence rate during exposure to the drug compared to a background incidence rate.) LGPS was developed in the EU-ADR project.[18]
c. **Automated Matched Case Control Method**. For every potential case identified, a predefined number of controls will be matched to the same age and sex. For both cases and controls, the exposure to the drug will be determined at the time of event (also known as the index date). A conditional logistic regression will be performed to determine the exposure odds ratio. To adjust for comorbidity and overall patient health status we will employ as proxy the 'drug count,'[19] which is the number of different drugs (chemical substance level, ATC codes) the patient was exposed to within one year prior to the event date, until one month prior to the event date.

Various parameter settings on the exposure window will be used as initial signal strengthening in each of the databases. For the association between bisphosphonates and cardiac valve disorders we assume that cumulative, rather than acute, exposure determines the hazard function since calcification will take time to occur. Consistency of the association measures across databases will be an important parameter in signal strengthening; the estimates will be pooled across the databases assuming random effects.

It has been previously shown that the potential for healthcare data-based surveillance systems can be maximised in the detection of safety signals associated with relatively frequent events (such as acute myocardial infarction) and that a greater amount of drug exposure would have to be present in the databases to enable detection of signals concerning rare events (such as rhabdomyolysis).[20] In addition to evaluating the feasibility of the conduct of the subsequent hypothesis-testing study for each outcome definition, the statistical power of the database network will be estimated based on empirically-derived incidence rates of the outcome and amount of exposure data of bisphosphonates available in the databases.

3.7.2. Sub-group analyses

Examination of Age and Sex Effects

The objective of these sub-analyses is to determine whether there is an interaction between age (≥ or < 65 years) and sex and the valvulopathy risk associated with the use of bisphosphonates. In particular, a study[1] showed different effects of BPs in younger and older patients with respect to valvular and vascular calcification.

Effect of Dosage and Duration of Use

The objective of these sub-analyses is to determine the effect of dosage and the length of treatment with the individual study drugs on the risk of cardiac valve disorder. In these analyses we will explore and quantify the association between each study outcome and different dosages [i.e. ≥ or < 1 Defined Daily dose (DDD)] and durations of use (≥ or < 180 days of cumulative exposure) of individual bisphosphonates.

Dosage and duration effects will be further evaluated in the confirmation study.

Effect of route of administration

The objective of these sub-analyses is to determine the effect of the route of administration of the study drugs on the risk of cardiac valve regurgitation. The association of bisphosphonates and the study outcomes will be also explored for intravenous and oral formulations, separately, whenever possible. ARS database will conduct an exploratory analysis to quantify how much each bisphosphonate (as oral or injectable formulation) is prescribed in hospital and as a consequence cannot be captured in EU-ADR Alliance databases.

Effect of indication of use

A subgroup analysis will be conducted stratifying the users of bisphosphonates by indication of use. An algorithm will be developed to distinguish the indication of use for bisphosphonates in each database.

Timing of signal detection

Whenever an association between each outcome definition and individual drugs is identified, we will investigate at which first point in time this network would have been able to detect such an association by conducting stratified analysis by quarter of years. This analysis is aimed towards further exploring the possible role of this database network in signal detection/strengthening.

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