Study Report P2-C1-001

08/11/2023

Version 3.0

TABLE OF CONTENTS

DOCUMENT HISTORY

Version	Date	Description
V1.1	**02/10/2023**	**Final version for EMA review**
V2.0	**30/10/2023**	**Second version for EMA review**
V3.0	**08/11/2023**	**Final version for archiving**

Study Title	DARWIN EU® - Multiple myeloma: patient characterisation, treatments and survival in the period 2012-2022
Study Report Version identifier	3.0
Dates Study Report updates	08/11/2023
EU PAS register number	EUPAS105033
Active substance	N/A
Medicinal product	N/A
Research question and objectives	The overall objective of this study is to characterise patients with multiple myeloma diagnosed in the period 2012-2022. The specific objectives of this study are: 1. To describe demographic and clinical characteristics of patients with multiple myeloma at the time of diagnosis. 2. To describe multiple myeloma treatments (including combinations and regimen types, e.g. induction, maintenance, etc.). 3. To describe multiple myeloma treatment sequences. 4. To estimate the overall survival of incident multiple myeloma patients during the study period (2012-2022). All results will be reported by country/database, overall and stratified by age and sex when possible.
Country(-ies) of study	Estonia, France, Germany, Spain, The Netherlands
Author	Talita Duarte-Salles (tduarte@darwin-eu.org); Daniel Prieto-Alhambra (d.prietoalhambra@darwin-eu.org)

1. DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
Study Project Manager/Principal Investigator	Talita Duarte-Salles Daniel Prieto-Alhambra	Erasmus MC Erasmus MC/University of Oxford
Epidemiologist	Talita Duarte-Salles Katia Verhamme	Erasmus MC Erasmus MC
Clinical Domain Expert	Daniel Prieto-Alhambra	Erasmus MC/University of Oxford
Data Analysts/programmers	Maarten van Kessel Ross Williams Edward Burn	Erasmus MC Erasmus MC University of Oxford
Data Partner*	**Names**	**Organisation – Database**
Local Study Coordinator/Data Analyst	James Brash Jasmine Gratton Dina Vojinovic Núria Mercadé Miguel-Angel Mayer Angela Leis Juan Manuel Ramirez Raivo Kolde Romain Griffier Peter Prinsen	IQVIA - DA Germany IQVIA - DA Germany IQVIA - DA Germany IDIAPJGol - SIDIAP PSMAR - IMASIS PSMAR - IMASIS PSMAR - IMASIS University Tartu - Estonian Biobank University of Bordeaux - CDWBordeaux Netherlands Cancer Registry - NCR

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role.
Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

2. DATA SOURCES

This study was conducted using routinely collected data from 6 databases in 5 European countries. All databases were previously mapped to the OMOP CDM.

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
4. Estonian Biobank, Estonia
5. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
6. Netherlands Cancer Registry (NCR), The Netherlands

Detailed information on data source is described below.

Country	Name of Database	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	End of calendar period covered
DE	IQVIA DA Germany	Primary care and outpatient specialist care	EHR	8.5 million	31/12/2022
ES	SIDIAP	Primary care with hospital linkage	EHR	5.8 million	31/12/2022
ES	IMASIS	Secondary care (in and outpatients)	EHR	0.6 million	31/12/2022
ET	EBB	Biobank	Claims	0.2 million	31/12/2021
FR	CWDBordeaux	Secondary care (in and outpatients)	EHR	1.9 million	10/04/2023
NL	NCR	Cancer registry	Registry	3.5 million	31/03/2023 with incident cancer patients included up to 01/01/2022

DE = Germany, EBB = Estonian Biobank, ES = Spain, ET = Estonia, FR = France, NL = The Netherlands, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IMASIS = Institut Municipal Assistencia Sanitaria Information System, DA = Disease Analyzer, CWDBordeaux = Clinical Data Warehouse of Bordeaux University Hospital, NCR = Netherlands Cancer Registry.

3. ABSTRACT

Title

DARWIN EU® - Multiple myeloma: patient characterisation, treatments and survival in the period 2012-2022.

Rationale and Background

Multiple myeloma is a rare type of blood cancer with an estimated overall crude and age-standardized incidence rates of 6.8 and 2.9 per 100,000 persons in 2020 in Europe, respectively (IARC – Cancer Today).

Survival rates have improved due to the better management of the disease and the development in recent years of new medicines such as immunomodulatory agents, proteasome inhibitors and monoclonal antibodies. However, there is still unmet need for new medicines for patients who do not respond to existing therapies.

The rarity of multiple myeloma makes it challenging to have a clear picture across Europe of the characteristics of these patients at the time of diagnosis, the different therapies they receive in subsequent lines and their overall survival. The goal of this study was to inform these aspects, which are important from a regulatory point of view to provide context and help understand the added value of the newest medicines under development or recently approved.

Research question and Objectives

The overall objective of this study was to characterise patients with multiple myeloma diagnosed in the period 2012-2022.

The specific objectives of this study were:

1. To describe demographic and clinical characteristics of patients with multiple myeloma at the time of diagnosis.
2. To describe multiple myeloma treatments (including combinations and regimen types, e.g. induction, maintenance, etc.).
3. To describe multiple myeloma treatment sequences.
4. To estimate the overall survival of incident multiple myeloma patients during the study period (2012-2022).

All results are reported by country/database, overall and stratified by age and sex when possible.

Research Methods

Study design

Population-based cohort study.

Population

The study population included all individuals identified in the contributing databases between 01/01/2012 and 31/12/2022 with a first diagnosis of multiple myeloma. Participants with a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma were excluded.

Additional eligibility criteria were applied for each study objective: cohort 1) at least 365 days of prior history available before date of multiple myeloma diagnosis (=index date) was applied for large-scale characterisation (objective 1), cohort 2) a minimum follow-up time of 30 days was applied to capture cancer treatment (objective 2) and treatment sequences (objective 3), and, cohort 3) a minimum of 1 year of potential follow-up time was imposed for the survival analyses (objective 4).

Variables

Two main outcomes of interest were studied: treatment/s initiated at index date, 1 to 30, 1 to 90 and/or 1 to 365 days post index date, and death. For the former, a pre-specified list of multiple myeloma treatments was generated (Objectives 2-3). Overall survival in patients with incident multiple myeloma was also calculated based on the registered date of death.

All co-morbidities and co-medications were used for large-scale patient characterisation, identified as concept/code and descendants. A list of pre-specified co-morbidities and co-medications was also described.

Data sources

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
4. Estonian Biobank, Estonia
5. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
6. Netherlands Cancer Registry (NCR), The Netherlands

Sample size

No sample size was calculated as this is a descriptive Disease Epidemiology Study where we were interested in the characteristics of all incident multiple myeloma patients.

Data analyses

Large-scale patient-level characterisation was conducted (objective 1) as follows: Age and sex at time of multiple myeloma diagnosis were described for each of the generated study cohorts; Medical history was assessed for anytime –and up to 365 days before index date, for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date; Medication use history was reported for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. We also reported medication use for 1 to 30, 1 to 90, and 1 to 365 days post index date.

The number and % of patients receiving each of a pre-specified list of multiple myeloma treatments (see Appendix 1) and treatment combinations (objective 2) were described at index date, 1 to 30, 1 to 90, and 1 to 365 days post index date. When available, treatment regimen types were described. Additionally, sunburst plots and Sankey diagrams were used to describe treatment sequences over time (objective 3).

Overall survival (objective 4) was calculated using data on time at risk of death from any cause and the Kaplan-Meier method. Results were reported as plots of the estimated survival curves as well as the estimated probability of survival at years 1, 3, and 5.

For all analyses n and % were reported. A minimum cell count of 5 was used when reporting results, with any smaller counts reported as "<5" or "0". All analyses were reported by country/database, overall and stratified by age and sex when possible (minimum cell count reached). Additionally, in order to capture treatments availability and survival changes over time, sunburst plots, Sankey diagrams and KM curves were further stratified by study periods (2012-2017 and 2018-2022).

Results

Large-scale characterisation

We provided large-scale characterisation for a total of 12,207 individuals (Cohort 1). Overall, the most frequent co-morbidities were hypertension, renal impairment, hyperlipidemia, osteoarthritis, urinary tract

infection, diabetes mellitus, and obesity. There were variations in the frequency of these conditions per database (e.g.: at index, hypertension was present in 27% of cases in SIDIAP vs 48% of cases in IQVIA DA Germany), however, the ranking of most and least frequent co-morbidities was similar (e.g.: at index, hypertension was the second most frequent co-morbidity in SIDIAP vs the first most frequent co-morbidity in IQVIA DA Germany). These results were similar when stratified by sex, but differed by age groups. The most common co-morbidities in younger age groups (18-59 years) also included anxiety, depression, and asthma, while renal impairment was one of the most frequent co-morbidities among those aged >=70 years.

As for medications, the most frequent medications were drugs for acid-related disorders, agents acting on the renin-angiotensin system, lipid-modifying agents, opioids and psycholeptics. The least frequent medications were antipsoriatics and psychostimulants. Medication use was similar in time windows prior to index date (anytime, up to 365 days, for 365 to 31 days, and for 30 to 1 day before index date) in most databases, while in post index periods an increase in frequency and number of medicines was observed. This was particularly observed in those databases with available information on cancer treatment. These results were similar by sex, but differed by age groups. Overall, medication use was more frequent in older age groups consistently across databases and time periods; with the exception of antineoplastic agents post index that was more frequently used in younger age groups.

Multiple Myeloma Treatments

13,258 individuals were included in Cohort 2 which was used to summarise multiple myeloma treatments. 18 out of the 32 pre-specified multiple myeloma treatments were ever used in the studied databases among individuals from 2012 to 2022. The most frequently used class of treatment in the year following diagnosis were glucocorticoids, with their use ranging from 50% to 63% across databases. Dexamethasone and prednisone were the most commonly used glucocorticoids. In the databases where their use was captured, use of proteasome inhibitors (PIs) ranged from 46% to 57% in the year following diagnosis. Meanwhile, over the same time period, use of chemotherapies ranged from 18% to 46%, use of immunomodulatory agents (IMiDs) ranged from 2% to 35%, and use of monoclonal antibodies ranged from 5% to 17%.

Use of treatments were similar when results were stratified by sex, but varied across age groups. In particular, both IMiDs and PIs were consistently seen to be used less in older individuals. However, while in one database (CDWBordeaux) those aged 70 or over were less frequently treated with chemotherapies, in another (NCR) this age group were in fact more frequently treated with chemotherapies.

Treatment sequences were described only in CDWBordeaux, where we found that the most common sequences of treatment were only Melphalan (27%), followed by the sequence Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan (7%), Daratumumab alone (6%), and the sequence Prednisone-Melphalan-Bortezomib (5%).

Survival

From 17,333 individuals in cohort 3, 7,981 (46%) died during the study period.

Overall, the median survival ranged from 4.8 years in IMASIS to 8.4 years in EBB. The 1-year survival probability (95%CI) ranged from 0.79 (0.74 to 0.84) in IMASIS to 0.92 (0.91 to 0.94) and 0.92 (0.87 to 0.98) in CDWBordeaux and EBB, respectively. The 3-year survival ranged from 0.62 (0.56 to 0.69) in IMASIS to 0.84 (0.82 to 0.86) in CDWBordeaux. The 5-year survival ranged from 0.49 (0.42 to 0.58) in IMASIS to 0.78 (0.75 to 0.81) in CDWBordeaux.

Survival was similar among females and males, and it decreased with older age, with survival among the age group of individuals of >=70 years of age being the lowest.

We estimated overall survival by study period: 2017 or earlier vs 2018 or later. The 1- and 3-year survival were similar between periods for most databases. In IMASIS, however, we observed a 1- and 3-year survival probability of 0.75 (0.69 to 0.83) and 0.55 (0.46 to 0.64), respectively, in 2017 or earlier, which increased to 0.83 (0.77 to 0.90) and 0.74 (0.65 to 0.83) in 2018 or later.

Discussion

In this study we provided a characterisation of 30,319 patients newly diagnosed with multiple myeloma in between 2012 and 2022 across Europe. The most frequently reported co-morbidities at and prior to the date of diagnoses were hypertension, renal impairment, hyperlipidemia, osteoarthritis, urinary tract infection, diabetes mellitus, and obesity, while the most frequent medications were drugs for acid related disorders, agents acting on the renin-angiotensin system, lipid modifying agents, opioids and psycholeptics.

Regarding multiple myeloma treatments, the most frequently used class of treatment in the year following diagnosis were glucocorticoids, followed by PIs, chemotherapies and IMiDs. Treatment sequences were described in CDWBordeaux, where the most common treatment sequences observed were only Melphalan, followed by Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan, Daratumumab, and Prednisone-Melphalan-Bortezomib. Overall, no difference in treatment was observed by sex, while IMiDs and PIs were consistently used less in older individuals.

The observed 5-year survival estimates were 0.49 (0.42 to 0.58) in IMASIS, 0.65 (0.64 to 0.66) in NCR, and 0.69 (0.67 to 0.7) in SIDIAP. Survival estimates were higher for CDWBordeaux and EBB, with 5-year survival estimates of 0.78 (0.75 to 0.81) and 0.76 (0.67 to 0.86). Survival probabilities were consistently similar by sex, but varied substantially by age groups, with a decrease in survival observed with older age.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
ADHD	Attention Deficit Hyperactivity Disorder
ASCT	Autologous Stem Cell Transplant
CAR	Chimeric Antigen Receptors
CDM	Common Data Model
CDWBordeaux	Clinical Data Warehouse of Bordeaux University Hospital
COPD	Chronic obstructive pulmonary disease
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DOI	Declaration Of Interests
EBB	Estonian Biobank
EGCUT	Estonian Genome Center at the University of Tartu
EHR	Electronic Health Records
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
GERD	Gastro-esophageal reflux disease
GP	General Practitioner
IMASIS	Institut Municipal Assistència Sanitària Information System
IMiDs	Immunomodulatory agents
MGUS	Monoclonal Gammapathy of Unknown Significance
NCR	Netherlands Cancer Registry
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PI	Proteasome Inhibitors
PSMar	Parc Salut Mar
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SINE	Selective inhibitors of nuclear export
SNOMED	Systematized Nomenclature of Medicine

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
NA				

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Protocol	5th May 2023	5th May 2023
Final Study Protocol	1st June 2023	1st June 2023
Creation of Analytical code	June 2023	June-August 2023
Execution of Analytical Code on the data	July-August 2023	July-September 2023
Interim Study Report (if applicable)	Not applicable	Not applicable
Draft Study Report	September 2023	September 2023
Final Study Report	29th September 2023	29th September 2023
Revised Study Report		30th October 2023

7. RATIONALE AND BACKGROUND

Multiple myeloma is a hematologic malignancy that is characterized by the abnormal proliferation of plasma cells in the bone marrow with substantial morbidity and mortality. The most common presenting signs and symptoms of multiple myeloma are anemia, bone pain, renal impairment, fatigue, hypercalcemia, infection and weight loss(1). Globally, it accounts for approximately 1% of all cancer cases and 13% of hematologic malignancies. The incidence of multiple myeloma varies geographically, it is more common and rising in developed countries with the highest incidences in Asia, Europe, and North America. In Europe, the crude and age-standardized incidence rates of multiple myeloma were 6.8 and 2.9 per 100,000 persons in 2020, respectively, with a higher incidence observed in men than women and a median age at diagnosis of 72 years(2,3).

Survival rates of patients with multiple myeloma have improved in the past decades due to the better management of the disease and the development of new medicines such as immunomodulatory agents (IMiDs), proteasome inhibitors (PIs) and monoclonal antibodies(3). More recently, the approval of chimeric antigen receptors (CAR) T-cell therapies represents a promising immunotherapeutic approach in the treatment of advanced relapsed multiple myeloma(4).

To date, the standard treatment for multiple myeloma is largely dependent on patient health status, underlying co-morbidities, tumour stage and age at time of diagnosis. For those younger than 70 to 75 years and no co-morbidities, the preferred treatment comprises a triplet novel agent regimen, typically including an IMiD and PI in combination with glucocorticoids, followed by autologous stem cell transplant (ASCT) and maintenance therapy with low-dose IMiD or PI. Induction with novel agents and low-dose maintenance therapy is recommended for those patients unable to undergo ASCT(3,5). However, there is still unmet need for new medicines for patients who do not respond to existing therapies.

The rarity of multiple myeloma makes it challenging to have a clear picture across Europe of the characteristics of these patients at the time of diagnosis, the different therapies they receive in subsequent lines and their overall survival. The goal of this study was to inform these aspects, which are important from a regulatory point of view to provide context and help understand how new medicines may add value for patients.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this study was to characterise patients with multiple myeloma diagnosed in the period 2012-2022.

The specific objectives of this study were:

1. To describe demographic and clinical characteristics of patients with multiple myeloma at the time of diagnosis.
2. To describe multiple myeloma treatments (including combinations and regimen types, e.g. induction, maintenance, etc.).
3. To describe multiple myeloma treatment sequences.
4. To estimate the overall survival of incident multiple myeloma patients during the study period (2012-2022).

All results were reported by country/database, overall and stratified by age and sex when possible.

Table 1: Primary and secondary research questions and objective

Objective:	To describe demographic and clinical characteristics, treatments, treatment sequences, and overall survival of patients with incident multiple myeloma, stratified by age, sex, and country/database.
Hypothesis:	N/A
Population *(mention key inclusion-exclusion criteria):*	All individuals with a first diagnosis of multiple myeloma identified in the database between 01/01/2012 and 31/12/2022. Participants with a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma were excluded. Additional eligibility criteria were applied for each study objective: cohort 1) at least 365 days of prior history available before date of cancer diagnosis (=index date) were applied for large-scale characterisation (objective 1), cohort 2) a minimum follow-up time of 30 days were applied to capture cancer treatments (objective 2) and treatment sequences (objective 3), and cohort 3) a minimum of 1 year of potential follow-up time for the survival analyses (objective 4).
Exposure:	N/A
Comparator:	N/A
Outcome:	Two main outcomes of interest were studied: treatment/s initiated within 30, 90 and/or 365 days after diagnosis, and death. For the former, a pre-specified list of multiple myeloma treatments was generated (objectives 2-

	3). Overall, 1-, 3-, and 5-year survival in patients with multiple myeloma were also calculated based on the registered date of death (objective 4).
Time *(when follow up begins and ends):*	Follow-up started from date of first multiple myeloma diagnosis (index date) until the earliest of the following: 1) loss to follow-up, 2) end of data availability, or 3) date of death.
Setting:	Inpatient and outpatient setting from 6 databases in 5 European countries.
Main measure of effect:	Proportions and probability of survival

9. RESEARCH METHODS

9.1 Study Type and Study Design

This was a **patient-level characterisation** study classified as "off-the-shelf" (C1) and as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses. A population-based cohort study of all incident multiple myeloma cases was conducted.

Table 2. Description of Potential Study Types and Related Study Designs

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Patient-level characterisation	Cohort analysis.	Off-the-shelf (C1)

9.2 Study Setting and Data Sources

This study was conducted using routinely collected health data from 7 databases in 6 European countries. All databases were previously mapped to the OMOP CDM.

Data sources:

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
4. Estonian Biobank, Estonia
6. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
7. Netherlands Cancer Registry (NCR), The Netherlands

We selected 7 out of the 10 databases onboarded in DARWIN EU® in 2022. The selection of databases for this study was performed based on data reliability and relevance for the proposed research question. The selected databases fulfil the criteria required for a patient-level characterisation study allowing for large-scale characterisation, while covering different settings and regions of Europe.

Complete hospital-based cancer treatment data (needed for objectives 2 and 3) was available in all databases except SIDIAP and IQVIA DA Germany. In turn, any potential outpatient therapies (e.g. pain management for bone complications) was captured in these primary care datasets. Additionally, with the exception of IQVIA DA Germany, all databases have information on date of death (needed for objective 4).

The included databases also contain high quality data on multiple myeloma diagnosis. NCR is a national oncological hospital registry in the Netherlands which includes data from all cancer patients in the country since 1989 (https://iknl.nl/en/ncr). The IMASIS database is linked to the hospital registry of tumours which is one of the oldest hospital-based cancer registries in Spain (created in 1978).(6) The EBB database is also regularly linked to the national cancer registry.(7) In SIDIAP, the diagnosis of multiple myeloma has been

previously validated with a reported sensitivity of 80%(8). The diagnosis of multiple myeloma in French hospitals has also been validated with a reported sensitivity from 70-90%.(9)

Detailed information on the selected data sources and their ability to answer the study research questions are described in **Table 3**.

Table 3. Description of the selected Data Sources

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update	Ability to answer study objectives
DE	IQVIA DA Germany	Covers primary care setting with information on cancer diagnoses.	Primary care and outpatient specialist care	EHR	8.5 million	31/12/2022	1
ES	SIDIAP	Covers primary care setting, data on cancer diagnoses previously validated, data on date of death available.	Primary care with hospital linkage	EHR	5.8 million	31/12/2022	1, 4
ES	IMASIS	Covers secondary care setting, database has information on cancer treatment in the in- and outpatient settings, mortality and other outcomes for in-house patients.	Secondary care (in and outpatients)	EHR	0.6 million	31/12/2022	1, 2 and 4
ET	EBB	Contains information on 200,000 participants with not only genetic information but also health insurance claims, digital prescriptions, discharge information and causes of death through linkage with the national death register. Data is linked to cancer registry.	Biobank	Claims	0.2 million	31/12/2021	1, 2 and 4
FR	CWDBordeaux	Covers secondary care setting, database has information on cancer treatment, mortality and other outcomes for in-house patients.	Secondary care (in and outpatients)	EHR	1.9 million	10/04/2023	1 to 4
NL	NCR	Cancer registry data with high quality information on cancer diagnoses, mortality, and cancer treatment.	Cancer registry	Registry	3.5 million	31/03/2023 with incident cancer patients included up to 01/01/2022	2 and 4

DE = Germany, EBB = Estonian Biobank, ES = Spain, ET = Estonia, FR = France, NL = The Netherlands, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IMASIS = Institut Municipal Assistencia Sanitaria Information System, DA = Disease Analyzer, CWDBordeaux = Clinical Data Warehouse of Bordeaux University Hospital, NCR = Netherlands Cancer Registry.

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. IQVIA DA Germany is a stratified random sample. The sample is drawn due to the distribution of practices by region, specialty, and physician age groups in Germany. Due to data privacy reasons the database itself includes the regions West and East Germany.

Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to various medical practices, with the following distribution 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

Information System for Research in Primary Care (SIDIAP), Catalonia, Spain

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams, consisting of GPs, nurses and non-clinical staff(7). The Catalan Health Institute manages 328 out of 370 such Primary Care Teams with a coverage of 5.8M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 15 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

Institut Municipal Assistència Sanitària Information System (IMASIS), Barcelona, Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

Estonian Biobank (EBB), Estonia

The Estonian Biobank (EBB) is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT)(8). Its cohort size is currently close to 200,000 participants ("gene donors" ≥ 18 years of age), which closely reflects the age, sex and geographical distribution of the Estonian population. Estonians represent 83%, Russians 14%, and other nationalities 3% of all participants. Genomic GWAS analyses have been performed on all gene donors. The database also covers health insurance claims, digital prescriptions, discharge reports, information about incident cancer cases, and causes of death from national sources for each donor.

Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The Bordeaux University Hospital serves as the primary public health facility for the entire population of the Bordeaux metropolitan area. Additionally, it functions as a referral and expertise center for the Nouvelle Aquitaine region. The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death)(9).

Netherlands Cancer Registry (NCR), The Netherlands

The NCR compiles clinical data of all individuals newly diagnosed with cancer in the Netherlands. Cancer registration clerks register newly diagnosed cancer patients since 1989 on a national basis, with 3 million patients included. Over the past 30 years, this registry has provided clinicians and researchers with a wealth of clinical data (e.g., patient and tumour characteristics, primary treatment, outcome) on cancer patients of all ages. Specifically, it also comprises information on tumour staging (according to the TNM-classification developed and maintained by the Union for International Cancer Control (UICC)), tumour site (topography) and morphology (histology) (according to the WHO International Classification of Diseases for Oncology (ICD-O-3)), co-morbidity at diagnosis and treatment received directly after diagnosis (first line). Overall, patients are followed-up for less than one year, with the exception of death which is collected any time after diagnosis. See https://iknl.nl/en for more information.

9.3 Study Period

The study period was from 01/01/2012 to end of available data in each of the data sources (see **Table 3** for more details).

9.4 Follow-up

Study participants were followed up from their date of first multiple myeloma diagnosis (index date) until the earliest of the following: 1) loss to follow-up, 2) end of data availability, or 3) date of death. In the survival analysis, patients in 1) were censored at the time of loss to follow-up. Patients in 2) were administratively censored at end of data availability.

Table 4: Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics /validation	Source of algorithm
All patients with incident multiple myeloma eligible for the study	Date of incident multiple myeloma diagnosis	Single entry	Incident	Anytime prior to multiple myeloma diagnosis	IP, OP, OT	SNOMED	Any	Any cancer diagnosis except non-melanoma skin cancer	N/A	N/A

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

9.5 Study Population with inclusion and exclusion criteria

The study population included all individuals with a first diagnosis of multiple myeloma identified in the database between 01/01/2012 and 31/12/2022. Participants with a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma were excluded (see https://atlas-demo.ohdsi.org/#/conceptset/1866029/included for a complete list of codes).

Multiple myeloma is a malignant uncontrolled proliferation of plasma cells derived from one single clone. It can affect many organs, typically bones and calcium metabolism, kidneys, immune system, blood, and more rarely neurologic. Diagnosis is typically obtained after bone marrow biopsy, where plasma cells, monoclonal kappa or lambda light chains were present. The most important differential diagnosis is monoclonal gammapathy of unknown significance (MGUS) or 'smoldering multiple myeloma'. For this study, cases were identified based on a record indicating a diagnosis or observation of multiple myeloma. Conditions in the OMOP CDM use the Systematized Nomenclature of Medicine (SNOMED) as the standard vocabulary for diagnosis codes. A clinical description along with a preliminary code list is provided in **Appendix 1**. This list was previously developed to define multiple myeloma for the DARWIN EU® study EUPAS50800.

Additional eligibility criteria were applied for each study objective:

Cohort 1) for large-scale characterisation (objective 1), at least 365 days of prior history available before date of multiple myeloma diagnosis (=index date) was required. This is needed to ensure a minimum prior observation time to exclude prevalent cases and to identify individuals' characteristics (e.g., co-morbidities and drug history);

Cohort 2) for cancer treatments (objective 2) and treatment sequences (objective 3), a minimum follow-up time of 30 days was applied to allow time to capture treatments, and finally;

Cohort 3) for survival analysis (objective 4), a minimum of 1 year of potential follow-up time was required.

Table 5. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics /validation	Source for algorithm
Prior database history of 1 year (objective 1)	Study participants were required to have a year of prior history observed before contributing observation time	After	1 year	IP, OP, OT	N/A	N/A	All study participants with incident multiple myeloma	N/A	N/A
Minimum potential follow-up (objectives 2 and 3)		After	30 days	IP, OP, OT	N/A	N/A	All study participants with incident multiple myeloma	N/A	N/A
Minimum potential follow-up time (objective 4)	Only participants with a diagnosis of multiple myeloma (index date) occurring one year prior to end of data availability in the database were included	After	1 year	IP, OP, OT	N/A	N/A	All study participants with incident multiple myeloma	N/A	N/A

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

Table 6. Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/validation	Source for algorithm
History of cancer diagnosis	Participants with a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma or prior to the start of the study period	After	Anytime prior to multiple myeloma diagnosis	IP, OP, OT	SNOMED	Any	All study participants with incident multiple myeloma	N/A	N/A

1 IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

9.6 Variables

9.6.1 Exposure /s

N/A

9.6.2 Outcome/s

Two main outcomes of interest were studied: treatment/s initiated within 30, 90 and/or 365 days after diagnosis, and death. For the former, a pre-specified list of multiple myeloma treatments was generated (Objectives 2-3).

Multiple Myeloma treatments included chemotherapies (melphalan, bendamustine, doxirubicin, cisplatin, cyclophosphamide, etoposide, vincristine), IMiDs (thalidomide, lenalidomide, pomalidomide), PI (bortezomib, carfilzomib, ixazomib, venetoclax), monoclonal antibodies (daratumumab, isatuximab, *denosumab, elotuzumab*), nuclear export inhibitor (selinexor), CAR T-cell (lisocabtagene maraleucel, idecabtagene vicleucel, brexucabtagene autoleucel, axicabtagene ciloleucel, tisagenlecleucel), glucocorticoids (dexamethasone, prednisone), bisphosphonates (zoledronate, pamidronate, clodronate, ibandronate, etidronate), and others (panobinostat)(3,10). Please check **Appendix 1 Table 2** for a list of codes to identify these treatments.

Overall survival in patients with incident multiple myeloma was also calculated based on the registered date of death for the latter. Individuals contributed with survival time as per the follow-up described in section 9.4.

Table 7. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Multiple myeloma treatments	Preliminary code lists provided in Appendix 1 Table 2	Yes	Counts	N/A	IP and OP care	RxNorm	N/A	All study participants with incident multiple myeloma	N/A	N/A
Overall survival		Yes	Time	N/A	IP and OP care	Date of death	N/A	All study participants with incident multiple myeloma	N/A	N/A

[1] IP = inpatient, OP = outpatient, n/a = not applicable

9.6.3 Other covariates, including confounders, effect modifiers and other variables (where relevant)

Age at multiple myeloma diagnosis was described. The following age grouping was used: 0-17; 18-44; 45-59; 60-69; 70 and over. The sex (male/ female) of study participants was also identified.

All co-morbidities and co-medications recorded prior and at index date were used for large-scale patient characterisation, identified as concept/code and descendants. Conditions and medications were defined based on SNOMED and RxNorm codes, respectively. Additionally, a list of pre-specified co-morbidities and co-medications were described. These included:

- Medical History: Asthma, COPD, Chronic Liver disease, Crohn's Disease, Diabetes mellitus, Gastro-esophageal reflux disease (GERD), GI-Bleeding, Human Immunodeficiency Virus (HIV), Hyperlipidemia, Hypertension, Obesity, Osteoarthritis, Pneumonia, Psoriasis, Renal impairment, Ulcerative Collitis, Urinary Tract infection, Viral Hepatitis, Visual system disorder [General] -- Schizophrenia, Dementia, Parkinson, Depressive disorder, Anxiety, Attention Deficit Hyperactivity Disorder (ADHD) [Neurology] --- Any cancer except non-melanoma skin cancer (for quality assessment purposes, this should be 0 in our study population before index date).

- Medication use: Agents acting on the renin-angiotensin system, Antibacterials for systemic use, Antidepressants, Antiepileptics, Antiinflammatory and antirheumatic products, Antineoplastic agents, Antipsoriatics, Antithrombotic agents, Beta blocking agents, Calcium channel blockers, Diuretics, Drugs for acid related disorders, Drugs for obstructive airway diseases, Drugs used in diabetes, Immunosuppressants, Lipid modifying agents, Opioids, Psycholeptics, Psychostimulants, agents used for ADHD and nootropics [General] -- contraceptives [contraceptives].

Table 8. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations:	Measurement characteristics /validation	Source for algorithm
Co-morbidities	Large-scale patient-level characterisation with regard to underlying co-morbidities	Counts	At index date (ID), for 30 to 1 day before ID, for 365 to 31 days before ID, at any time and up to 366 days before ID	OP, IP, OT	SNOMED	N/A	N/A	N/A	N/A
Concomitant medication	Large-scale patient-level characterisation with regard to use of concomitant drugs	Counts	At index date (ID), for 30 to 1 day before ID, for 365 to 31 days before ID, 1 to 30 post ID, 1 to 90 post ID, and 1 to 365 days post ID	OP, IP, OT	RxNorm	N/A	N/A	N/A	N/A

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

9.7 Study size

No sample size was calculated as this is a descriptive Disease Epidemiology Study where we are interested in the characteristics of all incident multiple myeloma patients. Based on a preliminary feasibility assessment the expected number of multiple myeloma records in the included databases for this study was approximately 88470. Please note that this number was based on the overall number of multiple myeloma registers in each database with no filter by study period or inclusion and exclusion criteria.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed and quality control checks were performed. After all the tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations were performed, and additional fine tuning of the code base was needed.

The study results of all data sources were checked after which they were made available to the team in the Digital Research Environment and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical Methods

Table 9. Description of Study Types and Type of analysis

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Disease epidemiology - Patient-level characterisation	Off-the-shelf (C1)	- large-scale characterisation - patient-level characteristics - Progression to a pre-specified outcome - Standard care description

9.9.1 Patient privacy protection

Cell suppression was applied as required by databases to protect people's privacy. Cell counts < 5 were masked.

9.9.2 Statistical model specification and assumptions of the analytical approach considered

R-packages

We used the R packages "PatientProfiles" for the patient-level characterization of demographics and clinical characteristics, "TreatmentPatterns" for the patient-level characterisation of treatments, and "CohortSurvival" for the estimation of overall survival.

Patient-level characterisation

Large-scale patient-level characterisation was conducted (objective 1). Age and sex at time of multiple myeloma diagnosis were described for each of the generated study cohorts. The index date was the date of the multiple myeloma diagnosis for each patient. Medical history was assessed for anytime –and up to 365 days before index date, for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. Medication use history was reported for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. We also reported medication use for 1 to 30, 1 to 90, and 1 to 365 days post index date. These time windows were defined based on the options currently available in the standard analytical tools that were used in this project. Co-variates to be presented in a summary baseline characteristics table were pre-defined as described in section 9.6.3.

The number and % of patients receiving each of a pre-specified list of multiple myeloma treatments (objective 2, as listed in section 9.6.2) were described at index date, 1 to 30, 1 to 90, and 1 to 365 days post index date. When available, treatment regimen types were also described. Additionally, sunburst plots and Sankey diagrams were used to describe treatment sequences over time (objective 3). Sankey diagrams were censored at end of treatment or end of follow-up as described in section 9.4.

Overall survival (objective 4) was calculated using data on time at risk of death from any cause and the Kaplan-Meier (KM) method. Results are reported as plots of the estimated survival curves as well as the estimated probability of survival at years 1, 3, and 5. Individuals who are lost to follow-up were censored at the time of loss of follow-up. The KM approach implicitly assumes censoring occurs at random. This analysis was conducted only for databases that collect systematically data on mortality (all except IQVIA DA Germany).

For all analyses n and % were reported. A minimum cell count of 5 was used when reporting results, with any smaller counts reported as "<5". All analyses were reported by country/database, overall and stratified by age and sex when possible (minimum cell count reached). Additionally, in order to capture treatments availability and survival changes over time, sunburst plots, Sankey diagrams and 1-year survival were further stratified by study periods (2012-2017 and 2018-2022).

9.10 Evidence synthesis

Results from analyses described in section 9.9 were presented separately for each database and no meta-analysis of results was conducted.

9.11 Deviations from the protocol

NA

10 DATA MANAGEMENT

10.1 Data management

All databases are mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites was then combined in tables and figures for this study report.

10.2 Data storage and protection

For this study, participants from various EU member states processed personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN Digital Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11 QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining multiple myeloma, a systematic search of possible codes for inclusion was previously identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP CDM so as to find potentially relevant codes. The codes returned were then reviewed by two clinical epidemiologist to consider their relevance. This work was done previously as part of study the DARWIN EU® study EUPAS50800. In addition, the CohortDiagnostics R package

(https://github.com/OHDSI/CohortDiagnostics) was run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This allowed for a consideration of the validity of the study cohort of patients with multiple myeloma in each of the databases, and informed decisions around whether multiple definitions were required.

The study code was based on three R packages to (1) characterise demographic and clinical characteristics, (2) characterise treatment sequences, and (3) estimate overall survival using the OMOP CDM. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R packages are publicly available via GitHub at https://github.com/darwin-eu-studies/P2-C1-001-MultipleMyeloma.
The study protocol was registered in the EUPAS Registry (EUPAS105033).

12 RESULTS

All results are available in a web-application ("shiny app") at https://data-dev.darwin-eu.org/EUPAS105033/.

The number of individuals contributing to each study objective by database is described in Table 10. Overall, there were 34,982 patients with a diagnosis of multiple myeloma between 2012 and 2022 in the participating databases (CDWBordeaux: 1,930, EBB: 182, IQVIA DA Germany: 14,218 , IMASIS: 386, NCR: 13,579, SIDIAP: 4,687). From these, 30,319 did not have a diagnosis of other cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma (CDWBordeaux: 1,781, EBB: 111, IQVIA DA Germany: 12,360, IMASIS: 329, NCR: 11,745, SIDIAP: 3,993).

Table 10. Study attrition of individuals included in each cohort per database

	IQVIA DA Germany	SIDIAP	IMASIS	EBB	CWDBordeaux	NCR
Database population	41,974,403	8,265,343	1,051,862	209,457	2,371,226	2,383,827
with a diagnosis of multiple myeloma identified in the database between 01/01/2012 and 31/12/2022	14,218	4,687	386	182	1,930	13,579
without a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma	12,360	3,993	329	111	1,7811	11,745
with at least 365 days of prior history available before date of multiple myeloma diagnosis (**Cohort 1**)	6,080	3,895	254	111	867	-
with a minimum follow-up time of 30 days (**Cohort 2**)	-	-	275	107	1,587	11,289
with a minimum of 1 year of potential follow-up time (**Cohort 3**)	-	3,558	301	90	1,639	11,745

Cohort 1 was not generated in NCR since history data is not available in this database. Cohort 2 was not generated in SIDIAP since the aim of this cohort was to answer objectives 2 and 3 on cancer treatments and

this information is not available in SIDIAP. Cohorts 2 and 3 were not generated in IQVIA DA Germany given that this database do not participate in objectives 2, 3 and 4.

Table 11 describes the demographic characteristics of all individuals identified with multiple myeloma in each database. The majority of individuals were 70 years of age or older at the time of multiple myeloma diagnosis, with a proportion of cases older than 70 ranging from 41% in EBB to 64% in IMASIS. The median age at diagnosis ranged from 66 years in EBB to 71 years in IMASIS. No cases among individuals aged between 0 and 17 years were observed in NCR and EBB, less than 5 cases were observed in CDWBordeaux and IMASIS, 19 cases were observed in IQVIA DA Germany, and 101 cases were identified in SIDIAP.

The proportion of males was higher than the proportion of females in CDWBordeaux (54% vs 46%, respectively), IQVIA DA Germany (51% vs 49%), and NCR (58% vs 42%), while no difference was observed in IMASIS (50% in both), and higher proportion of females vs. males was observed in EBB (59% vs 41%, respectively) and SIDIAP (51% vs 49%).

Table 11. Demographic characteristics of incident multiple myeloma patients* per database

		CDWBordeaux	IQVIA DA Germany	EBB	IMASIS	NCR	SIDIAP
Number of individuals		1,781	12,360	111	329	11,745	3,993
Cohort start date (minimum)		2012-01-03	2021-02-01	2012-01-20	2012-01-04	2012-01-01	2012-01-01
Cohort end date (maximum)		2023-08-02	2023-01-04	2021-12-31	2023-05-12	2023-01-31	2022-06-30
Age, median [min; q25 - q75; max]		67 [16; 59 - 76; 97]	71 [1; 61 - 78; 98]	66 [19; 57 - 73; 86]	75 [1; 64 - 83; 97]	70 [18; 62 - 77; 98]	71 [0; 59 - 79; 104]
Age group, N (%)	0 to 17	<5	19 (0%)	<5	<5	<5	101 (3%)
	18 to 44	51 (3%)	412 (3%)	8 (7%)	12 (4%)	227 (2%)	226 (6%)
	45 to 59	428 (24%)	2,192 (18%)	30 (27%)	34 (10%)	2,069 (18%)	687 (17%)
	60 to 69	559 (31%)	3,015 (24%)	27 (24%)	70 (21%)	3,346 (28%)	878 (22%)
	>=70	760 (42%)	6,722 (54%)	46 (41%)	210 (64%)	6,103 (52%)	2,101 (53%)
Sex, N (%)	Female	823 (46%)	6,017 (49%)	65 (59%)	164 (50%)	4,918 (42%)	2,043 (51%)
	Male	976 (54%)	6,332 (51%)	46 (41%)	165 (50%)	6,827 (58%)	1,950 (49%)
	None	<5	11 (0%)	<5	<5	<5	<5

*All individuals with a diagnosis of multiple myeloma identified in the database between 01/01/2012 and 31/12/2022, without a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma.

12.1. Large-scale characterisation

12.1.1 Number of Participants and demographic characteristics

A total of 12,207 individuals were included in Cohort 1 (CDWBordeaux: 867, EBB: 111, IQVIA DA Germany: 6,080, IMASIS: 254, SIDIAP: 3,895) (Table 12). These were individuals with a first diagnosis of multiple myeloma, with no history of other cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma, and with at least 365 days of prior history available before date of multiple myeloma diagnosis between 01/01/2012 and 31/12/2022. NCR was not included in these analyses since previous history before cancer diagnoses is not recorded in real time but just collected on the date of registration in NCR.

Table 12 describes the demographic characteristics of multiple myeloma individuals included in Cohort 1 per database. The majority of individuals were 70 years of age or older at time of multiple myeloma diagnosis, with a proportion of cases older than 70 ranging from 48% in CDWBordeaux to 69% in IMASIS. The median age ranged from 69 years in CDWBordeaux to 76 years in IMASIS. No cases among individuals aged between 0 and 17 years were observed in CDWBordeaux, less than 5 cases were observed in IMASIS, 10 cases were observed in IQVIA DA Germany, and 89 cases were identified in SIDIAP.

The proportion of males was higher than the proportion of females in CDWBordeaux (52% vs 48%, respectively) and NCR (58% vs 42%), while no difference was observed in IQVIA DA Germany (50% in both), and a higher proportion of females vs. males was observed in EBB (59% vs 41%, respectively), IMASIS (52% vs 48%) and SIDIAP (51% vs 49%).

Table 12. Demographic characteristics of multiple myeloma patients in Cohort 1* per database

		CDWBordeaux	IQVIA DA Germany	EBB	IMASIS	SIDIAP
Number of individuals		867	6,080	111	254	3,895
Age, median [min; q25 - q75; max]		69 [30; 61 - 78; 97]	71 [1; 61 - 78; 96]	66 [19; 57 - 73; 86]	76 [1; 67 - 84; 97]	71 [1; 60 - 79; 104]
Age group, N(%)	0 to 17	<5	10 (0%)	<5	<5	89 (2%)
	18 to 44	23 (3%)	253 (4%)	8 (7%)	8 (3%)	213 (5%)
	45 to 59	171 (20%)	1,079 (18%)	30 (27%)	24 (9%)	666 (17%)
	60 to 69	256 (29%)	1,457 (24%)	27 (24%)	44 (17%)	865 (22%)
	>=70	422 (48%)	3,281 (54%)	46 (41%)	176 (69%)	2,062 (53%)
Sex, N(%)	Female	418 (48%)	3,036 (50%)	65 (59%)	131 (52%)	1,997 (51%)
	Male	454 (52%)	3,039 (50%)	46 (41%)	123 (48%)	1,898 (49%)
	Unknown	<5	5 (0%)	<5	<5	<5

*Cohort 1: individuals with a first diagnosis of multiple myeloma, with no history of other cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma, and with at least 365 days of prior history available before date of multiple myeloma diagnosis between 01/01/2012 and 31/12/2022.

12.1.2 Co-morbidities and co-medications

In large-scale characterisation, all co-morbidities and co-medications recorded prior, at, and post index time windows were described for individuals in cohort 1. For simplicity, only the list of pre-specified co-morbidities and co-medications were described in this report. However, all results can be found in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

Pre-specified co-morbidities

In Table 13, the frequency of the list of pre-specified conditions are reported for each database at index date. The results of different time windows, for 30 to 1 day before index date, and for 365 to 31 days before index date, were provided in Table 1 of Appendix II. For simplicity, we did not include the results of the time window "anytime and up to 366 days before index date" in this table, but all results are presented in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

At index date, the **most frequent co-morbidities** were hypertension (ranging from 27% in SIDIAP to 48% in IQVIA DA Germany), renal impairment (from 14% in IQVIA DA Germany to 34% in IMASIS), hyperlipidemia (from 11% in CWDBordeaux to 30% in IMASIS), osteoarthritis (from 4% in CDWBordeaux to 59% in IQVIA DA Germany), urinary tract infection (from 4% in CDWBordeaux to 20% in SIDIAP), diabetes mellitus (from 11% in CDWBordeaux to 19% in IQVIA DA Germany), and obesity (from 1% in CDWBordeaux to 18% in SIDIAP). The **least frequent conditions** were schizophrenia, ADHD, HIV, Crohn's disease, and ulcerative colitis which were all below 1% in all databases.

When looking at the frequency of pre-specified co-morbidities in time windows prior to index date (Table 1 of Appendix II), these were similar as the ones registered at index (hypertension, osteoarthritis, hyperlipidemia, urinary tract infection). In CDWBordeaux, the frequency of co-morbidities registered prior to index date was much lower than at index, although the most frequent conditions were similar to the ones registered at index. For example, in this database, the most frequent co-morbidities 30 days prior to index day and from 30 to 1 year prior to index date were hypertension (17% and 16%, respectively), renal impairment (9% and 6%), hyperlipidemia (6% in both time windows), and diabetes mellitus (5% in both time windows).

Table 13. Number and % of pre-specified co-morbidities among all individuals in Cohort 1 by database at index date

	IQVIA DA Germany	CDWBordeaux	EBB	IMASIS	SIDIAP
Anxiety	625 (10.28%)	89 (10.21%)	32 (28.83%)	10 (3.94%)	659 (16.92%)
Asthma	527 (8.67%)	24 (2.75%)	24 (21.62%)	14 (5.51%)	144 (3.7%)
Attention deficit hyperactivity disorder (ADHD)	23 (0.38%)	0 (0%)	0 (0%)	0 (0%)	11 (0.28%)
Chronic liver disease	88 (1.45%)	18 (2.06%)	6 (5.41%)	13 (5.12%)	51 (1.31%)
COPD	645 (10.61%)	38 (4.36%)	16 (14.41%)	28 (11.02%)	213 (5.47%)
Crohn´s disease	41 (0.67%)	<5	<5	<5	6 (0.15%)
Dementia	245 (4.03%)	20 (2.29%)	0 (0%)	11 (4.33%)	132 (3.39%)
Depressive disorder	1027 (16.89%)	50 (5.73%)	34 (30.63%)	28 (11.02%)	434 (11.14%)
Diabetes mellitus	1164 (19.14%)	95 (10.89%)	16 (14.41%)	32 (12.6%)	446 (11.45%)
Gastro-esophageal reflux disease (GERD)	295 (4.85%)	22 (2.52%)	38 (34.23%)	<5	254 (6.52%)
GI-Bleeding	199 (3.27%)	21 (2.41%)	5 (4.5%)	12 (4.72%)	192 (4.93%)
Hepatitis	79 (1.3%)	<5	<5	<5	57 (1.46%)
Hyperlididemia	1538 (25.3%)	94 (10.78%)	26 (23.42%)	77 (30.31%)	544 (13.97%)
Hypertension	2898 (47.66%)	309 (35.44%)	65 (58.56%)	116 (45.67%)	1051 (26.98%)
Obesity	681 (11.2%)	11 (1.26%)	16 (14.41%)	23 (9.06%)	706 (18.13%)
Osteoarthritis	1998 (32.86%)	39 (4.47%)	65 (58.56%)	52 (20.47%)	1073 (27.55%)
Parkinson disease	92 (1.51%)	10 (1.15%)	<5	6 (2.36%)	37 (0.95%)
Pneumonia	420 (6.91%)	71 (8.14%)	24 (21.62%)	36 (14.17%)	414 (10.63%)
Psoriasis	177 (2.91%)	9 (1.03%)	12 (10.81%)	6 (2.36%)	91 (2.34%)
Renal impairment	868 (14.28%)	183 (20.99%)	26 (23.42%)	86 (33.86%)	698 (17.92%)
Schizophrenia	13 (0.21%)	0 (0%)	<5	0 (0%)	11 (0.28%)
Ulcerative collitis	33 (0.54%)	<5	<5	<5	15 (0.39%)
Urinary tract infection	739 (12.15%)	32 (3.67%)	19 (17.12%)	47 (18.5%)	765 (19.64%)

Table 2 of Appendix II shows the distribution of the complete list of pre-specified co-morbidities **stratified by sex** and database **at index date**. Since the results for the frequency of co-morbidities by time windows were very similar as shown above, we will only show the results stratified by sex for the time window of at index date. Also, given the small number of individuals in EBB and IMASIS, we will not show the results stratified by sex for these databases in this report. However, all results can be found in detail in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

Results for the frequency of co-morbidities stratified by sex were similar to the results reported in the overall population, with hypertension, osteoarthritis, hyperlipidemia, urinary tract infection, diabetes mellitus and renal impairment being **the most frequent co-morbidities**, and schizophrenia, ADHD, HIV, Crohn's disease, and ulcerative colitis the **least frequent co-morbidities** in both women and men at index date. However, when compared with men, women had higher prevalence of urinary tract infection (17% in women vs 7% in men in IQVIA DA Germany, and 27% vs 12%, respectively, in SIDIAP), osteoarthritis (37% vs 29% in IQVIA DA Germany and 34% vs 20% in SIDIAP), anxiety (13% vs 7% in IQVIA DA Germany and 22% vs 12% in SIDIAP), and depression (22% vs 12% in IQVIA DA Germany and 15% vs 7% in SIDIAP), but lower prevalence of hypertension (46% vs 50% in IQVIA DA Germany and 26% vs 28% in SIDIAP) and COPD (in SIDIAP only: 3% vs 8%).

Table 3 of Appendix II shows the distribution of the complete list of pre-specified co-morbidities stratified by age group and database at index date. Results for the age group of 0 to 17 years are omitted due to the small number of individuals in this age group in all databases (the highest number of patients was in SIDIAP where 89 individuals were identified). Results for the age group of 18 to 44 years was also not shown for CDWBordeaux since there were only 51 individuals in this age group. As above, we are also omitting the results for different time windows and for EBB and IMASIS. However, all results can be found in detail in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

The **most frequent co-morbidities** in the group of individuals from **18 to 44 years of age** at index date were urinary tract infection (23% in IQVIA DA Germany and 21% in SIDIAP) and anxiety (19% in IQVIA DA Germany and 20% in SIDIAP). Depression was the most frequent co-morbidity in this age group in IQVIA DA Germany (26%), but not as frequent in SIDIAP (6%). Hypertension, osteoarthritis, and asthma were also frequent in this age group in the IQVIA DA Germany database (15%, 15%, and 13%, respectively), but not as frequent in SIDIAP (5%, 4%, and 7%).

In the age group of individuals from **45 to 59 years of age**, the most frequent co-morbidities were anxiety (15% in CDWBordeaux, 15% in IQVIA DA Germany, and 24% in SIDIAP), obesity (12% in IQVIA DA Germany and 18% in SIDIAP, but not registered in CDWBordeaux), and depression (20% in IQVIA DA Germany, 11% in SIDIAP, and 6% in CDWBordeaux).

The ranking of most frequent co-morbidities at index in the age groups from **60 to 69 and >=70 years of age** were similar, with hypertension, osteoarthritis, hyperlipidemia the most frequent ones. Renal impairment was one of the most frequent co-morbidities among individuals >=70 years (26% in CDWBordeaux, 20% in IQVIA DA Germany, and 27% in SIDIAP), but not amongst the younger group of individuals from 60 to 69 years (18% in CDWBordeaux, 10% in IQVIA DA Germany, and 12% in SIDIAP).

Pre-specified co-medications

In Table 16, the frequency of the pre-specified list of medication is reported for each database at index date. All results are presented in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

At **index date**, the most frequent **medications** were drugs for acid related disorders (from 8% in CDWBordeaux to 51% in SIDIAP), agents acting on the renin-angiotensin system (ranging from 2% in CDWBordeaux and 7% in IMASIS to 34% in SIDIAP,), opioids (from 9% in IQVIA DA Germany to 28% in SIDIAP), psycholeptics (from 3% in IQVIA DA Germany to 29% in SIDIAP) and lipid modifying agents (from 5% in CDWBordeaux and 9% in EBB to 24% in SIDIAP). The least frequent medications were antipsoriatics and psychostimulants which were below 1% in all databases.

Table 16. Number and % of pre-specified medication use among individuals in Cohort 1 at index date

	IQVIA DA Germany	CDWBordeaux	EBB	IMASIS	SIDIAP
Agents acting on the renin-angiotensin system	1255 (20.64%)	17 (1.95%)	26 (23.42%)	19 (7.48%)	1318 (33.84%)
Antibacterials for systemic use	244 (4.01%)	47 (5.39%)	15 (13.51%)	33 (12.99%)	404 (10.37%)
Antidepressants	333 (5.48%)	18 (2.06%)	<5	8 (3.15%)	660 (16.94%)
Antiepileptics	184 (3.03%)	30 (3.44%)	6 (5.41%)	28 (11.02%)	445 (11.42%)
Antiinflammatory and antirheumatic products	430 (7.07%)	12 (1.38%)	19 (17.12%)	17 (6.69%)	655 (16.82%)
Antineoplastic agents	33 (0.54%)	139 (15.94%)	5 (4.5%)	<5	93 (2.39%)
Antipsoriatics	<5	0 (0%)	0 (0%)	0 (0%)	11 (0.28%)
Antithrombotic agents	456 (7.5%)	92 (10.55%)	9 (8.11%)	44 (17.32%)	717 (18.41%)
Beta blocking agents	947 (15.58%)	30 (3.44%)	17 (15.32%)	13 (5.12%)	575 (14.76%)
Calcium channel blockers	526 (8.65%)	21 (2.41%)	11 (9.91%)	8 (3.15%)	624 (16.02%)
Diuretics	721 (11.86%)	29 (3.33%)	12 (10.81%)	25 (9.84%)	739 (18.97%)
Drugs for acid related disorders	1116 (18.36%)	69 (7.91%)	23 (20.72%)	68 (26.77%)	1978 (50.78%)
Drugs for obstructive airway diseases	172 (2.83%)	27 (3.1%)	12 (10.81%)	17 (6.69%)	536 (13.76%)
Drugs used in diabetes	354 (5.82%)	27 (3.1%)	<5	19 (7.48%)	523 (13.43%)
Immunosuppressants	41 (0.67%)	52 (5.96%)	<5	<5	34 (0.87%)
Lipid modifying agents modifying	607 (9.98%)	42 (4.82%)	10 (9.01%)	26 (10.24%)	921 (23.65%)
Opioids	544 (8.95%)	98 (11.24%)	18 (16.22%)	29 (11.42%)	1093 (28.06%)
Psycholeptics	205 (3.37%)	98 (11.24%)	15 (13.51%)	39 (15.35%)	1118 (28.7%)
Psychostimulants	<5	0 (0%)	0 (0%)	0 (0%)	35 (0.9%)

In Table 17, the frequency of the pre-specified list of medication is reported for each database at different time windows before index date (30 to 1 day before index date, and 365 to 31 days before index date). All results are presented in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

When looking at the frequency of **medications** in time window **30 to 1 day prior to index date** (Table 17), these were similar as the ones registered at the index date (drugs for acid related disorders, agents acting on the renin-angiotensin system, opioids, psycholeptics, lipid modifying agents) in IQVIA DA Germany, EBB and SIDIAP. In CDWBordeaux and IMASIS, the frequency of medication registered 30 to 1 day prior index date was notably lower than at index. In CDWBordeaux database, most frequent medications 30 to 1 day prior index date were opioids, psycholeptics and antithrombotic agents (each exhibiting frequency of 3%). In IMASIS, most frequent medications 30 to 1 day prior index date were dugs for acid related disorders, opioids, antithrombotic agents and antineoplastic agents (each with frequency of 7%).

When looking at the frequency of **medications** in time window **365 to 31 days prior to index date** (Table 17), these were notably higher than the ones registered at the index date. The most frequent medications registered 365 days to 31 days prior index date were anti-inflammatory and antirheumatic products (from 20% in IQVIA DA Germany to 50% in EBB, but only 1% in CDWBordeaux and 8% in IMASIS), antibacterials for systemic use (from 11% in IMASIS to 45% in EBB, but only 3% in CDWBordeaux) and products similar to the ones registered at index (drugs for acid related disorders, agents acting on the renin-angiotensin system, opioids, and psycholeptics).

Table 17. Number and % of pre-specified medication use among individuals in Cohort 1 at time windows prior to index date

	IQVIA DA Germany		CDWBordeaux		EBB		IMASIS		SIDIAP	
	30 to 1 days prior	365 to 31 days prior	30 to 1 days prior	365 to 31 days prior	30 to 1 days prior	365 to 31 days prior	30 to 1 days prior	365 to 31 days prior	30 to 1 days prior	365 to 31 days prior
Agents acting on the renin-angiotensin system	1308 (21.51%)	1612 (26.51%)	12 (1.38%)	37 (4.24%)	39 (35.14%)	50 (45.05%)	6 (2.36%)	22 (8.66%)	1387 (35.61%)	1481 (38.02%)
Antibacterials for systemic use	206 (3.39%)	899 (14.79%)	17 (1.95%)	28 (3.21%)	18 (16.22%)	50 (45.05%)	11 (4.33%)	29 (11.42%)	579 (14.87%)	1488 (38.2%)
Antidepressants	251 (4.13%)	396 (6.51%)	9 (1.03%)	13 (1.49%)	7 (6.31%)	8 (7.21%)	8 (3.15%)	19 (7.48%)	685 (17.59%)	753 (19.33%)
Antiepileptics	161 (2.65%)	225 (3.7%)	9 (1.03%)	8 (0.92%)	10 (9.01%)	8 (7.21%)	13 (5.12%)	18 (7.09%)	459 (11.78%)	513 (13.17%)
Antiinflammatory and antirheumatic products	450 (7.4%)	1193 (19.62%)	8 (0.92%)	10 (1.15%)	30 (27.03%)	55 (49.55%)	12 (4.72%)	20 (7.87%)	846 (21.72%)	1595 (40.95%)
Antineoplastic agents	26 (0.43%)	57 (0.94%)	14 (1.61%)	11 (1.26%)	<5	5 (4.5%)	18 (7.09%)	18 (7.09%)	101 (2.59%)	118 (3.03%)
Antipsoriatics	<5	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (0.26%)	13 (0.33%)
Antithrombotic agents	433 (7.12%)	578 (9.51%)	26 (2.98%)	36 (4.13%)	10 (9.01%)	12 (10.81%)	19 (7.48%)	37 (14.57%)	683 (17.54%)	617 (15.84%)
Beta blocking agents	969 (15.94%)	1195 (19.65%)	14 (1.61%)	31 (3.56%)	24 (21.62%)	39 (35.14%)	5 (1.97%)	14 (5.51%)	584 (14.99%)	595 (15.28%)
Calcium channel blockers	518 (8.52%)	688 (11.32%)	11 (1.26%)	21 (2.41%)	11 (9.91%)	18 (16.22%)	5 (1.97%)	14 (5.51%)	641 (16.46%)	660 (16.94%)
Diuretics	681 (11.2%)	814 (13.39%)	17 (1.95%)	31 (3.56%)	15 (13.51%)	23 (20.72%)	8 (3.15%)	24 (9.45%)	791 (20.31%)	834 (21.41%)
Drugs for acid related disorders	870 (14.31%)	1225 (20.15%)	20 (2.29%)	39 (4.47%)	21 (18.92%)	38 (34.23%)	19 (7.48%)	51 (20.08%)	1952 (50.12%)	1978 (50.78%)
Drugs for obstructive airway diseases	181 (2.98%)	440 (7.24%)	<5	10 (1.15%)	13 (11.71%)	22 (19.82%)	9 (3.54%)	19 (7.48%)	598 (15.35%)	929 (23.85%)
Drugs used in diabetes	369 (6.07%)	490 (8.06%)	6 (0.69%)	11 (1.26%)	7 (6.31%)	11 (9.91%)	<5	15 (5.91%)	530 (13.61%)	538 (13.81%)
Immunosuppressants	38 (0.62%)	64 (1.05%)	7 (0.8%)	10 (1.15%)	<5	<5	<5	<5	35 (0.9%)	37 (0.95%)
Lipid modifying agents modifying	661 (10.87%)	843 (13.87%)	13 (1.49%)	26 (2.98%)	12 (10.81%)	16 (14.41%)	<5	18 (7.09%)	952 (24.44%)	1025 (26.32%)
Opioids	443 (7.29%)	596 (9.8%)	26 (2.98%)	31 (3.56%)	19 (17.12%)	16 (14.41%)	19 (7.48%)	26 (10.24%)	1122 (28.81%)	1230 (31.58%)
Psycholeptics	199 (3.27%)	351 (5.77%)	30 (3.44%)	47 (5.39%)	17 (15.32%)	25 (22.52%)	12 (4.72%)	32 (12.6%)	1174 (30.14%)	1386 (35.58%)
Psychostimulants	<5	7 (0.12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	41 (1.05%)	70 (1.8%)

In Table 18, **medication use** was also reported over varying time windows post index date, ranging from 1 to 30 days, 1 to 90 days and 1 to 365 days. When looking at the frequency of medication, upward trend was observed as the time intervals lengthened beyond the index date.

The most frequent medication 1 to 30 days post index date aligned with the ones recorded at index date (drugs for acid related disorders, agents acting on the renin-angiotensin system, opioids, psycholeptics). Additionally, within this time window, frequent medication encompassed antineoplastic agents (from 11% in EBB to 45% in CDWBordeaux, but 4% in SIDIAP and 1% in IQVIA DA Germany), antibacterials for systemic use (from 19% in SIDIAP to 43% in IMASIS, but 9% in IQVIA DA Germany), antithrombotic agents (from 17% in EBB to 55% in IMASIS, but 7% in IQVIA DA Germany) and diuretics (from 13% in IQVIA DA Germany to 37% in IMASIS). When looking at frequency of medication in 1 to 90 days and 1 to 365 days time windows, similar pattern and higher frequency were observed as shown in Table 18.

Table 18. Number and % of pre-specified medication use among individuals in Cohort 1 at time windows post index date

	IQVIA DA Germany			CDWBordeaux			EBB		
	1 to 30 days post	**1 to 90 days post**	**1 to 365 days post**	**1 to 30 days post**	**1 to 90 days post**	**1 to 365 days post**	**1 to 30 days post**	**1 to 90 days post**	**1 to 365 days post**
Agents acting on the renin-angiotensin system	1382 (22.73%)	1504 (24.74%)	1691 (27.81%)	143 (16.4%)	157 (18%)	185 (21.22%)	40 (36.04%)	46 (41.44%)	51 (45.95%)
Antibacterials for systemic use	413 (6.79%)	657 (10.81%)	1219 (20.05%)	221 (25.34%)	261 (29.93%)	308 (35.32%)	32 (28.83%)	48 (43.24%)	76 (68.47%)
Antidepressants	384 (6.32%)	440 (7.24%)	587 (9.65%)	77 (8.83%)	92 (10.55%)	114 (13.07%)	7 (6.31%)	9 (8.11%)	13 (11.71%)
Antiepileptics	228 (3.75%)	283 (4.65%)	412 (6.78%)	70 (8.03%)	84 (9.63%)	108 (12.39%)	14 (12.61%)	19 (17.12%)	32 (28.83%)
Antiinflammatory and antirheumatic products	523 (8.6%)	673 (11.07%)	1019 (16.76%)	36 (4.13%)	45 (5.16%)	55 (6.31%)	23 (20.72%)	27 (24.32%)	44 (39.64%)
Antineoplastic agents	36 (0.59%)	49 (0.81%)	79 (1.3%)	396 (45.41%)	462 (52.98%)	500 (57.34%)	12 (10.81%)	19 (17.12%)	23 (20.72%)
Antipsoriatics	<5	<5	<5	<5	<5	<5	0 (0%)	0 (0%)	0 (0%)
Antithrombotic agents	561 (9.23%)	675 (11.1%)	826 (13.59%)	266 (30.5%)	291 (33.37%)	335 (38.42%)	19 (17.12%)	21 (18.92%)	32 (28.83%)
Beta blocking agents	1063 (17.48%)	1194 (19.64%)	1362 (22.4%)	123 (14.11%)	133 (15.25%)	161 (18.46%)	31 (27.93%)	35 (31.53%)	45 (40.54%)
Calcium channel blockers	602 (9.9%)	685 (11.27%)	812 (13.36%)	113 (12.96%)	123 (14.11%)	150 (17.2%)	13 (11.71%)	16 (14.41%)	24 (21.62%)
Diuretics	817 (13.44%)	951 (15.64%)	1159 (19.06%)	126 (14.45%)	142 (16.28%)	170 (19.5%)	22 (19.82%)	35 (31.53%)	44 (39.64%)
Drugs for acid related disorders	1292 (21.25%)	1479 (24.33%)	1782 (29.31%)	226 (25.92%)	257 (29.47%)	295 (33.83%)	50 (45.05%)	72 (64.86%)	80 (72.07%)
Drugs for obstructive airway diseases	222 (3.65%)	304 (5%)	481 (7.91%)	67 (7.68%)	82 (9.4%)	120 (13.76%)	12 (10.81%)	15 (13.51%)	16 (14.41%)
Drugs used in diabetes	427 (7.02%)	478 (7.86%)	535 (8.8%)	61 (7%)	66 (7.57%)	73 (8.37%)	7 (6.31%)	7 (6.31%)	11 (9.91%)
Immunosuppressants	45 (0.74%)	56 (0.92%)	75 (1.23%)	194 (22.25%)	229 (26.26%)	252 (28.9%)	11 (9.91%)	22 (19.82%)	36 (32.43%)
Lipid modifying agents modifying	684 (11.25%)	766 (12.6%)	882 (14.51%)	87 (9.98%)	90 (10.32%)	107 (12.27%)	11 (9.91%)	13 (11.71%)	19 (17.12%)
Opioids	717 (11.79%)	853 (14.03%)	1067 (17.55%)	208 (23.85%)	237 (27.18%)	278 (31.88%)	31 (27.93%)	43 (38.74%)	57 (51.35%)
Psycholeptics	294 (4.84%)	372 (6.12%)	556 (9.14%)	240 (27.52%)	268 (30.73%)	324 (37.16%)	26 (23.42%)	35 (31.53%)	45 (40.54%)
Psychostimulants	<5	5 (0.08%)	9 (0.15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 18 (continued). Number and % of pre-specified medication use among individuals in Cohort 1 at time windows post index date

	IMASIS			SIDIAP		
	1 to 30 days post	1 to 90 days post	1 to 365 days post	1 to 30 days post	1 to 90 days post	1 to 365 days post
Agents acting on the renin-angiotensin system	69 (27.17%)	81 (31.89%)	98 (38.58%)	1333 (34.22%)	1372 (35.22%)	1475 (37.87%)
Antibacterials for systemic use	108 (42.52%)	124 (48.82%)	149 (58.66%)	731 (18.77%)	1154 (29.63%)	2147 (55.12%)
Antidepressants	51 (20.08%)	57 (22.44%)	73 (28.74%)	717 (18.41%)	797 (20.46%)	1031 (26.47%)
Antiepileptics	53 (20.87%)	60 (23.62%)	79 (31.1%)	514 (13.2%)	663 (17.02%)	1025 (26.32%)
Antiinflammatory and antirheumatic products	38 (14.96%)	46 (18.11%)	66 (25.98%)	814 (20.9%)	980 (25.16%)	1443 (37.05%)
Antineoplastic agents	69 (27.17%)	87 (34.25%)	98 (38.58%)	138 (3.54%)	186 (4.78%)	289 (7.42%)
Antipsoriatics	0 (0%)	0 (0%)	<5	11 (0.28%)	11 (0.28%)	12 (0.31%)
Antithrombotic agents	139 (54.72%)	153 (60.24%)	170 (66.93%)	967 (24.83%)	1183 (30.37%)	1501 (38.54%)
Beta blocking agents	48 (18.9%)	53 (20.87%)	63 (24.8%)	601 (15.43%)	633 (16.25%)	741 (19.02%)
Calcium channel blockers	43 (16.93%)	49 (19.29%)	60 (23.62%)	666 (17.1%)	719 (18.46%)	812 (20.85%)
Diuretics	94 (37.01%)	102 (40.16%)	122 (48.03%)	849 (21.8%)	992 (25.47%)	1241 (31.86%)
Drugs for acid related disorders	161 (63.39%)	172 (67.72%)	194 (76.38%)	2281 (58.56%)	2504 (64.29%)	2808 (72.09%)
Drugs for obstructive airway diseases	59 (23.23%)	75 (29.53%)	97 (38.19%)	613 (15.74%)	733 (18.82%)	1094 (28.09%)
Drugs used in diabetes	63 (24.8%)	73 (28.74%)	82 (32.28%)	550 (14.12%)	575 (14.76%)	617 (15.84%)
Immunosuppressants	5 (1.97%)	8 (3.15%)	12 (4.72%)	36 (0.92%)	37 (0.95%)	50 (1.28%)
Lipid modifying agents modifying	48 (18.9%)	55 (21.65%)	62 (24.41%)	941 (24.16%)	965 (24.78%)	1036 (26.6%)
Opioids	100 (39.37%)	121 (47.64%)	145 (57.09%)	1323 (33.97%)	1503 (38.59%)	1852 (47.55%)
Psycholeptics	107 (42.13%)	123 (48.43%)	151 (59.45%)	1250 (32.09%)	1432 (36.77%)	1785 (45.83%)
Psychostimulants	0 (0%)	0 (0%)	<5	37 (0.95%)	51 (1.31%)	76 (1.95%)

Tables 4 of Appendix II shows the distribution of the complete list of pre-specified medication **stratified by sex** and database **at index**. Given the small number of individuals in EBB and IMASIS, we will not show the results stratified by sex for these databases in this report. However, all results can be found in detail in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

Results for the frequency of medication stratified by sex were similar to the results reported in the overall population, with drugs for acid related disorders, agents acting on the renin-angiotensin system, opioids, psycholeptics and lipid modifying agents being the most frequent medication and antipsoriatics and psychostimulants the least frequent medication in both women and men at index date. However, when compared with men, women had higher frequency of antidepressants use (7% in women vs 4% in men in IQVIA DA Germany, and 23% vs 11%, respectively, in SIDIAP), but lower frequency of drugs used in diabetes (5% in women vs 7% in men in IQVIA DA Germany, 11% vs. 16%, respectively, in SIDIAP) and lipid modifying agents (9% in woman vs 11% in men in IQVIA DA Germany, 2% vs 7%, respectively, in CDWBordeaux, and 21% vs 27%, respectively, in SIDIAP).

Tables 5 and 6 in Appendix II show the distribution of the pre-specified list of medication **stratified by sex** and database at different time windows before index date (30 to 1 day before index date and 365 to 31 days before index date) and post index date (1 to 30, 1 to 90 and 1 to 365 days post index date). Given the small number of individuals in EBB and IMASIS, we will not show the results stratified by sex for these databases in this report. However, all results can be found in detail in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

Results for frequency of medication stratified by sex were similar to the results reported in overall population in both women and man across various time windows before index date and post index date. When compared with men, women demonstrated higher frequency of antidepressants use (5% in women vs 3% in men in IQVIA DA Germany, and 24% vs 11%, respectively, in SIDIAP) as well as psycholeptics (36% in women vs 24% in men in SIDIAP) within 30 to 1 day period before index. The results for alternative time frames preceding the index date can be found in Table 5. Additionally, similar pattern was observed across 1 to 30 days after index date for antidepressants (8% in women vs 4% in men in IQVIA DA Germany, and 24% vs 12%, respectively, in SIDIAP) and psycholeptics (38% in women vs 26% in men, respectively, in SIDIAP), but lower frequency of antithrombotic agents (28% in women vs 33% in men in CDWBordeaux, and 23% vs 27%, respectively, in SIDIAP). The results for other time windows are listed in Table 6.

Table 7 in Appendix II shows the distribution of pre-specified medication use stratified by age group and database at index date. Results for the age group of 0 to 17 years are omitted due to the small number of individuals in this age group in all databases (the highest number of patients was in IQVIA DA Germany where 70 individuals were identified). Results for the age group of 18 to 44 years were also omitted due to small numbers of individuals (the highest number of individuals was in IQVIA DA Germany where 80 individuals were identified). As above, we are also omitting the results for different time windows and for EBB and IMASIS. However, all results can be found in detail in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

The most frequent medications in the age group from 45 to 59 years of age at index were drugs for acid related disorders (18% in IQVIA DA Germany and 37% in SIDIAP), psycholeptics (27% in SIDIAP), and opioids (7% in IQVIA DA Germany, 8% in CDWBordeaux and 25% in SIDIAP).

In the age group of individuals from 60 to 69 and >=70 years of age, the ranking of most frequent medications was similar, with agents acting on the renin-angiotensin system, drugs for acid related disorders, psycholeptics and opioids. When looking at frequency, frequency of medication was higher among individuals >=70 years of age for all medication except for antineoplastic agents (1% in IQVIA DA Germany, 12% in CDWBordeaux and 3% in SIDIAP for age group >=70 vs 0% in IQVIA DA Germany, 23% in CDWBoreaux and 2% in SIDIAP amongst the youngest group of individuals from 60 to 69 years) and antiinflammatory and antirheumatic products (6% in IQVIA DA Germany and 13% in SIDIAP for age group >=70 vs 7% in IQVIA DA Germany and 21% in SIDIAP from 60 to 69 years).

Tables 8 and 9 in Appendix II show the distribution of pre-specified medication use stratified by age group and database at different time windows before index date (30 to 1 day before index date and 365 to 31 days before index date) and post index date (1 to 30, 1 to 90 and 1 to 365 days post index date). Results for the age group of 0 to 17 years and 18 to 44 years were omitted due to the small number of individuals in this age group in all databases. As above, we are also omitting the results for different time windows and for EBB and IMASIS. However, all results can be found in detail in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

Results for frequency of medication stratified by age group at different time windows before and post index date were similar to the results reported in overall population by age group. The frequency of medications across different time windows showed similar pattern and upward trend was observed as the time intervals lengthened.

12.2 Multiple Myeloma Treatments

12.2.1 Number of Participants

A total of 13,258 individuals were included in Cohort 2 (CDWBordeaux: 1,587, EBB: 107, IMASIS: 275, NCR: 11,289) (Table 31). These were individuals with a first diagnosis of multiple myeloma and with a minimum of 30 days of follow-up time available after the date of multiple myeloma diagnosis between 01/01/2012 and 31/12/2022. This cohort was not generated in IQVIA DA Germany and SIDIAP since cancer treatment information was not available in these databases.

12.2.2 Demographic characteristics

Table 25 describes the demographic characteristics of multiple myeloma individuals included in Cohort 2 per database. The majority of individuals were 70 years of older at time of multiple myeloma diagnosis, with a proportion of cases older than 70 ranging from 39% in CDWBordeaux to 61% in IMASIS. The median age ranged from 66 years in CDWBordeaux and EBB to 74 years in IMASIS. No cases among individuals aged between 0 and 17 years were observed in EBB and NCR, and less than 5 cases were observed in CDWBordeaux and IMASIS.

The proportion of males was higher than the proportion of females in CDWBordeaux (55% vs 45%, respectively), IMASIS (53% vs 47%), and NCR (58% vs 42%), while a higher proportion of females vs males was observed in EBB (61% vs 39%, respectively).

Table 25. Demographic characteristics of multiple myeloma patients in Cohort 2* per database.

		CDWBordeaux	EBB	IMASIS	NCR
Number of individuals		1,587	107	275	11,289
Age, median [min; q25 - q75; max]		66 [16; 58 - 75; 97]	66 [19; 57 - 73; 86]	74 [1; 64 -82; 97]	70 [18; 62 - 77; 98]
Age group, N (%)	0 to 17	<5	<5	<5	<5
	18 to 44	51 (3%)	8 (7%)	10 (4%)	226 (2%)
	45 to 59	409 (26%)	29 (27%)	31 (11%)	2,042 (18%)
	60 to 69	502 (32%)	27 (25%)	62 (23%)	3,282 (29%)
	>=70	624 (39%)	43 (40%)	169 (61%)	5,739 (51%)
Sex, N (%)	Female	722 (45%)	65 (61%)	128 (47%)	4,736 (42%)
	Male	865 (55%)	42 (39%)	147 (53%)	6,553 (58%)

*Cohort 2: individuals with a first diagnosis of multiple myeloma, with no history of other cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma, and with at least 365 days of prior history available before date of multiple myeloma diagnosis between 01/01/2012 and 31/12/2022.

12.2.3 Treatments received

Outcomes of interest were multiple myeloma treatment/s initiated within 30, 90 and/or 365 days after diagnosis and were available in CDWBordeaux, EBB, IMASIS and NCR. Only first line treatments were available in NCR. Figure 1 to 6 show the frequency of use of cancer treatments per ingredient and class in different time windows (1 to 30 days, 1 to 90 days, and 1 to 365 days). From the 32 multiple myeloma treatments that

were pre-specified in this study, there were 14 that were not found in any of the participating databases during the study period. These included: one chemotherapy (bendamustine), one PI (venetoclax), one monoclonal antibody (elotuzumab), the nuclear export inhibitor (selinexor), all CAR T-cell (lisocabtagene maraleucel, idecabtagene vicleucel, brexucabtagene autoleucel, axicabtagene ciloleucel, tisagenlecleucel), three bisfosfonaten (pamidronate, ibandronate, etidronate), and others (panobinostat). These were therefore not included in the figures below to facilitate interpretability.

In the first 30 days post cancer diagnosis (Figure 1), the most frequent class of treatments were glucocorticoids (32% in EBB, 43% in CDWBordeaux and NCR, and 45% in IMASIS), PIs (24% in IMASIS, 37% in CDWBordeaux, 39% in NCR, and not found in EBB), IMiDs (8% in EBB, 17% in NCR, 22% in CDWBordeaux, and not registered in IMASIS), and chemotherapies (8% in EBB, 12% in IMASIS, 19% in CDWBordeaux, and 23% in NCR). Bisphosphonates (zoledronic acid) were found in IMASIS (28%) and CDWBordeaux (4%) only. Monoclonal antibodies were more frequently observed in CDWBordeaux (11%), followed by NCR (4%), and IMASIS (2%).

Overall, a higher proportion of individuals were treated when looking at the full year following diagnosis (Figures 1 to 3). In NCR for example, the proportion of individuals treated with glucocorticoids went from 42% in the first 30 days, to 58% in the first 90 days and 63% in the 365 days post index date. In CDWBordeaux for example, the proportion of individuals treated with chemotherapies went from 19% in the first 30 days, to 28% in the first 90 days and 46% in the 365 days post index date.

In the first 30 days pots index, Dexamethasone was the glucocorticoid most frequently used in all databases (ranging from 26% in IMASIS to 36% in CDWBordeaux) (Figure 4). The glucocorticoid prednisone was less frequently used (from 10% in CDWBordeaux to 24% in IMASIS, and not detected in EBB). Bortezomib was the PI most frequently used (24% in IMASIS, 35% in CDWBordeaux, 37% in NCR, and not registered in EBB). Thalidomide was the IMiD most frequently used in NCR (13%), while lenalidomide was the most frequent IMiD registered in CDWBordeaux (13%). Melphalan and Cyclophosphamide were the most frequent used chemotherapies (16% and 3% in CDWBordeaux, respectively; 14% and 8% in NCR, 8% and 3% in IMASIS; and 8% and 10% in EBB). Daratumumab was the most frequently used monoclonal antibody (11% in CDWBordeaux, 4% in NCR, and 2% in IMASIS). Zoledronic acid was the only bisphosphonate used (28% in IMASIS and 4% in CDWBordeaux). We also observed a higher proportion of individuals treated with time at ingredient level (Figures 4 to 6).

Figure 1. Frequency of use of cancer treatment class from 1 to 30 days after diagnosis

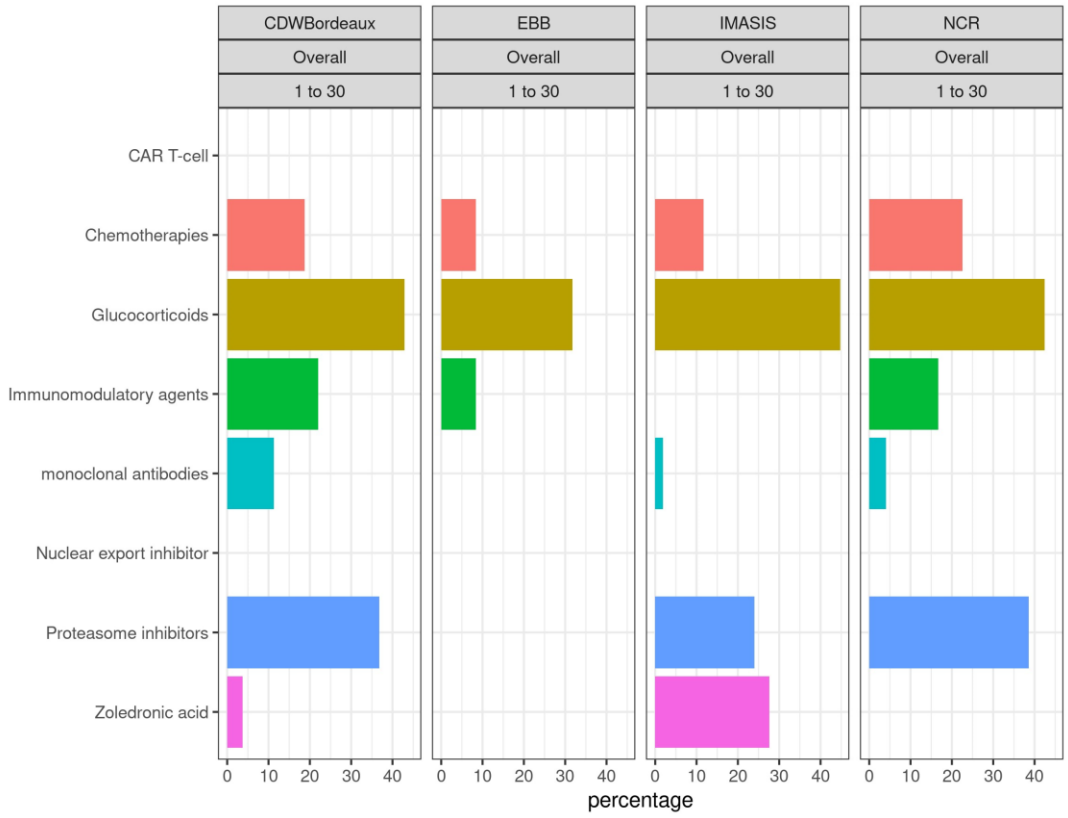


Figure 2. Frequency of use of cancer treatment class from 1 to 90 days after diagnosis

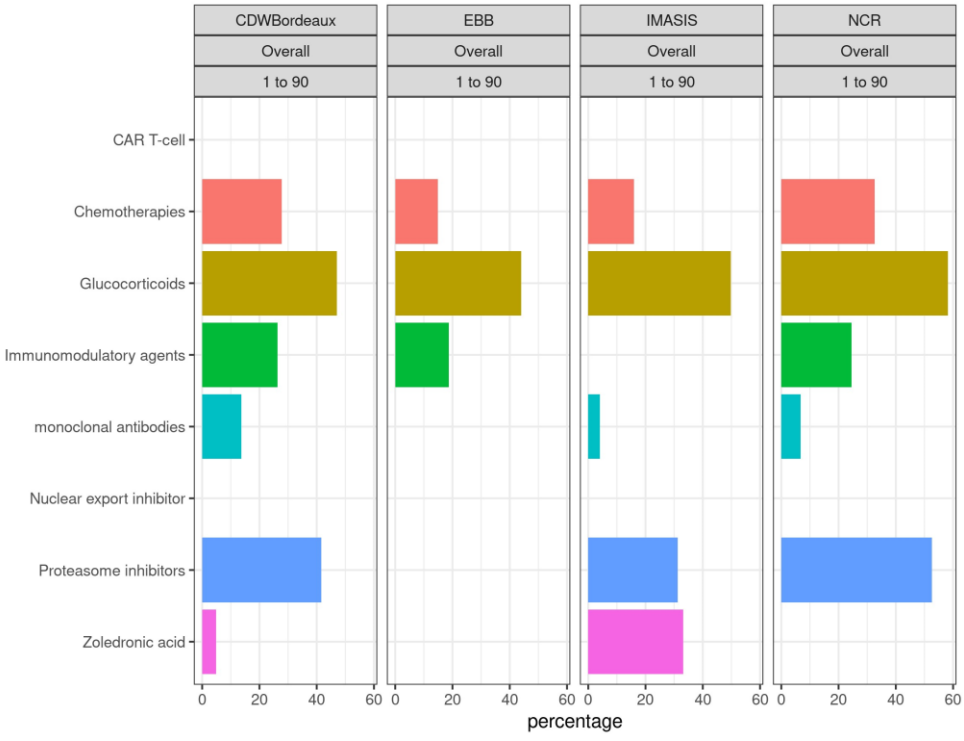


Figure 3. Frequency of use of cancer treatment class from 1 to 365 days after diagnosis

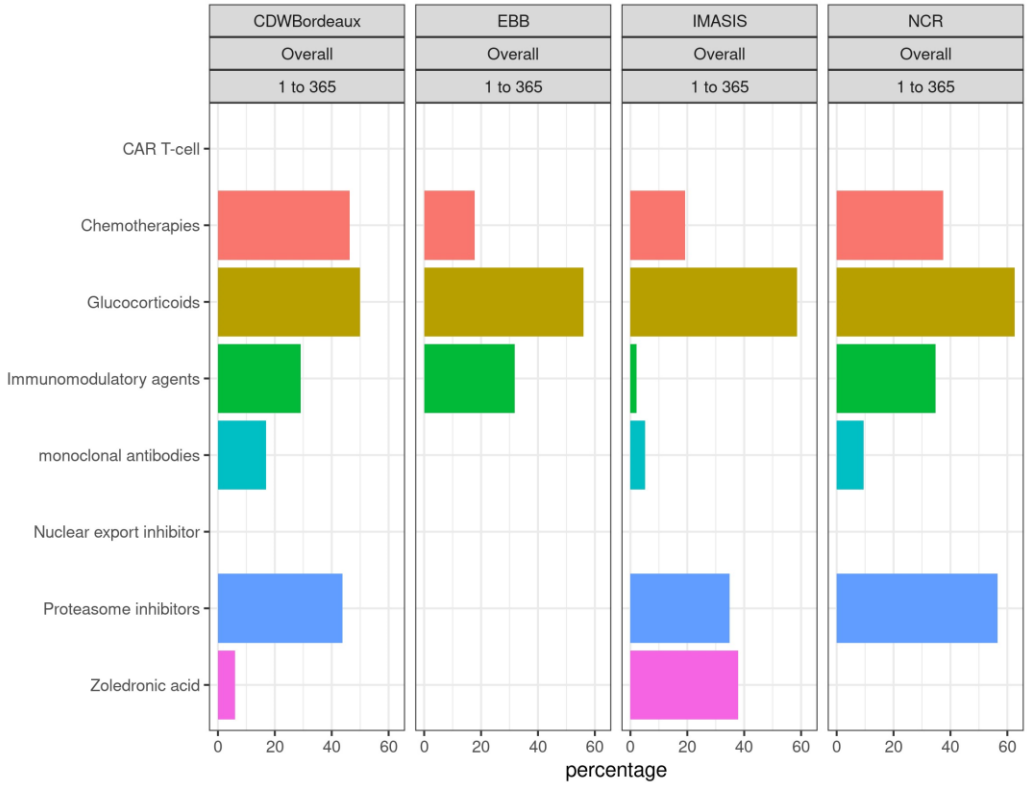


Figure 4. Frequency of use of cancer treatments from 1 to 30 days after diagnosis

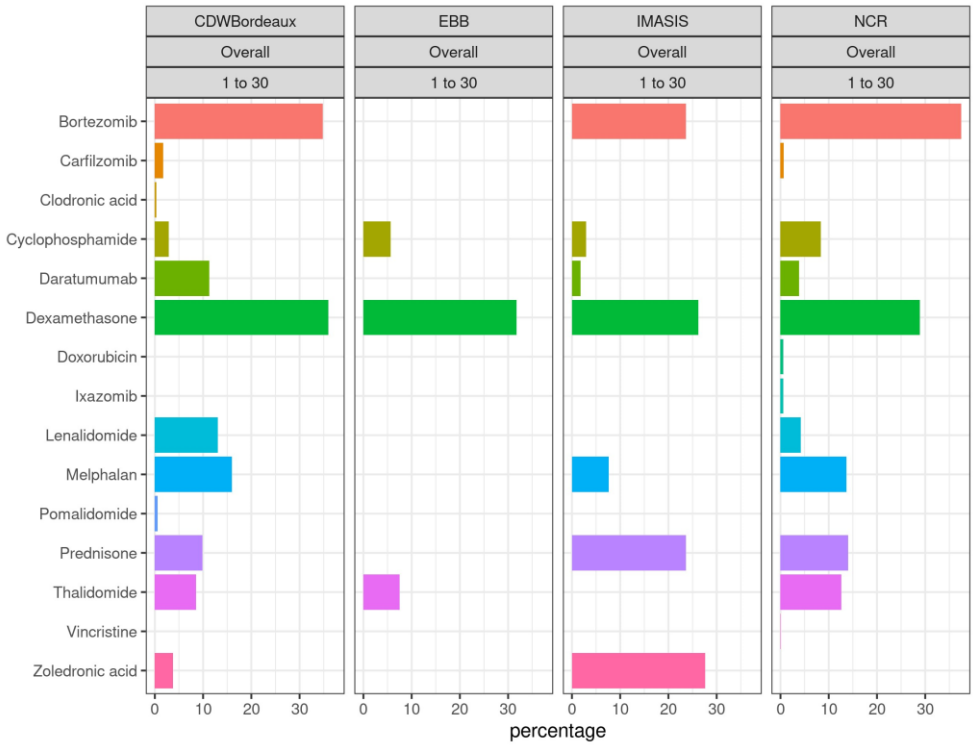


Figure 5. Frequency of use of cancer treatments from 1 to 90 days after diagnosis

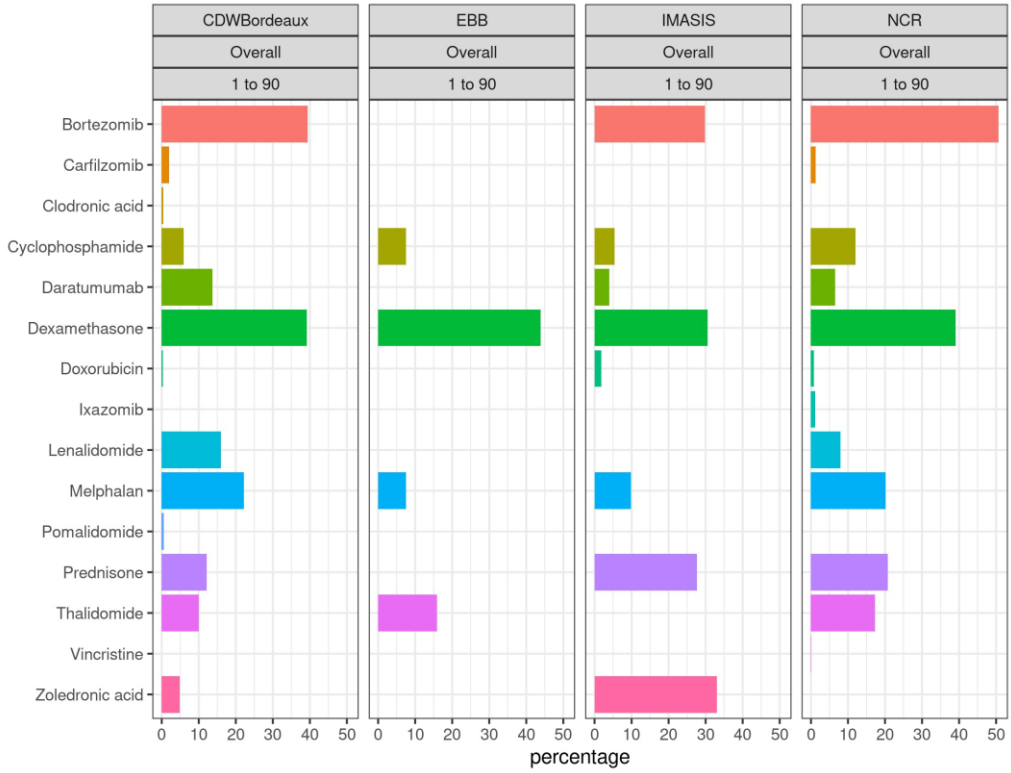
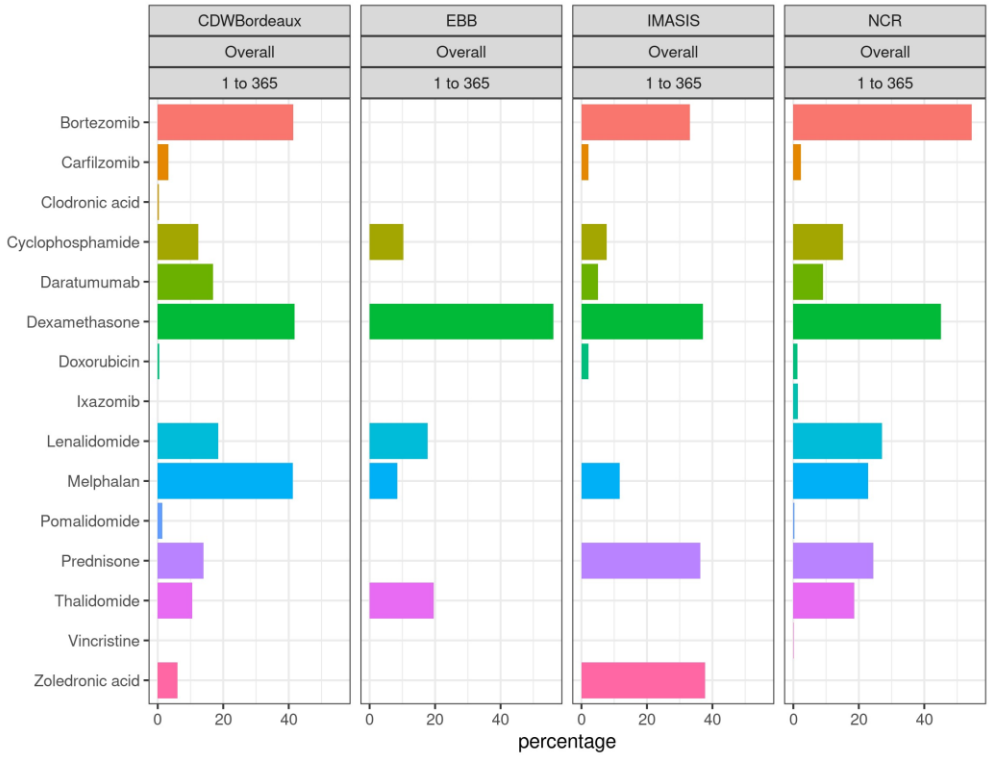


Figure 6. Frequency of use of cancer treatments from 1 to 365 days after diagnosis



Results stratified by sex are only shown for CDWBordeaux and NCR given the small number of individuals in the cohorts of EBB and IMASIS. Also, for simplicity, we are only showing the results by class of treatment. However, all results can be found in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

As shown in Figures 1 to 3 in Appendix III, no meaningful differences can be observed for cancer treatments by sex at 30, 90, or 365 days post index. For example, the use of chemotherapies in NCR was 23%, 32%, and 37% in both males and females during the first 30, 90, and 365 days pots index, respectively.

Results stratified by age groups are also only shown for CDWBordeaux and NCR given the small number of individuals in the cohorts of EBB and IMASIS. Also, for simplicity, we are only showing the results by class of treatment. However, all results can be found in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

Figures 4 to 6 in Appendix III show the proportion of treatment class used in multiple myeloma individuals by age groups at 30, 90, or 365 days post index. In CDWBordeaux, individuals aged >=70 years were less frequently treated with chemotherapies, IMiDs and PIs than younger individuals. For example, at 365 days pots index, the proportion of individuals aged >=70 years treated with chemotherapies, IMiDs and PIs was 23%, 21%, and 36%, respectively, compared to 67%, 37%, and 48% observed in invididuals aged 45 to 59 years. On the other hand, individuals aged >=70 years in CDWBordeaux were more frequently treated with glucocorticoids and monoclonal antibodies than younger age groups. At 365 days pots index, the proportion of individuals aged >=70 years treated with glucocorticoids and monoclonal antibodies was 52%, and 17%, respectively, compared to 44%, and 14% observed in invididuals aged 45 to 59 years.

In NCR, individuals aged >=70 years were less frequently treated with glucocorticoids, IMiDs and PIs than younger individuals. For example, at 365 days pots index, the proportion of individuals aged >=70 years treated with glucocorticoids, IMiDs and PIs was 55%, 14%, and 45%, respectively, compared to 62%, 38%, and 61% observed in invididuals aged 45 to 59 years. On the other hand, individuals aged >=70 years in NCR were more frequently treated with chemotherapies and monoclonal antibodies than younger age groups. At 365 days pots index, the proportion of individuals aged >=70 years treated with chemotherapies and monoclonal antibodies was 38%, and 10%, respectively, compared to 25%, and 3% observed in invididuals aged 45 to 59 years.

The observed differences in treatments by age groups were similar in the studied time windows.

12.2.4 Treatment sequences

CDWBordeaux was the only database where it was possible to study treatment sequences, as the EBB and IMASIS cohort were too small and NCR only included first-line therapies. In CDWBordeaux, the most common treatment sequence observed was Melphalan without subsequent therapies (27%). This was followed by the treatment sequence Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan (7%), Daratumumab without subsequent therapies (6%), and the sequence of treatments Prednisone-Melphalan-Bortezomib (5%). A full picture of overall treatment sequences is shown as a sunburst plot in Figure 13 and as a sankey diagram in Figure 14.

Figure 13. Sunburst plot of multiple myeloma treatments in CDWBordeaux, overall

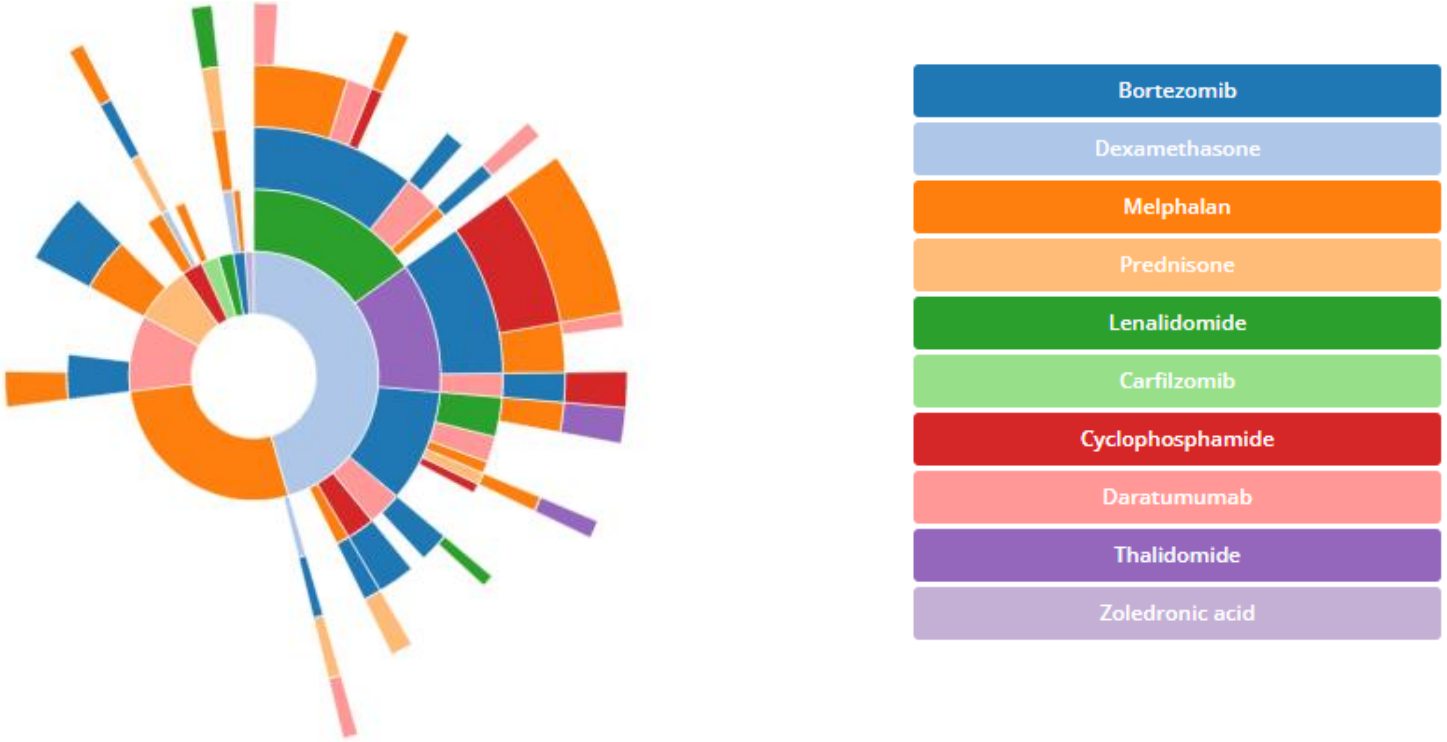
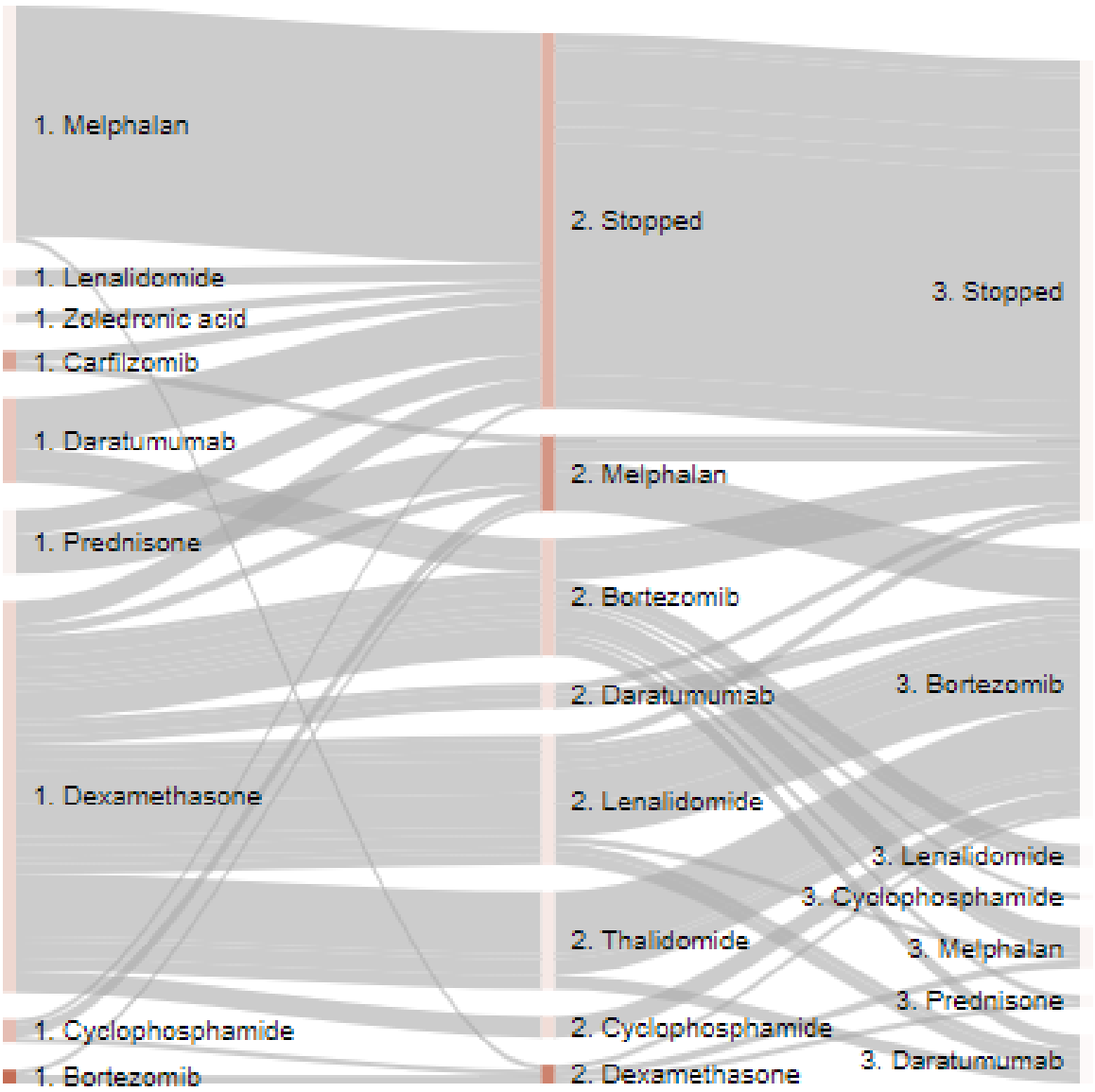


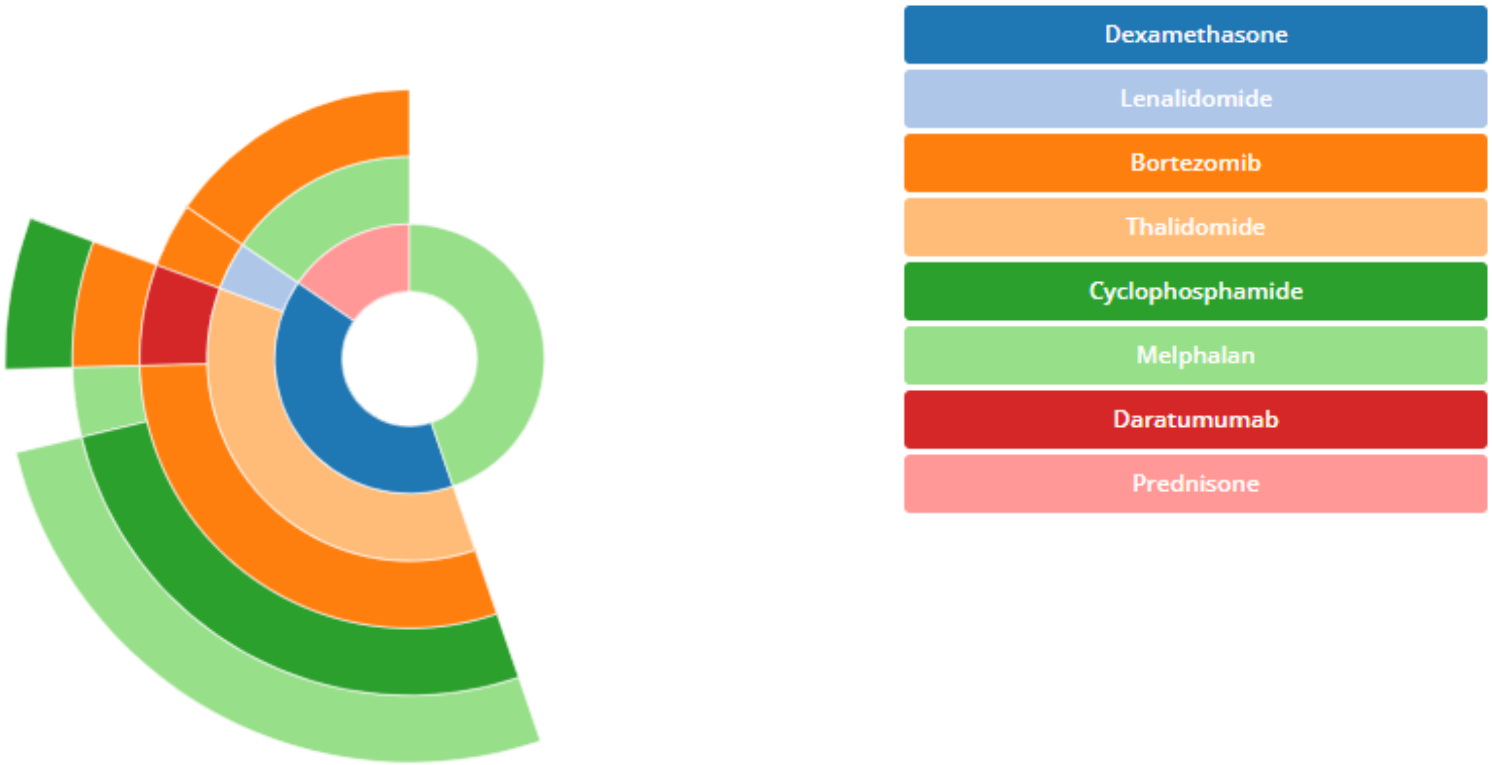
Figure 14. Sankey diagram of multiple myeloma treatments in CDWBordeaux, overall



When stratifying results by study period, the most common treatment sequences in 2017 or earlier were 1) Melphalan only (45%), 2) Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan (27%), and 3) Prednisone-Melphalan-Bortezomib (15%). However, from 2018 onwards this changed to 1) Melphalan only (47%), 2) Daratumumab only (15%), and 3) Dexamethasone-Lenalidomide-Bortezomib-Melphalan (9%). See sunburst, Figure 15A and Figure 15B, and sankey diagrams, Figure 16A and Figure 16B, by study period below.

Figure 15. Sunburst plot of multiple myeloma treatments in CDWBordeaux, by study period

A) 2017 or earlier



B) 2018 or later


Carfilzomib
Melphalan
Daratumumab
Bortezomib
Dexamethasone
Lenalidomide

Figure 16. Sankey diagram of multiple myeloma treatments in CDWBordeaux, by study period

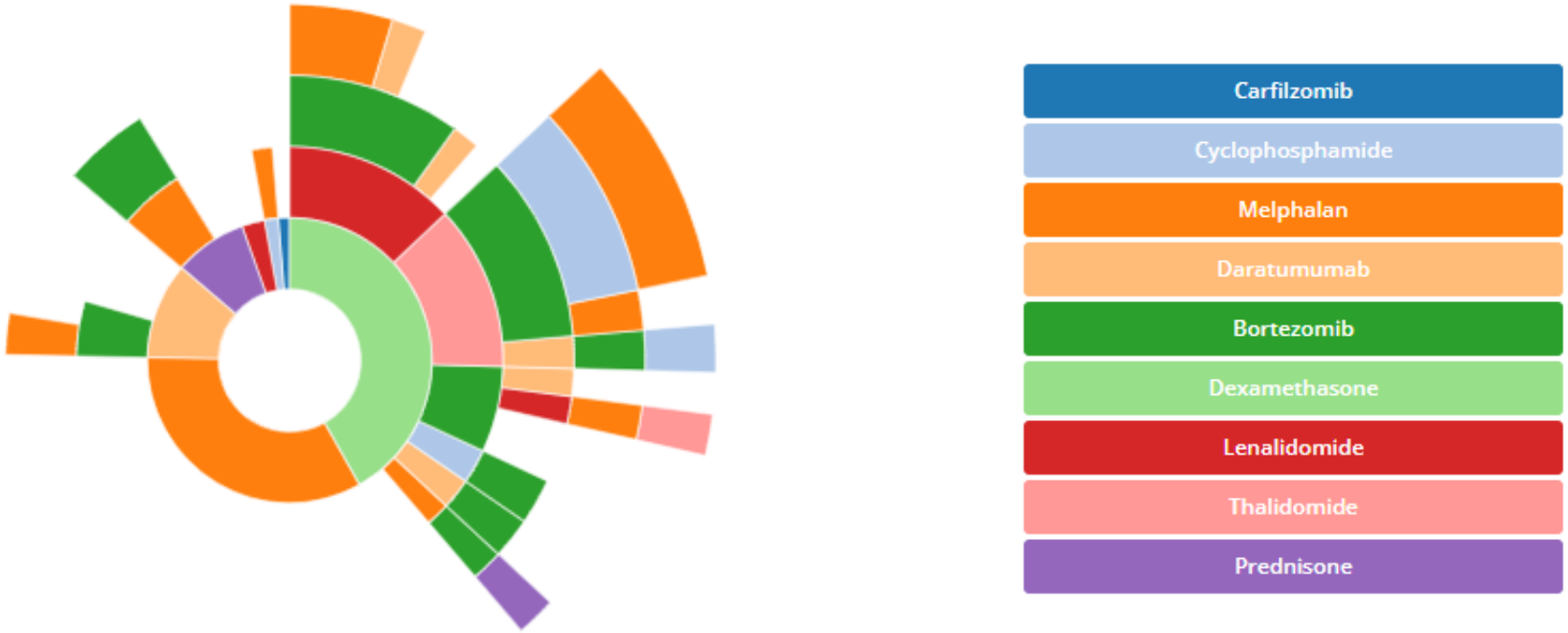
A) 2017 or earlier

B) 2018 or later

Treatment sequences were consistent by sex. For males the most common treatment sequences were 1) Melphalan (34%), 2) Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan (9%), and 3) Daratumumab (7%). Meanwhile, for females the most common treatment sequences were 1) Melphalan (28%), 2) Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan (8%), and 3) Daratumumab (7%) (Figures 17 and 18).

Figure 17. Sunburst plot of multiple myeloma treatments in CDWBordeaux, by sex

A) Males



B) Females

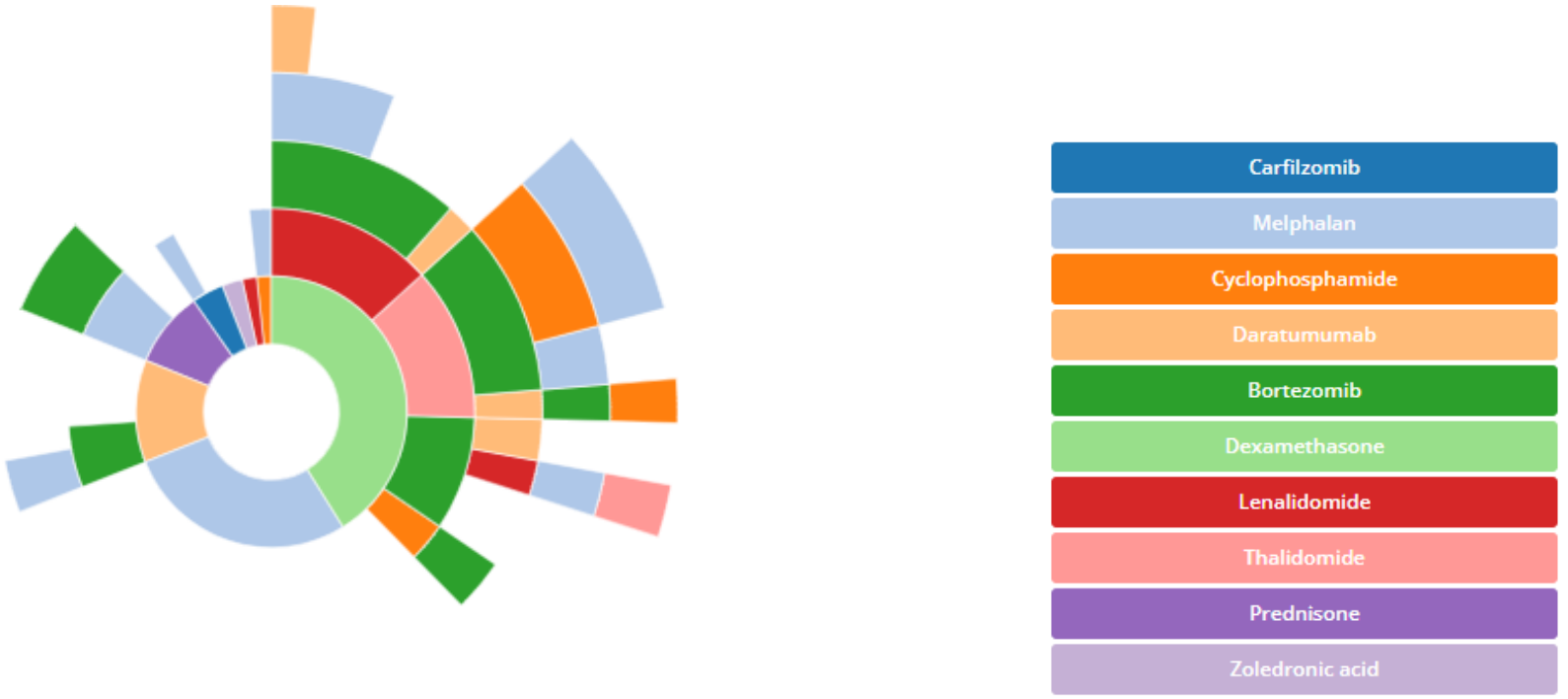
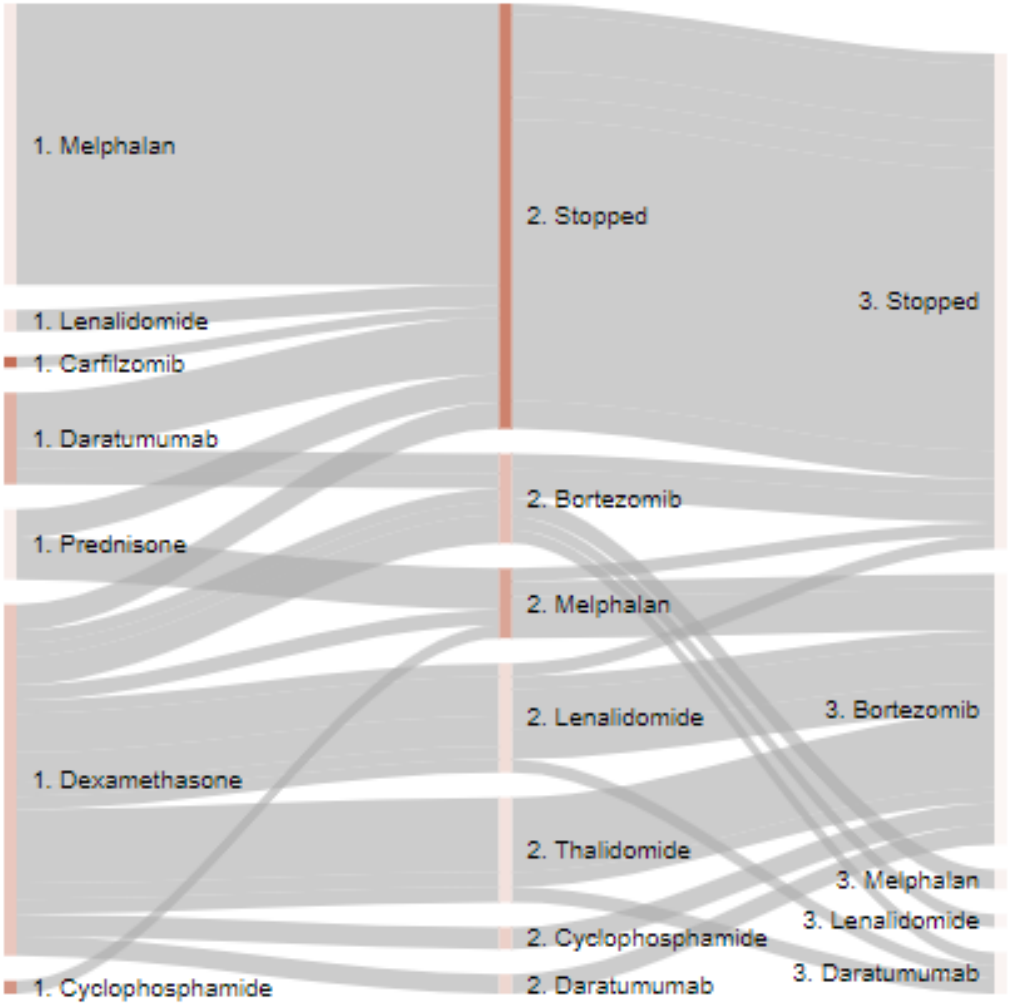

Carfilzomib
Melphalan
Cyclophosphamide
Daratumumab
Bortezomib
Dexamethasone
Lenalidomide
Thalidomide
Prednisone
Zoledronic acid

Figure 18. Sankey diagram plot of multiple myeloma treatments in CDWBordeaux, by sex

A) Males

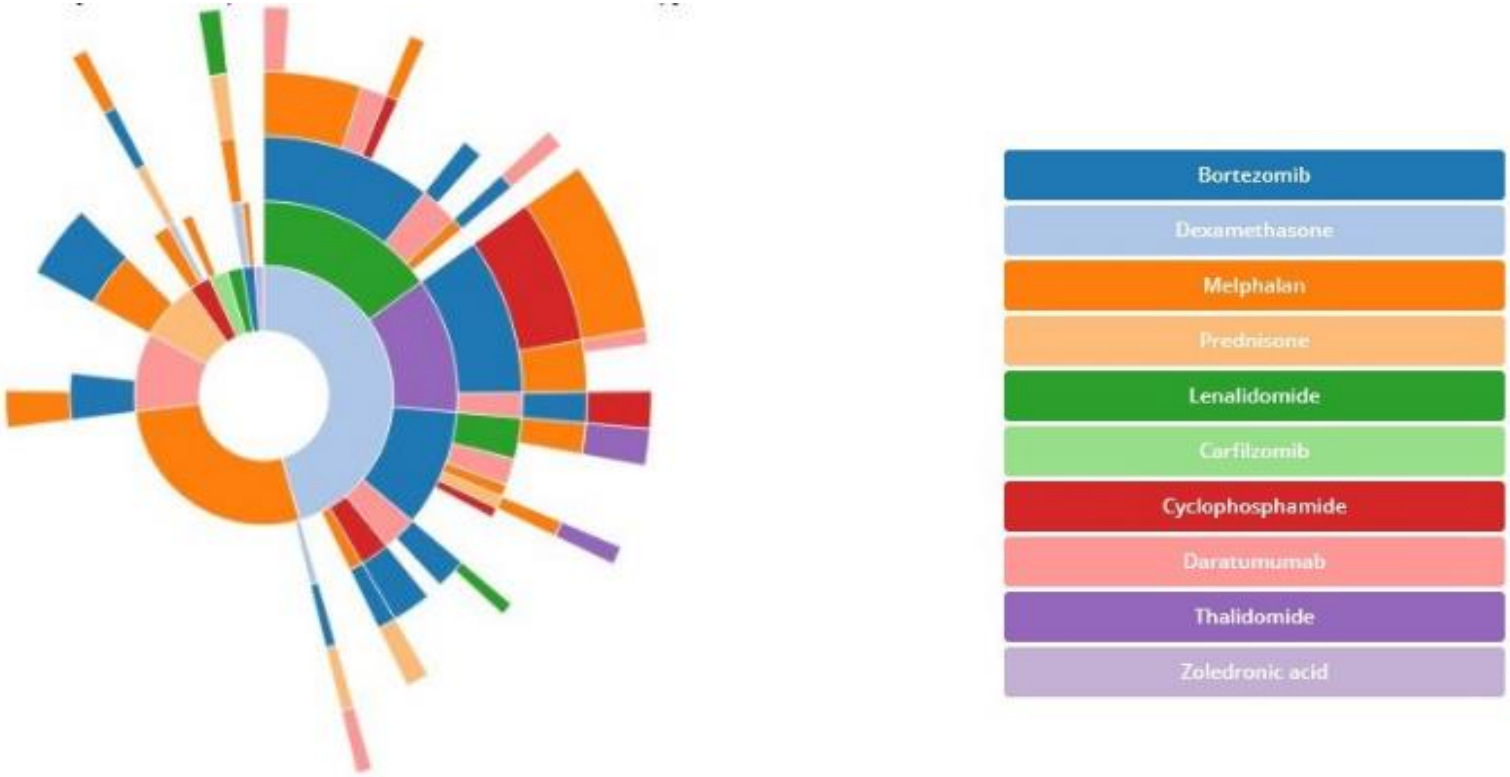


B) Females

Treatment sequences varied by age group. For those aged between 44 and 59 the most common treatment sequences were 1) Melphalan (45%), 2) Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan (15%), and 3) Dexamethasone-Lenalidomide-Bortezomib-Melphalan (9%). However, for those aged 70 or older, the most common treatment sequences were 1) Daratumumab (15%), 2) Prednisone-Melphalan-Bortezomib (13%), and 3) Dexamethasone-Bortezomib (8%) (Figures 19 and 20).

Figure 19. Sunburst plot of multiple myeloma treatments in CDWBordeaux, by age group

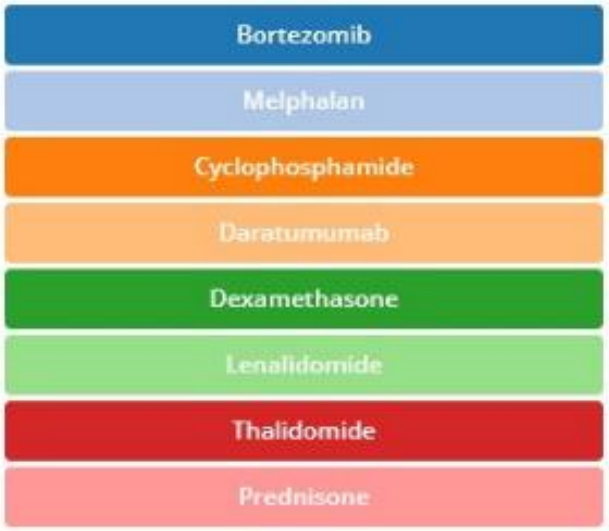
A) 18 to 44



B) 45 to 59


Carfilzomib
Melphalan
Cyclophosphamide
Daratumumab
Bortezomib
Dexamethasone
Lenalidomide
Thalidomide

C) 60 to 69

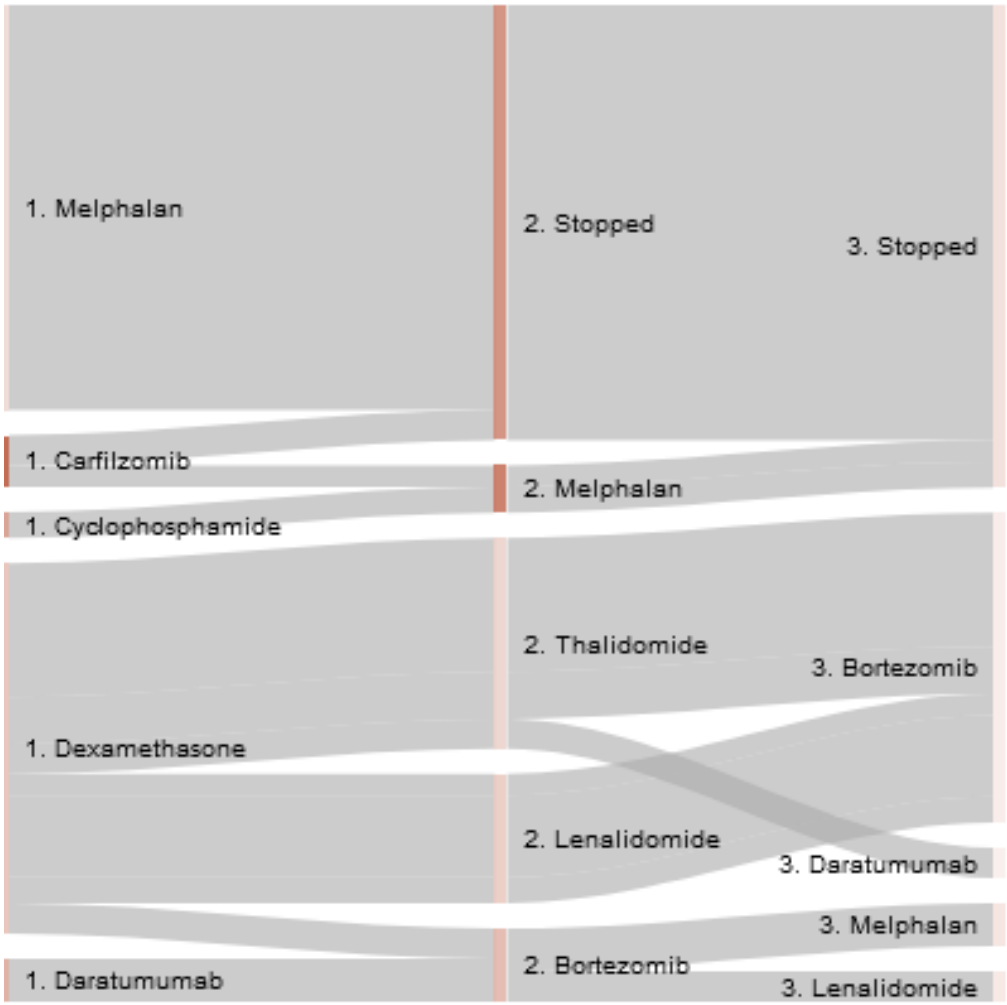

Bortezomib
Melphalan
Cyclophosphamide
Daratumumab
Dexamethasone
Lenalidomide
Thalidomide
Prednisone

D) 70 or older


Bortezomib
Dexamethasone
Melphalan
Prednisone
Lenalidomide
Daratumumab
Cyclophosphamide
Zoledronic acid

Figure 18. Sankey diagram plot of multiple myeloma treatments in CDWBordeaux, by age group

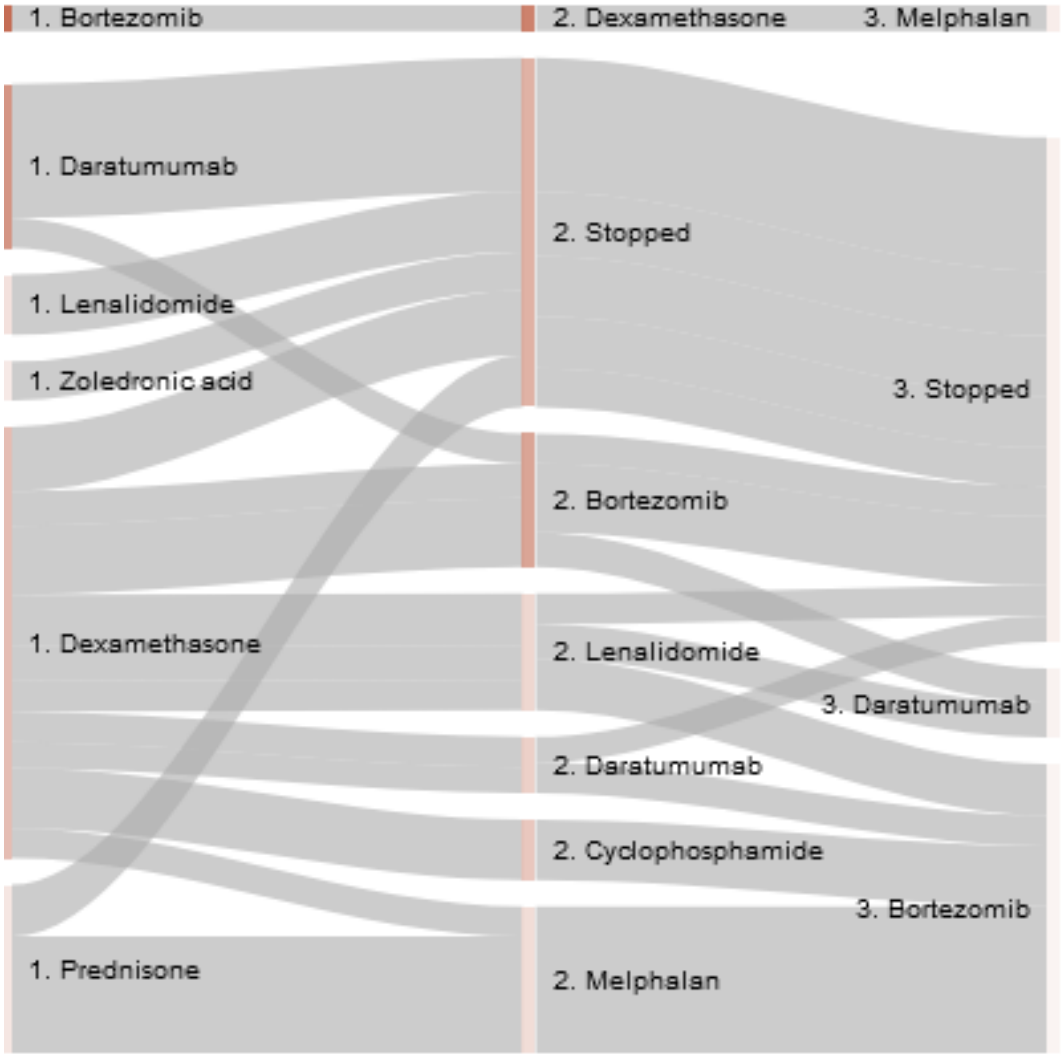
A) 45 to 59



B) 60 to 69


1. Melphalan
1. Daratumumab
1. Prednisone
1. Bortezomib
1. Cyclophosphamide
1. Dexamethasone
2. Stopped
2. Melphalan
2. Bortezomib
2. Lenalidomide
2. Thalidomide
3. Stopped
3. Melphalan
3. Lenalidomide
3. Bortezomib

C) 70 or older



12.3 Survival

12.3.1 Number of Participants

A total of 17,333 individuals were included in Cohort 3 (CDWBordeaux: 1,639, EBB: 90, IMASIS: 301, NCR: 11,745, SIDIAP: 3,558) (Table 26). These were individuals with a first diagnosis of multiple myeloma and with a minimum of 1 year of potential follow-up time available after the date of multiple myeloma diagnosis between 01/01/2012 and 31/12/2022. This cohort was not generated in IQVIA DA Germany since date of death is not systematically available in this database.

12.3.2 Demographic characteristics

Table 32 describes the demographic characteristics of multiple myeloma individuals included in Cohort 3 per database. The majority of individuals were 70 years of older at time of multiple myeloma diagnosis,

with a proportion of cases older than 70 ranging from 39% in EBB to 64% in IMASIS. The median age ranged from 65 years in EBB to 75 years in IMASIS. No cases among individuals aged between 0 and 17 years were observed in EBB and NCR, less than 5 cases were observed in CDWBordeaux and IMASIS, and 77 cases were observed in SIDIAP.

The proportion of males was higher than the proportion of females in CDWBordeaux (54% vs 46%, respectively) and NCR (58% vs 42%), and the same proportion of males and females was observed in IMASIS and SIDIAP (50% in both).

Table 26. Demographic characteristics of multiple myeloma patients in Cohort 3* per database.

		CDWBordeaux	EBB	IMASIS	NCR	SIDIAP
Number subjects		1,639	90	301	11,745	3,558
Age, median [min; q25 - q75; max]		67 [16; 59 - 76; 97]	65 [19; 57 - 73; 86]	75 [1; 64 - 83; 95]	70 [18; 62 - 77; 98]	71 [0; 60 - 80; 104]
Age group, N (%)	0 to 17	<5	<5	<5	<5	77 (2%)
	18 to 44	46 (3%)	7 (8%)	11 (4%)	227 (2%)	167 (5%)
	45 to 59	398 (24%)	26 (29%)	31 (10%)	2,069 (18%)	617 (17%)
	60 to 69	522 (32%)	22 (24%)	64 (21%)	3,346 (28%)	800 (22%)
	>=70	687 (42%)	35 (39%)	192 (64%)	6,103 (52%)	1,897 (53%)
Sex, N (%)	Female	756 (46%)	52 (58%)	150 (50%)	4,918 (42%)	1,795 (50%)
	Male	898 (54%)	38 (42%)	151 (50%)	6,827 (58%)	1,763 (50%)

*Cohort 3: individuals with a first diagnosis of multiple myeloma, with no history of other cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma, and with a minimum of 1 year of potential follow-up time available after the date of multiple myeloma diagnosis between 01/01/2012 and 31/12/2022.

12.3.3 Proportion of deaths

From 17,333 individuals in cohort 3, 7,981 (46%) died during the study period. The overall proportion of deaths among multiple myeloma cases in cohort 3 was 16% in CDWBordeaux, 29% in EBB, 38% in IMASIS, 45% in SIDIAP, and 50% in NCR (Table 27). The low proportion of death in CDWBordeaux suggests that deaths might have been partially captured in this database.

12.3.4 Survival probabilities

Overall survival was calculated using data on time at risk of death from any cause and the Kaplan-Meier (KM) method. Results are reported as plots of the estimated survival curves (Figures 19-22) as well as the estimated probability of survival at years 1, 3, 5(Table 27).

Overall, the restricted mean survival ranged from 5.2 years in IMASIS to 8.0 years in CDWBordeaux. The median survival ranged from 4.8 years in IMASIS to 8.4 years in EBB. The 1-year survival probability (95%CI) ranged from 0.79 (0.74 to 0.84) in IMASIS to 0.92 (0.91 to 0.94) and 0.92 (0.87 to 0.98) in CDWBordeaux and EBB, respectively. The 3-year survival probability ranged from 0.62 (0.56 to 0.69) to 0.84 (0.82 to 0.86) in CDWBordeaux. The 5-year survival probability ranged from 0.49 (0.42 to 0.58) in IMASIS to 0.78 (0.75 to 0.81) in CDWBordeaux. Results from IMASIS, NCR and SIDIAP were very similar, with a 5-year probability of 0.49

(0.42 to 0.58), 0.51 (0.5 to 0.52), and 0.54 (0.52 to 0.56), respectively. Figure 19 shows the Kaplan-Meier overall survival curves for each database.

Survival was similar among females and males in all databases with the exception of EBB in which the 5-year survival probability was 0.88 (0.79 to 0.97) in females and 0.57 (0.40 to 0.79) in males. However, it must be noted that these differences might be due to the small number of events in this database (10 and 16 deaths were reported in females and males, respectively). Figure 20 shows the Kaplan-Meier survival curves stratified by sex.

Overall survival decreased with age, with survival among the age group of individuals of >=70 years of age being the lowest. In SIDIAP, for example, the 5-year survival probability was of 0.90 (0.83 to 0.96) among the age group of 18 to 44 years, 0.76 (0.72 to 0.8) among those from 45 to 59, 0.69 (0.65 to 0.73) among those from 60 to 69, and 0.39 (0.36 to 0.41) among those aged >=70. Figure 21 shows the Kaplan-Meier survival curves stratified by age group.

We estimated overall survival by study period: 2017 or earlier and 2018 or later. The 1- and 3-year survival probability was similar between periods for most databases. In SIDIAP for example, the 3-year survival probability in 2017 or earlier was 0.68 (0.66 to 0.7) and 0.71 (0.68 to 0.73) in 2018 or later. In IMASIS, however, we observed a 1- and 3-year survival probability of 0.75 (0.69 to 0.83) and 0.55 (0.46 to 0.64), respectively, in 2017 or earlier, and a probability of 0.83 (0.77to 0.90) and 0.74 (0.65 to 0.83) in 2018 or later. Figure 22 shows the Kaplan-Meier survival curves stratified by study period.

All results can be found in the shiny app https://data-dev.darwin-eu.org/EUPAS105033/.

Table 27. Survival of multiple myeloma patients in Cohort 3 overall and stratified by sex, age group and study period

Database	Population subgroups	Cases (N)	Events (N)	Restricted mean survival (years)*	Median survival (years)**	1 year survival probability (95%CI)	3 year survival probability (95%CI)	5 year survival probability (95%CI)
CDWBordeaux	Overall	1644	262	7.96		0.92 (0.91 to 0.94)	0.84 (0.82 to 0.86)	0.78 (0.75 to 0.81)
CDWBordeaux	Female	752	120	7.92		0.93 (0.91 to 0.95)	0.83 (0.79 to 0.86)	0.78 (0.74 to 0.82)
CDWBordeaux	Male	892	142	8.00		0.92 (0.9 to 0.94)	0.85 (0.83 to 0.88)	0.77 (0.74 to 0.81)
CDWBordeaux	0 to 17					NA (NA to NA)	NA (NA to NA)	NA (NA to NA)
CDWBordeaux	18 to 44	46	2	9.59		0.98 (0.93 to 1)	0.95 (0.89 to 1)	0.95 (0.89 to 1)
CDWBordeaux	45 to 59	398	26	9.22		0.99 (0.98 to 1)	0.95 (0.92 to 0.97)	0.91 (0.88 to 0.95)
CDWBordeaux	60 to 69	518	71	8.34		0.95 (0.93 to 0.97)	0.86 (0.82 to 0.89)	0.81 (0.76 to 0.85)
CDWBordeaux	>=70	681	163	6.29	6.81	0.85 (0.82 to 0.88)	0.74 (0.7 to 0.78)	0.62 (0.56 to 0.68)
CDWBordeaux	2017 or earlier	890	117	2.71		0.92 (0.9 to 0.94)	0.84 (0.81 to 0.86)	
CDWBordeaux	2018 or later	754	76	2.72		0.93 (0.91 to 0.95)	0.85 (0.82 to 0.89)	
EBB	Overall	90	26	6.96	8.35	0.92 (0.87 to 0.98)	0.79 (0.71 to 0.89)	0.76 (0.67 to 0.86)
EBB	Female	52	10	8.22	9.88	0.96 (0.91 to 1)	0.88 (0.79 to 0.97)	0.88 (0.79 to 0.97)
EBB	Male	38	16	4.85	5.03	0.87 (0.77 to 0.98)	0.66 (0.52 to 0.86)	0.57 (0.4 to 0.79)
EBB	18 to 44	7	0	9.88		1 (1 to 1)	1 (1 to 1)	1 (1 to 1)
EBB	45 to 59	26	6	6.89	8.35	0.96 (0.89 to 1)	0.92 (0.81 to 1)	0.85 (0.71 to 1)
EBB	60 to 69	22	5	8.21	9.88	0.95 (0.87 to 1)	0.85 (0.71 to 1)	0.85 (0.71 to 1)
EBB	>=70	35	15	5.22	5.44	0.86 (0.75 to 0.98)	0.61 (0.45 to 0.82)	0.55 (0.38 to 0.79)
EBB	2017 or earlier	51	12	2.59		0.92 (0.85 to 1)	0.76 (0.66 to 0.89)	
EBB	2018 or later	39	5	2.71		0.92 (0.84 to 1)	0.85 (0.74 to 0.99)	
IMASIS	Overall	301	114	5.16	4.82	0.79 (0.74 to 0.84)	0.62 (0.56 to 0.69)	0.49 (0.42 to 0.58)
IMASIS	Female	150	55	5.28	4.82	0.73 (0.66 to 0.81)	0.62 (0.53 to 0.72)	0.49 (0.38 to 0.62)
IMASIS	Male	151	59	5.00	4.76	0.84 (0.78 to 0.9)	0.62 (0.53 to 0.72)	0.5 (0.4 to 0.62)
IMASIS	0 to 17					NA (NA to NA)	NA (NA to NA)	NA (NA to NA)
IMASIS	18 to 44	11	0	10.00		1 (1 to 1)	1 (1 to 1)	1 (1 to 1)
IMASIS	45 to 59	31	6	7.24		0.93 (0.84 to 1)	0.76 (0.59 to 0.98)	0.76 (0.59 to 0.98)
IMASIS	60 to 69	64	20	6.34		0.83 (0.74 to 0.93)	0.7 (0.59 to 0.85)	0.61 (0.48 to 0.78)
IMASIS	>=70	192	88	3.78	3.45	0.74 (0.67 to 0.81)	0.54 (0.47 to 0.64)	0.37 (0.28 to 0.49)
IMASIS	2017 or earlier	163	59	2.12		0.75 (0.69 to 0.83)	0.55 (0.46 to 0.64)	
IMASIS	2018 or later	138	29	2.42		0.83 (0.77 to 0.9)	0.74 (0.65 to 0.83)	

NCR	Overall	11745	5964	5.47	5.25	0.83 (0.82 to 0.83)	0.65 (0.64 to 0.66)	0.51 (0.5 to 0.52)
NCR	Female	4918	2502	5.50	5.32	0.83 (0.82 to 0.84)	0.65 (0.64 to 0.66)	0.52 (0.5 to 0.53)
NCR	Male	6827	3462	5.45	5.21	0.83 (0.82 to 0.84)	0.65 (0.64 to 0.66)	0.51 (0.5 to 0.52)
NCR	18 to 44	227	46	8.18		0.92 (0.89 to 0.96)	0.84 (0.79 to 0.89)	0.81 (0.76 to 0.87)
NCR	45 to 59	2069	589	7.59		0.93 (0.92 to 0.94)	0.82 (0.81 to 0.84)	0.75 (0.73 to 0.77)
NCR	60 to 69	3346	1391	6.37	7.15	0.89 (0.88 to 0.9)	0.75 (0.74 to 0.77)	0.63 (0.61 to 0.64)
NCR	>=70	6103	3938	4.10	3.28	0.76 (0.74 to 0.77)	0.53 (0.51 to 0.54)	0.36 (0.34 to 0.37)
NCR	2017 or earlier	6891	2480	2.35		0.82 (0.82 to 0.83)	0.64 (0.63 to 0.65)	
NCR	2018 or later	4854	1435	2.39		0.83 (0.82 to 0.84)	0.67 (0.65 to 0.68)	
SIDIAP	Overall	3558	1615	5.70	5.70	0.86 (0.85 to 0.87)	0.69 (0.67 to 0.7)	0.54 (0.52 to 0.56)
SIDIAP	Female	1795	781	5.90	5.82	0.87 (0.86 to 0.89)	0.71 (0.69 to 0.73)	0.56 (0.54 to 0.59)
SIDIAP	Male	1763	834	5.49	5.40	0.84 (0.83 to 0.86)	0.67 (0.64 to 0.69)	0.52 (0.49 to 0.55)
SIDIAP	0 to 17	77	0	10.00		1 (1 to 1)	1 (1 to 1)	1 (1 to 1)
SIDIAP	18 to 44	167	13	9.03		0.98 (0.96 to 1)	0.96 (0.92 to 0.99)	0.9 (0.83 to 0.96)
SIDIAP	45 to 59	617	145	7.71		0.94 (0.92 to 0.96)	0.84 (0.81 to 0.87)	0.76 (0.72 to 0.8)
SIDIAP	60 to 69	800	267	6.98	8.19	0.93 (0.92 to 0.95)	0.83 (0.8 to 0.86)	0.69 (0.65 to 0.73)
SIDIAP	>=70	1897	1190	4.30	3.56	0.79 (0.77 to 0.8)	0.56 (0.53 to 0.58)	0.39 (0.36 to 0.41)
SIDIAP	2017 or earlier	2147	676	2.45		0.86 (0.84 to 0.87)	0.68 (0.66 to 0.7)	
SIDIAP	2018 or later	1411	336	2.48		0.86 (0.84 to 0.88)	0.71 (0.68 to 0.73)	

* Restricted mean survival was calculated for up to 10 years

** Note, median survival is not calculated for groups where survival was more than 50% in the group at the last time point.

Figure 19. Kaplan-Meier survival curves in Cohort 3 per database

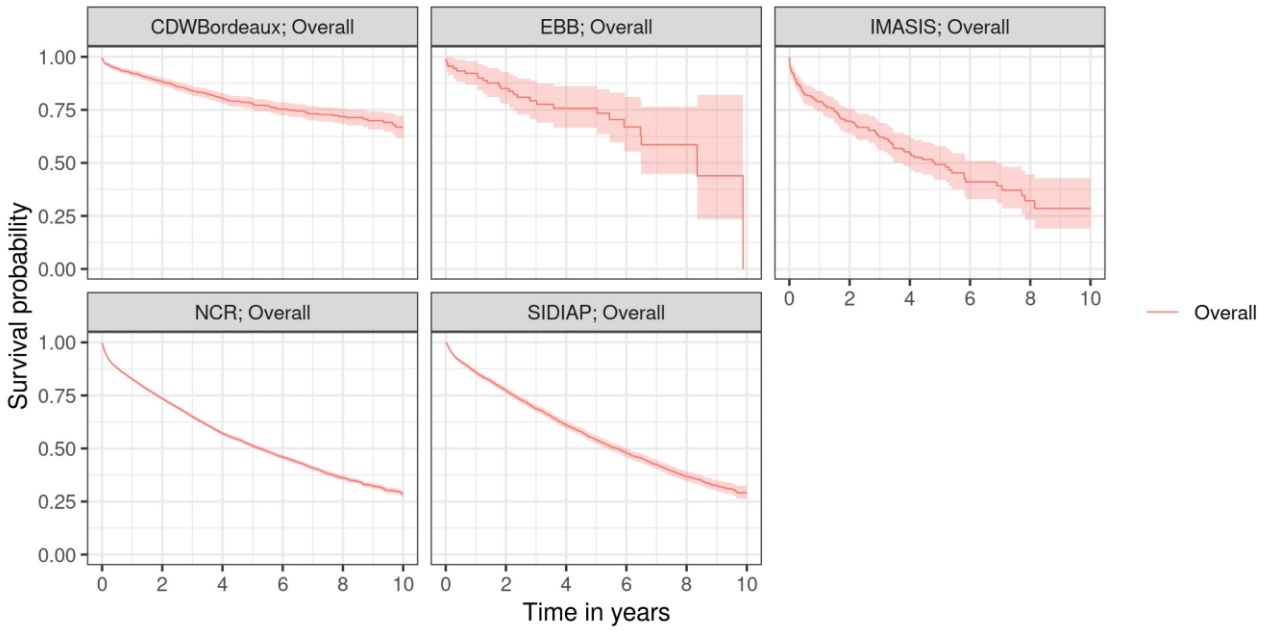


Figure 20. Kaplan-Meier survival curves stratified by sex

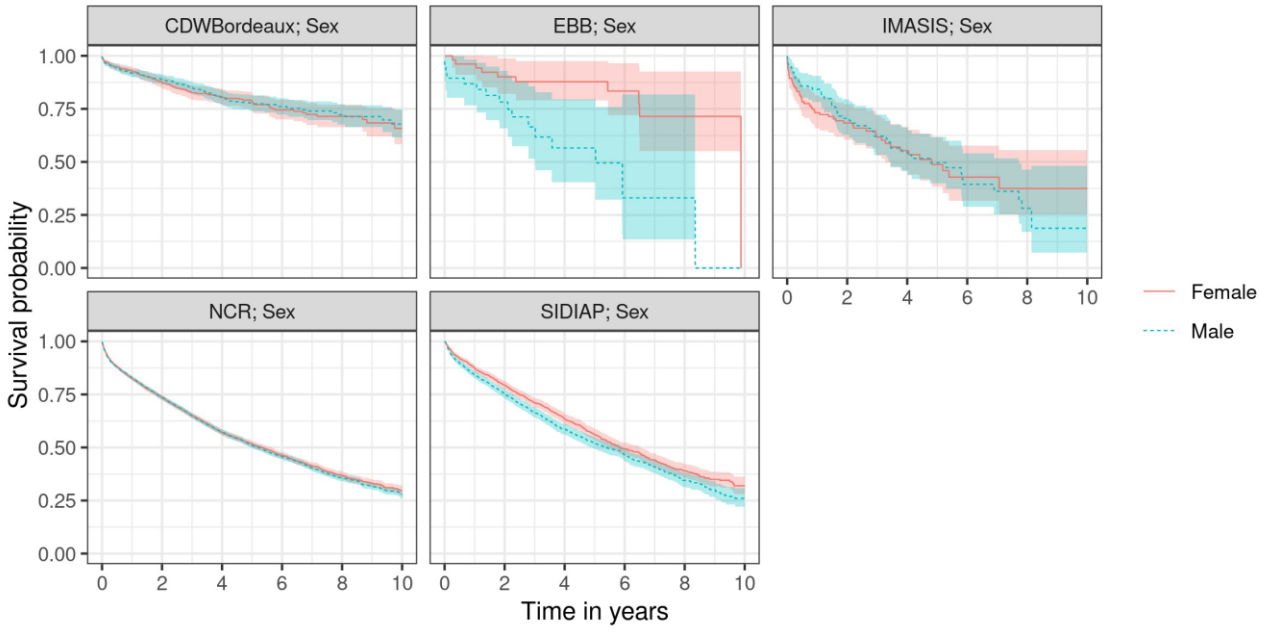


Figure 21. Kaplan-Meier survival curves stratified by age group

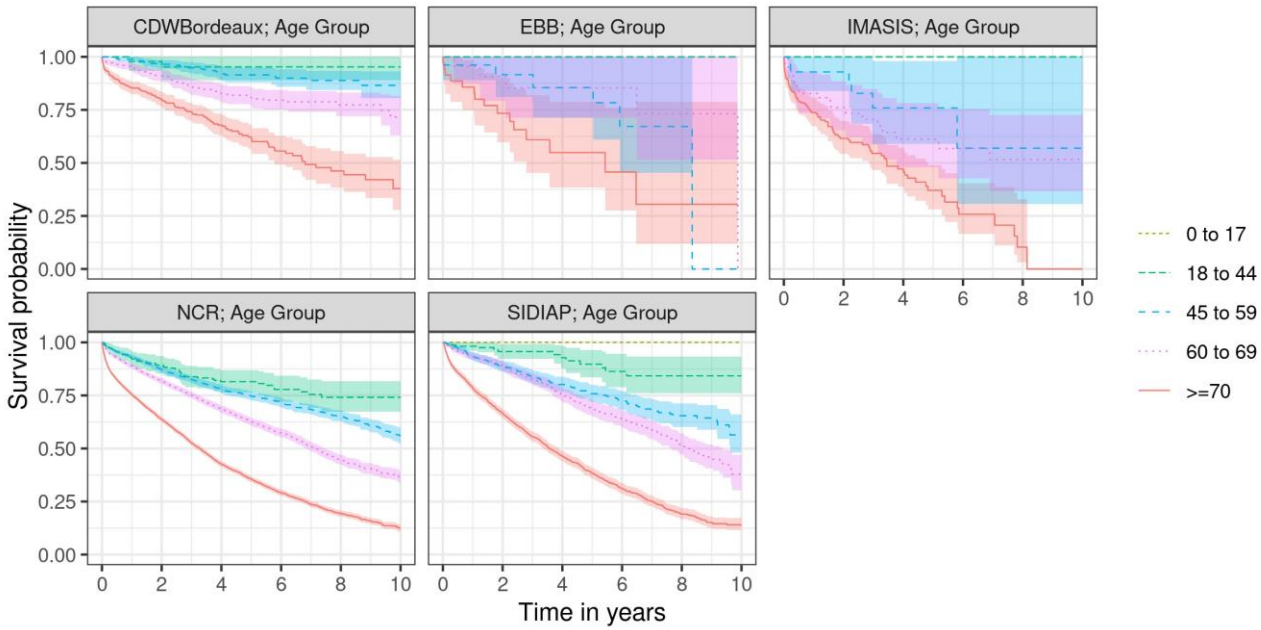
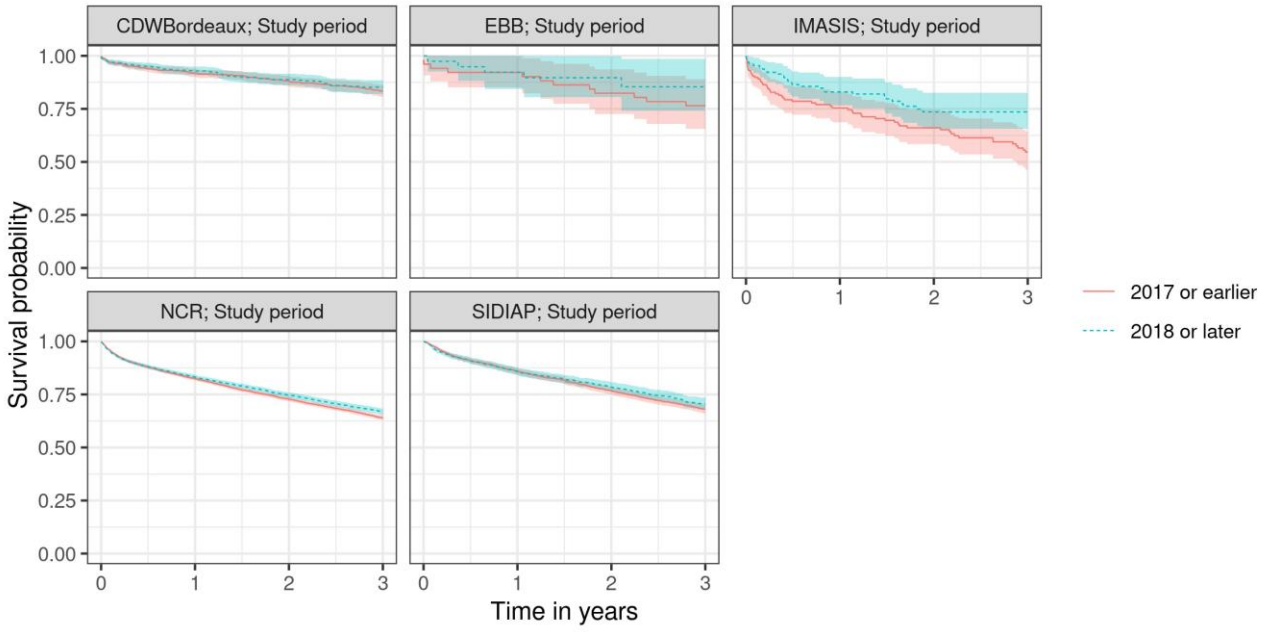


Figure 22. Kaplan-Meier survival curves stratified by study period



13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the new guideline on good pharmacovigilance practice (EMA/873138/2011), there was no requirement for expedited reporting of adverse drug reactions as only secondary data was used.

14 DISCUSSION

14.1 Key Results

In this study, we identified 30,319 individuals newly diagnosed with multiple myeloma from 2012 and 2022 in 6 databases from 5 countries (CDWBordeaux: 1,781, EBB: 111, IQVIA DA Germany: 12,360, IMASIS: 329, NCR: 11,745, SIDIAP: 3,993). The majority of individuals were 70 years of age or older at the time of multiple myeloma diagnosis, with a proportion of cases older than 70 ranging from 41% in EBB to 64% in IMASIS. In most databases, approximately 50% of cases were men. In NCR, however, the majority of cases were men (58%), while in EBB, the majority of cases were women (59%).

Large-scale characterisation

We provided large-scale characterisation for a total of 12,207 individuals (Cohort 1), describing all conditions and medications registered in each database at different time windows prior, at, and post index date, and stratified by sex and age groups. Overall, the most frequent co-morbidities were hypertension, renal impairment, hyperlipidemia, osteoarthritis, urinary tract infection, diabetes mellitus, and obesity. The least frequent conditions were schizophrenia, ADHD, HIV, Crohn's disease, and ulcerative colitis. There were variations in the frequency of these conditions per database (e.g.: at index, hypertension was present in 27% of cases in SIDIAP vs 48% if cases in IQVIA DA Germany), however, the ranking of most and least frequent co-morbidities was similar (e.g.: at index, hypertension was the second most frequent co-morbidity in SIDIAP vs the first most frequent co-morbidity in IQVIA DA Germany). These results were similar when stratified by sex, but differed by age groups. The most common co-morbidities in younger age groups (18-59 years) also included anxiety, depression and asthma, while renal impairment was one of the most frequent co-morbidities among those aged >=70 years.

As for co-medications, the most frequently used were medicines for acid related disorders, agents acting on the renin-angiotensin system, lipid modifying agents, opioids and psycholeptics. The least frequent medications were antipsoriatics and psychostimulants. Medication use was similar in time windows prior to index date in most databases, while in post index periods an increase in frequency and number of medicines was observed. These results were similar by sex, but differed by age groups. Overall, medication use was more frequent in older age groups consistently across databases and time periods; with the exception of antineoplastic agents post index that was more frequently used in younger age groups.

Multiple Myeloma Treatments

13,258 individuals were included in Cohort 2 which was used to summarise multiple myeloma treatments. 18 out of the 32 multiple myeloma treatments were ever used in the studied databases among individuals from 2012 to 2022. The most frequently used class of treatment in the year following diagnosis were glucocorticoids, with their use ranging from 50% to 63% across databases. Dexamethasone and prednisone were the most commonly used glucocorticoids. In the databases where their use was captured, use of PIs ranged from 46% to 57% in the year following diagnosis. Meanwhile, over the same time period, use of chemotherapies ranged from 18% to 46%, use of IMiDs ranged from 2% to 35%, and use of monoclonal antibodies ranged from 5% to 17%.

Use of treatments were similar when results were stratified by sex, but varied across age groups. In particular, both IMiDs and PIs were consistently seen to be used less in older individuals. However, while in one database (CDWBordeaux) those aged 70 or over were less frequently treated with chemotherapies, in another (NCR) this age group were in fact more frequently treated with chemotherapies.

Treatment sequences were described only in CDWBordeaux, where we found that the most common treatment sequences were only Melphalan (27%), followed by Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan (7%), Daratumumab (6%), and Prednisone-Melphalan-Bortezomib (5%). When stratifying results by study period, the most common treatment sequences in 2017 or earlier were Melphalan only (45%), followed by Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan (27%), and Prednisone-Melphalan-Bortezomib (15%). However, from 2018 onwards this changed to Melphalan only (47%), Daratumumab only (15%), and Dexamethasone-Lenalidomide-Bortezomib-Melphalan (9%).

Survival

From 17,333 individuals in Cohort 3, 7,981 (46%) died during the study period. Overall estimates of survival were similar for IMASIS, NCR, and SIDIAP, with 5-year survival estimates of 0.49 (0.42 to 0.58), 0.65 (0.64 to 0.66), and 0.69 (0.67 to 0.7) respectively. Mortality estimates were lower for CDWBordeaux and EBB, with 5-year survival estimated at 0.78 (0.75 to 0.81) and 0.76 (0.67 to 0.86). These results might be due to the small sample size in EBB (n in Cohort 2=107), or potential incompleteness of mortality data in CDWBordeaux

Across all of the databases, similar survival patterns were seen across different age groups and sex. While survival was consistently seen to be similar by sex, survival varied substantially by age. We also estimated overall survival by study period: 2017 or earlier and 2018 or later. The 1- and 3-year survival probability was similar between periods for most databases. In IMASIS, however, we observed a 1- and 3-year survival probability of 0.75 (0.69 to 0.83) and 0.55 (0.46 to 0.64), respectively, in 2017 or earlier, and a probability of 0.83 (0.77to 0.90) and 0.74 (0.65 to 0.83) in 2018 or later. This could be due to improvement of multiple myeloma cases and/or treatment, however, these results should be interpreted with caution given the small number of patients in this database (n in Cohort 3=301).

14.2 Limitations of the research methods

The study was informed by routinely collected health care data from different settings and so data quality and completeness issues must be considered. In particular, the identification of multiple myeloma patients and the recording of the co-morbidities and co-medications may vary across databases and settings; and while relatively few false positives were expected, false negatives may be more likely especially for databases without patient-level linkage to secondary care data. Nevertheless, the diagnosis of multiple myeloma has been previously validated in the SIDIAP database(8), and databases from or linked to cancer registries (NCR,

IMASIS, and EBB) are known to contain high quality data on cancer diagnoses. Also, it is important to acknowledge the potential recording bias of co-morbidities and co-medications depending on setting (e.g.: hospital vs. primary care). This might have resulted in an under- or over-estimation of their prevalence in our study population (e.g.: at index, the prevalence of hypertension 27% in SIDIAP vs 48% in IQVIA DA Germany).

Since date of death is not available in IQVIA DA Germany, overall survival was not estimated in this database. Limitations in patient-level linkage to death records may also explain observed mortality being considerably lower for CDWBordeaux than for other databases. In addition, the recording of events used for patient characterisation may vary across databases; and in databases with information on cancer treatment, the recording of treatment use may be incomplete. This may have occurred particularly for new available treatments such as CAR T-cell drugs, as well as the short follow-up in NCR (less than one year) and the availability of only first line treatment in this database.

14.3 Interpretation

Previous studies have shown that multiple myeloma patients are more frequently men and older than 70 years of age (14). This is in line with our results in which we found that most individuals were consistently 70 or older at time of diagnosis across all databases. A higher proportion of men was also observed in some, but not all databases . Recent data have also shown a slightly higher incidence of MM among women after age standardization (15).

In our study, the list of most frequent co-morbidities and co-medications among individuals with multiple myeloma recorded prior to index date differed by age groups. Indeed, the co-morbidities and co-medications observed to be common prior to index date seem to be in line with those known to be more frequent in individuals of a certain age. For example, among individuals with multiple myeloma that were older than 70 at date of diagnosis, the most frequent co-morbidities were hypertension, osteoarthritis, and hyperlipidemia, which are also known to be some of the most frequent conditions among individuals in this age group in the general population. As for the conditions recorded at index date, anaemia, osteoporosis, and renal impairment were common, and are known forms of presentation of multiple myeloma at diagnosis (16).

Regarding multiple myeloma treatments, our findings are in line with the recommendations from guidelines for these patients (14), with the most frequently used class of treatments in the year following diagnosis being glucocorticoids, followed by PIs, chemotherapies, and IMiDs.

Overall survival estimates in our study, particularly those from IMASIS, NCR, and SIDIAP, are consistent with those in the literature. For example, 5-year survival has been estimated at 60% in the US (17). Moreover, as also seen consistently across the databases included in this study, survival rates for those diagnosed with multiple myeloma have been seen to be substantially lower for older age groups, but similar by sex.

14.4 Generalisability

This study included data from 6 databases from 5 different European countries/regions (Estonia, France, Germany, The Netherlands, Catalonia) and healthcare systems (primary care in SIDIAP and IQVIA Germany, secondary care in IMASIS and CDWBordeaux, biobank in EBB, and cancer registry in NCR). However, not all data sources could inform all objectives, with e.g. treatment sequence characterisation being informed by only one data source, and sometimes the sources had data limitations advising caution in interpretation of results (e.g. CDWBordeaux survival rates). While we consider results largely representative of individuals

newly diagnosed with multiple myeloma in the respective countries/regions, results should not be generalised to the whole of Europe as differences in population characteristics, treatments and survival may vary by country.

14.5 Other information

NA

15 CONCLUSION

In this study we provided a characterisation of 30,319 patients newly diagnosed with multiple myeloma in between 2012 and 2022 across Europe. The most frequent co-morbidities at and prior to the date of diagnoses were hypertension, renal impairment, hyperlipidemia, osteoarthritis, urinary tract infection, diabetes mellitus, and obesity, while the most frequent medications were drugs for acid related disorders, agents acting on the renin-angiotensin system, lipid modifying agents, opioids and psycholeptics.

Regarding multiple myeloma treatments, the most frequently used class of treatment in the year following diagnosis were glucocorticoids, followed by PIs, chemotherapies and IMiDs. Treatment sequences were described in CDWBordeaux, where the most common treatment sequences observed were only Melphalan, followed by Dexamethasone-Thalidomide-Bortezomib-Cyclophosphamide-Melphalan, Daratumumab, and Prednisone-Melphalan-Bortezomib. No difference in treatment was observed by sex, while IMiDs and PIs were consistently seen to be used less in older individuals.

The observed 5-year survival estimates were 0.49 (0.42 to 0.58) in IMASIS, 0.65 (0.64 to 0.66) in NCR, and 0.69 (0.67 to 0.7) in SIDIAP. Survival estimates were higher for CDWBordeaux and EBB, with 5-year survival estimated at 0.78 (0.75 to 0.81) and 0.76 (0.67 to 0.86). Survival probabilities were consistently similar by sex, but varied substantially by age groups, with a decrease in survival observed with older age.

16 REFERENCES

1. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003 Jan;78(1):21–33.

2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209–49.

3. Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2021 Mar;32(3):309–22.

4. Gagelmann N, Sureda A, Montoto S, Murray J, Bolaños N, Kenyon M, et al. Access to and affordability of CAR T-cell therapy in multiple myeloma: an EBMT position paper. Lancet Haematol. 2022 Oct;9(10):e786–95.

5. Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016 Jul;91(7):719–34.

6. Planas Domingo J, Gallén Castillo M, Malats Riera N, Porta Serra M, Guasch Jordán I, Cardona Hernández T, et al. [Tumors registered in Hospital del Mar (Barcelona). Descriptive analysis from 1978 to 1986]. Rev Clin Esp. 1988 Sep;183(4):175–9.

7. Leitsalu L, Haller T, Esko T, Tammesoo ML, Alavere H, Snieder H, et al. Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. Int J Epidemiol. 2015 Aug;44(4):1137–47.

8. Recalde M, Manzano-Salgado CB, Díaz Y, Puente D, Garcia-Gil MDM, Marcos-Gragera R, et al. Validation Of Cancer Diagnoses In Electronic Health Records: Results From The Information System For Research In Primary Care (SIDIAP) In Northeast Spain. Clin Epidemiol. 2019 Dec 3;11:1015–24.

9. Palmaro A, Gauthier M, Conte C, Grosclaude P, Despas F, Lapeyre-Mestre M. Identifying multiple myeloma patients using data from the French health insurance databases: Validation using a cancer registry. Medicine (Baltimore). 2017 Mar;96(12):e6189.

10. Rathmann W, Bongaerts B, Carius HJ, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database. Int J Clin Pharmacol Ther. 2018 Oct;56(10):459–66.

11. Recalde M, Rodríguez C, Burn E, Far M, García D, Carrere-Molina J, et al. Data Resource Profile: The Information System for Research in Primary Care (SIDIAP). Int J Epidemiol. 2022 Dec 13;51(6):e324–36.

12. Brat GA, Weber GM, Gehlenborg N, Avillach P, Palmer NP, Chiovato L, et al. International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium. Npj Digit Med. 2020 Aug 19;3(1):109.

13. Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Bisphosphonates in multiple myeloma: an updated network meta-analysis. Cochrane Haematological Malignancies Group, editor. Cochrane Database Syst Rev [Internet]. 2017 Dec 18 [cited 2023 Apr 10];2017(12). Available from: http://doi.wiley.com/10.1002/14651858.CD003188.pub4

14. Van de Donk NWCJ, Pawlyn C, Yong KL. Multiple myeloma. The Lancet, 397(10272), 410–427.

15. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov,68(6):394-424.

15. Bianchi G, Anderson KC. Understanding biology to tackle the disease: Multiple myeloma from bench to bedside, and back. CA Cancer J Clin. 2014 Nov-Dec; 64(6):422-44.

16. https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed on the 30th of October 2023.

17 ANNEXES

Appendix I: Definition of Multiple Myeloma Diagnosis and Treatments

Clinical description

Overview

Multiple myeloma (MM) is a malignant uncontrolled proliferation of plasma cells derived from one single clone. MM can affect many organs, typically bones and calcium metabolism (e.g. fractures or bone pain, hypercalcemia), kidneys (renal failure/ckd/aki), immune system (e.g. infection), blood (anemia, clotting), and more rarely neurologic.

The etiology of MM is unknown, and it is one of the most common blood cancers, with an estimated crude and age-standardized incidence rates of 6.8 and 2.9 per 100,000 persons in 2020 in Europe, respectively, with a higher incidence observed in men than women and a median age at diagnosis of 72 years(2,3).

Presentation

Bone pain, fractures, and hypercalcemia are the most common manifestations of MM. Radiology would show (on top of fracture/pathologic fracture where present) lytic/osteolytic lesions in plain x-ray or ct scan. Bone lysis results in hypercalcemia, and related complications.

Other typical features that lead to diagnosis include renal failure (ckd or aki) or bacterial infections like pneumonia or pyelonephritis. Recurrent infections are common.

Bloods and urine labs are typically used to investigate/diagnose MM, and will show hypogammaglobulinemia, bence-jones proteins, hypercalcemia, and other alterations of proteinogram.

Assessment

Assessment will typically include imaging e.g. x-ray, ct scan, and sometimes bone gammagraphy or similar techniques. Also, bloods and urine are included often during investigation/diagnosis, typically including full blood counts, biochemistry, immunology, proteinogram, serum electrophoresis, β2Microglobulin, LDH and serum albumin, and bence jones proteins

Diagnosis is typically obtained after bone marrow biopsy, where plasma cells monoclonal kappa or lambda light chains were present.

The most important differential diagnosis is MGUS (monoclonal gammapathy of unknown significance) or 'smoldering multimple myeloma'. These are far more common than MM, and sometimes preclude or transition to MM proper. It is estimated that about 1% of patients with MGUS transition every year to MM. Patients with MGUS would not have a bone marrow biopsy, but they will/should have repeat bloods over time to monitor/rule out MM.

Diagnostic Criteria

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Serum monoclonal protein (non-IgM type) <30 g/L
- Clonal bone marrow plasma cells <10%

- Absence of myeloma-defining events or amyloidosis that can be attributed to the plasma cell proliferative disorder

Smoldering Multiple Myeloma (Asymptomatic Myeloma)
Both criteria must be met:
-Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
-Absence of myeloma-defining events or amyloidosis

Symptomatic Multiple Myeloma Clonal bone marrow plasma cells or biopsy-proven bony or extramedullary plasmacytomaa and any one or more of the following myeloma-defining events:

Evidence of one or more indicators of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL/minb or serum creatinine >177 µmol/L (>2 mg/dL)
- Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CTc
- Any one or more of the following biomarkers of malignancy: i.Clonal bone marrow plasma cell percentagea ≥60%; ii.Involved: uninvolved serum free light chain ratiod ≥100; and/or iii.>1 focal lesion on MRI studies

Plan Common treatments for MM include:

- Immunomodulatory drugs (IMiD) like Thalidomide, Lenalidomide, Pomalidomide
- Proteasome inhibitors (PI) like Bortezomib, Carfilzomib, Ixazomib
- Antibodies/monoclonal antibodies like Daratumumab, Elotuzumab, Isatuximab, Belantamab mafodotin
- Selective inhibitors of nuclear export (SINE) like Selinexor
- Histone deacetylase inhibitors like Panobinostat
- Alkylating agents like Melphalan, Cyclophosphamide, Bendamustine, Melflufen
- Cellular therapy like Idecabtagene vicleucel
- Glucocorticoids like Dexamethasone or Prednisone

Prognosis
Medial survival ranges from 30 to 60 months, with some advanced diagnoses surviving for no more than 6 months.

Strengtheners
Any of the treatments mentioned above, use of imaging and specific bloods also mentioned above.

Table 1: Code list for multiple myeloma.

Id	Name
4224628	Amyloid light chain amyloidosis due to multiple myeloma
4258135	Asymptomatic multiple myeloma
4043447	Bone marrow: myeloma cells
4094548	Extramedullary plasmacytoma
37209514	Hypogammaglobulinemia due to multiple myeloma
4111355	IgA myeloma
4112310	IgD myeloma
4111356	IgG myeloma
4259972	Indolent multiple myeloma
4188299	Kappa light chain myeloma
4197600	Lambda light chain myeloma
4082464	Light chain myeloma
37016161	Light chain nephropathy due to multiple myeloma
437233	Multiple myeloma
4210177	Multiple myeloma
436059	Multiple myeloma in remission
4214660	Multiple solitary plasmacytomas
4019477	Myeloma-associated amyloidosis
4137433	Myeloma kidney
4043713	Neuropathy due to multiple myeloma
4079684	Non-secretory myeloma
42538151	Osteoporosis co-occurrent and due to multiple myeloma
4137510	Osteosclerotic myeloma
133154	Plasma cell leukemia
4028859	Plasma cell leukemia
760936	Plasma cell leukemia in relapse
133158	Plasma cell leukemia in remission
4190641	Plasma cell myeloma - category
4190642	Plasma cell myeloma/plasmacytoma
4163558	Plasma cell myeloma/plasmacytoma
4216139	Plasmacytoma
4024874	Plasmacytoma
4300702	Primary cutaneous plasmacytoma
764229	Relapse multiple myeloma
4184985	Smoldering myeloma
4145040	Solitary osseous myeloma

Multiple Myeloma Treatments

Table 2: Code list for Multiple Myeloma treatments.

Class	Treatment	ATC code	ConceptID
Chemotherapies	Melphalan	L01AA03	21601392
	Bendamustine	L01AA09	21601397
	Doxorubicin	L01DB01	21603732
	Cisplatin	L01XA01	21603748
	Cyclophosphamide	L01AA01	21601390
	Etoposide	L01CB01	21603718
	Vincristine	L01CA02	21601448
IMiDs	Thalidomide	L04AX02	21603928
	Lenalidomide	L04AX04	21603930
	Pomalidomide	L04AX06	43534824
PI	Bortezomib	L01XX32	21603804
	Carfilzomib	L01XG02	947958
	Ixazomib	L01XG03	947997
	Venetoclax	L01XX52	1123676
Monoclonal antibodies	Daratumumab	L01XC24	1123898
	Isatuximab	L01XC38	947956
	Denosumab	M05BX04	21604169
	Elotuzumab	L01XC23	1123776
Nuclear export inhibitor	Selinexor	L01XX66	715834
CAR T-cell	Lisocabtagene maraleucel	L01XX88	739860
	Idecabtagene vicleucel	L01XL07	36026872
	Brexucabtagene autoleucel	L01XL06	37002393
	Axicabtagene ciloleucel	L01XX70	947849
	Tisagenlecleucel	L01XX71	947930
Glucocorticoids	Dexamethasone	H02AB02	21602730
	Prednisone	H02AB07	21602735
Bisphosphonates	Zoledronic acid	M05BA08	21604156
	Pamidronic acid	M05BA03	21604151
	Clodronic acid	M05BA02	21604150
	Ibandronic acid	M05BA06	21604154
	Etidronate	M05BA01	21604149
Others	Panobinostat	L01XH03	947750

*Please note that the selection of treatments was based on the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (reference number 3).

Appendix II: Supplementary tables

Table 1. Number and % of pre-specified co-morbidities among all individuals in Cohort 1 by database and time window

	IQVIA DA Germany		CDWBordeaux		EBB	
	30 to 1 day prior	**365 to 31 day prior**	**30 to 1 day prior**	**365 to 31 day prior**	**30 to 1 day prior**	**365 to 31 day prior**
Anxiety	594 (9.77%)	577 (9.49%)	30 (3.44%)	26 (2.98%)	32 (28.83%)	32 (28.83%)
Asthma	510 (8.39%)	505 (8.31%)	16 (1.83%)	16 (1.83%)	23 (20.72%)	23 (20.72%)
Attention deficit hyperactivity disorder (ADHD)	23 (0.38%)	22 (0.36%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chronic liver disease	79 (1.3%)	74 (1.22%)	8 (0.92%)	5 (0.57%)	6 (5.41%)	5 (4.5%)
COPD	616 (10.13%)	607 (9.98%)	20 (2.29%)	18 (2.06%)	16 (14.41%)	14 (12.61%)
Crohn´s disease	39 (0.64%)	38 (0.62%)	<5	<5	<5	<5
Dementia	224 (3.68%)	215 (3.54%)	11 (1.26%)	8 (0.92%)	0 (0%)	0 (0%)
Depressive disorder	982 (16.15%)	961 (15.81%)	27 (3.1%)	24 (2.75%)	34 (30.63%)	34 (30.63%)
Diabetes mellitus	1110 (18.26%)	1090 (17.93%)	46 (5.28%)	43 (4.93%)	16 (14.41%)	16 (14.41%)
Gastro-esophageal reflux disease (GERD)	277 (4.56%)	273 (4.49%)	15 (1.72%)	15 (1.72%)	38 (34.23%)	38 (34.23%)
GI-Bleeding	185 (3.04%)	171 (2.81%)	15 (1.72%)	15 (1.72%)	5 (4.5%)	<5
Hepatitis	71 (1.17%)	66 (1.09%)	<5	<5	<5	<5
Hyperlididemia	1496 (24.61%)	1484 (24.41%)	55 (6.31%)	49 (5.62%)	25 (22.52%)	25 (22.52%)
Hypertension	2767 (45.51%)	2735 (44.98%)	152 (17.43%)	138 (15.83%)	65 (58.56%)	63 (56.76%)
Obesity	658 (10.82%)	654 (10.76%)	8 (0.92%)	7 (0.8%)	15 (13.51%)	14 (12.61%)
Osteoarthritis	1911 (31.43%)	1880 (30.92%)	22 (2.52%)	19 (2.18%)	64 (57.66%)	63 (56.76%)
Parkinson disease	90 (1.48%)	82 (1.35%)	7 (0.8%)	7 (0.8%)	<5	<5
Pneumonia	398 (6.55%)	379 (6.23%)	34 (3.9%)	29 (3.33%)	23 (20.72%)	23 (20.72%)
Psoriasis	166 (2.73%)	164 (2.7%)	5 (0.57%)	5 (0.57%)	12 (10.81%)	12 (10.81%)
Renal impairment	711 (11.69%)	651 (10.71%)	80 (9.17%)	55 (6.31%)	20 (18.02%)	10 (9.01%)
Schizophrenia	12 (0.2%)	12 (0.2%)	0 (0%)	0 (0%)	<5	<5
Ulcerative collitis	32 (0.53%)	32 (0.53%)	<5	<5	<5	<5
Urinary tract infection	712 (11.71%)	687 (11.3%)	14 (1.61%)	13 (1.49%)	18 (16.22%)	16 (14.41%)

Table 1 (continued). Number and % of pre-specified co-morbidities among all individuals in Cohort 1 by database and time window

	IMASIS		SIDIAP	
	30 to 1 days prior	**365 to 31 days prior**	**30 to 1 days prior**	**365 to 31 days prior**
Anxiety	6 (2.36%)	6 (2.36%)	650 (16.69%)	640 (16.43%)
Asthma	11 (4.33%)	10 (3.94%)	142 (3.65%)	142 (3.65%)
Attention deficit hyperactivity disorder (ADHD)	0 (0%)	0 (0%)	11 (0.28%)	11 (0.28%)
Chronic liver disease	9 (3.54%)	9 (3.54%)	47 (1.21%)	46 (1.18%)
COPD	19 (7.48%)	17 (6.69%)	208 (5.34%)	204 (5.24%)
Crohn´s disease	<5	<5	5 (0.13%)	5 (0.13%)
Dementia	5 (1.97%)	5 (1.97%)	119 (3.06%)	118 (3.03%)
Depressive disorder	16 (6.3%)	16 (6.3%)	430 (11.04%)	424 (10.89%)
Diabetes mellitus	21 (8.27%)	20 (7.87%)	430 (11.04%)	427 (10.96%)
Gastro-esophageal reflux disease (GERD)	<5	<5	247 (6.34%)	243 (6.24%)
GI-Bleeding	6 (2.36%)	6 (2.36%)	190 (4.88%)	187 (4.8%)
Hepatitis	<5	<5	53 (1.36%)	51 (1.31%)
Hyperlididemia	46 (18.11%)	46 (18.11%)	537 (13.79%)	536 (13.76%)
Hypertension	76 (29.92%)	74 (29.13%)	1026 (26.34%)	1016 (26.08%)
Obesity	15 (5.91%)	15 (5.91%)	703 (18.05%)	700 (17.97%)
Osteoarthritis	39 (15.35%)	37 (14.57%)	1057 (27.14%)	1039 (26.68%)
Parkinson disease	<5	<5	36 (0.92%)	36 (0.92%)
Pneumonia	28 (11.02%)	27 (10.63%)	391 (10.04%)	375 (9.63%)
Psoriasis	6 (2.36%)	6 (2.36%)	91 (2.34%)	91 (2.34%)
Renal impairment	35 (13.78%)	31 (12.2%)	641 (16.46%)	577 (14.81%)
Schizophrenia	0 (0%)	0 (0%)	10 (0.26%)	10 (0.26%)
Ulcerative collitis	<5	<5	15 (0.39%)	15 (0.39%)
Urinary tract infection	23 (9.06%)	21 (8.27%)	751 (19.28%)	727 (18.66%)

Table 2. Number and % of pre-specified co-morbidities among individuals in Cohort 1 at index date by database and sex

	IQVIA DA Germany		CDWBordeaux		SIDIAP	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Anxiety	400 (13.18%)	225 (7.4%)	57 (13.64%)	32 (7.05%)	435 (21.78%)	224 (11.8%)
Asthma	315 (10.38%)	212 (6.98%)	12 (2.87%)	12 (2.64%)	89 (4.46%)	55 (2.9%)
Attention deficit hyperactivity disorder (ADHD)	9 (0.3%)	14 (0.46%)	0 (0%)	0 (0%)	<5	7 (0.37%)
Chronic liver disease	38 (1.25%)	50 (1.65%)	12 (2.87%)	6 (1.32%)	19 (0.95%)	32 (1.69%)
COPD	308 (10.14%)	337 (11.09%)	10 (2.39%)	28 (6.17%)	61 (3.05%)	152 (8.01%)
Crohn´s disease	20 (0.66%)	21 (0.69%)	<5	<5	<5	<5
Dementia	141 (4.64%)	103 (3.39%)	13 (3.11%)	7 (1.54%)	81 (4.06%)	51 (2.69%)
Depressive disorder	674 (22.2%)	352 (11.58%)	24 (5.74%)	26 (5.73%)	300 (15.02%)	134 (7.06%)
Diabetes mellitus	517 (17.03%)	645 (21.22%)	32 (7.66%)	63 (13.88%)	194 (9.71%)	252 (13.28%)
Gastro-esophageal reflux disease (GERD)	161 (5.3%)	134 (4.41%)	8 (1.91%)	14 (3.08%)	153 (7.66%)	101 (5.32%)
GI-Bleeding	87 (2.87%)	112 (3.69%)	5 (1.2%)	16 (3.52%)	83 (4.16%)	109 (5.74%)
Hepatitis	41 (1.35%)	38 (1.25%)	<5	<5	27 (1.35%)	30 (1.58%)
Human Immunodeficiency Virus (HIV)	<5	<5	0 (0%)	<5	<5	6 (0.32%)
Hyperlididemia	735 (24.21%)	801 (26.36%)	33 (7.89%)	61 (13.44%)	291 (14.57%)	253 (13.33%)
Hypertension	1389 (45.75%)	1505 (49.52%)	134 (32.06%)	175 (38.55%)	515 (25.79%)	536 (28.24%)
Obesity	344 (11.33%)	336 (11.06%)	7 (1.67%)	<5	381 (19.08%)	325 (17.12%)
Osteoarthritis	1114 (36.69%)	881 (28.99%)	16 (3.83%)	23 (5.07%)	685 (34.3%)	388 (20.44%)
Parkinson disease	40 (1.32%)	52 (1.71%)	<5	7 (1.54%)	17 (0.85%)	20 (1.05%)
Pneumonia	186 (6.13%)	234 (7.7%)	20 (4.78%)	51 (11.23%)	203 (10.17%)	211 (11.12%)
Psoriasis	86 (2.83%)	91 (2.99%)	<5	8 (1.76%)	40 (2%)	51 (2.69%)
Renal impairment	409 (13.47%)	457 (15.04%)	84 (20.1%)	99 (21.81%)	352 (17.63%)	346 (18.23%)
Schizophrenia	11 (0.36%)	<5	0 (0%)	0 (0%)	5 (0.25%)	6 (0.32%)
Ulcerative collitis	12 (0.4%)	21 (0.69%)	<5	<5	9 (0.45%)	6 (0.32%)
Urinary tract infection	526 (17.33%)	212 (6.98%)	17 (4.07%)	15 (3.3%)	531 (26.59%)	234 (12.33%)
Viral hepatitis	<5	<5	8 (1.91%)	5 (1.1%)	<5	<5

Table 3. Number and % of pre-specified co-morbidities among individuals in Cohort 1 at index date by database and age group

	IQVIA DA Germany				CDWBordeaux*			SIDIAP			
	18 to 44 years	**45 to 59 years**	**60 to 69 years**	**>=70 years**	**45 to 59 years**	**60 to 69 years**	**>=70 years**	**18 to 44 years**	**45 to 59 years**	**60 to 69 years**	**>=70 years**
Anxiety	47 (18.58 %)	158 (14.64 %)	144 (9.88%)	275 (8.38%)	25 (14.62 %)	15 (5.86%)	48 (11.37 %)	43 (20.19 %)	158 (23.72 %)	157 (18.15 %)	296 (14.35 %)
Asthma	33 (13.04 %)	105 (9.73%)	120 (8.24%)	268 (8.17%)	5 (2.92%)	6 (2.34%)	12 (2.84%)	14 (6.57%)	26 (3.9%)	27 (3.12%)	69 (3.35%)
Attention deficit hyperactivity disorder	0 (0%)	6 (0.56%)	9 (0.62%)	8 (0.24%)	0 (0%)	0 (0%)	0 (0%)	<5	<5	0 (0%)	<5
Chronic liver disease	6 (2.37%)	19 (1.76%)	21 (1.44%)	42 (1.28%)	<5	8 (3.12%)	6 (1.42%)	0 (0%)	6 (0.9%)	11 (1.27%)	34 (1.65%)
COPD	17 (6.72%)	99 (9.18%)	161 (11.05 %)	366 (11.16 %)	5 (2.92%)	14 (5.47%)	19 (4.5%)	<5	14 (2.1%)	41 (4.74%)	154 (7.47%)
Crohn´s disease	<5	11 (1.02%)	11 (0.75%)	16 (0.49%)	<5	<5	<5	<5	<5	<5	<5
Dementia	10 (3.95%)	11 (1.02%)	17 (1.17%)	207 (6.31%)	0 (0%)	<5	19 (4.5%)	0 (0%)	0 (0%)	<5	130 (6.3%)
Depressive disorder	67 (26.48 %)	220 (20.39 %)	248 (17.02 %)	491 (14.96 %)	10 (5.85%)	10 (3.91%)	29 (6.87%)	12 (5.63%)	70 (10.51 %)	97 (11.21 %)	253 (12.27 %)
Diabetes mellitus	27 (10.67 %)	143 (13.25 %)	256 (17.57 %)	738 (22.49 %)	7 (4.09%)	25 (9.77%)	63 (14.93 %)	10 (4.69%)	51 (7.66%)	101 (11.68 %)	282 (13.68 %)
Gastro-esophageal reflux disease (GERD)	12 (4.74%)	45 (4.17%)	55 (3.77%)	183 (5.58%)	<5	8 (3.12%)	11 (2.61%)	7 (3.29%)	42 (6.31%)	47 (5.43%)	157 (7.61%)
GI-Bleeding	<5	36 (3.34%)	44 (3.02%)	115 (3.51%)	<5	9 (3.52%)	10 (2.37%)	7 (3.29%)	29 (4.35%)	37 (4.28%)	118 (5.72%)
Hepatitis	8 (3.16%)	16 (1.48%)	23 (1.58%)	32 (0.98%)	<5	<5	<5	<5	15 (2.25%)	11 (1.27%)	27 (1.31%)
Human Immunodeficiency Virus (HIV)	0 (0%)	<5	<5	<5	<5	0 (0%)	0 (0%)	<5	5 (0.75%)	0 (0%)	<5
Hyperlididemia	19 (7.51%)	211 (19.56 %)	359 (24.64 %)	949 (28.92 %)	<5	<5	<5	<5	86 (12.91 %)	156 (18.03 %)	299 (14.5%)
Hyperlipidemia	<5	<5	<5	<5	10 (5.85%)	31 (12.11 %)	52 (12.32 %)	<5	<5	<5	<5

Hypertension	38 (15.02 %)	355 (32.9%)	690 (47.36 %)	1815 (55.32 %)	24 (14.04 %)	86 (33.59 %)	198 (46.92 %)	10 (4.69%)	121 (18.17 %)	254 (29.36 %)	666 (32.3%)
Obesity	22 (8.7%)	127 (11.77 %)	192 (13.18 %)	339 (10.33 %)	<5	5 (1.95%)	<5	26 (12.21 %)	123 (18.47 %)	164 (18.96 %)	385 (18.67 %)
Osteoarthritis	38 (15.02 %)	280 (25.95 %)	461 (31.64 %)	1219 (37.15 %)	0 (0%)	11 (4.3%)	27 (6.4%)	9 (4.23%)	73 (10.96 %)	213 (24.62 %)	777 (37.68 %)
Parkinson disease	<5	<5	14 (0.96%)	76 (2.32%)	<5	<5	6 (1.42%)	0 (0%)	0 (0%)	<5	33 (1.6%)
Pneumonia	24 (9.49%)	58 (5.38%)	87 (5.97%)	250 (7.62%)	8 (4.68%)	12 (4.69%)	50 (11.85 %)	9 (4.23%)	69 (10.36 %)	88 (10.17 %)	241 (11.69 %)
Psoriasis	12 (4.74%)	35 (3.24%)	42 (2.88%)	88 (2.68%)	<5	<5	5 (1.18%)	7 (3.29%)	22 (3.3%)	27 (3.12%)	34 (1.65%)
Renal impairment	12 (4.74%)	72 (6.67%)	141 (9.68%)	643 (19.6%)	19 (11.11 %)	47 (18.36 %)	111 (26.3%)	7 (3.29%)	42 (6.31%)	102 (11.79 %)	547 (26.53 %)
Schizophrenia	<5	<5	<5	5 (0.15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	<5	5 (0.58%)	<5
Ulcerative collitis	<5	9 (0.83%)	8 (0.55%)	14 (0.43%)	<5	<5	<5	0 (0%)	<5	<5	10 (0.48%)
Urinary tract infection	58 (22.92 %)	111 (10.29 %)	156 (10.71 %)	411 (12.53 %)	<5	<5	27 (6.4%)	45 (21.13 %)	91 (13.66 %)	141 (16.3%)	474 (22.99 %)
Viral hepatitis	<5	<5	<5	<5	<5	5 (1.95%)	<5	<5	<5	<5	<5

*Results for the age group 18-44 years were excluded for CDWBordeaux because of the small number of individuals in this age group and database.

Table 4. Number and % of pre-specified medication use among individuals in Cohort 1 at index date, by sex

	IQVIA DA Germany		CDWBordeaux		SIDIAP	
	Female	**Male**	**Female**	**Male**	**Female**	Male
Agents acting on the renin-angiotensin system	585 (19.27%)	669 (22.01%)	8 (1.91%)	9 (1.98%)	634 (31.75%)	684 (36.04%)
Antibacterials for systemic use	110 (3.62%)	134 (4.41%)	18 (4.31%)	29 (6.39%)	208 (10.42%)	196 (10.33%)
Antidepressants	219 (7.21%)	113 (3.72%)	10 (2.39%)	8 (1.76%)	458 (22.93%)	202 (10.64%)
Antiepileptics	101 (3.33%)	83 (2.73%)	11 (2.63%)	19 (4.19%)	249 (12.47%)	196 (10.33%)
Antiinflammatory and antirheumatic products	205 (6.75%)	225 (7.4%)	6 (1.44%)	6 (1.32%)	349 (17.48%)	306 (16.12%)
Antineoplastic agents	18 (0.59%)	15 (0.49%)	74 (17.7%)	65 (14.32%)	44 (2.2%)	49 (2.58%)
Antipsoriatics	0 (0%)	<5	0 (0%)	0 (0%)	<5	10 (0.53%)
Antithrombotic agents	208 (6.85%)	247 (8.13%)	46 (11%)	46 (10.13%)	332 (16.62%)	385 (20.28%)
Beta blocking agents	484 (15.94%)	461 (15.17%)	18 (4.31%)	12 (2.64%)	296 (14.82%)	279 (14.7%)
Calcium channel blockers	275 (9.06%)	250 (8.23%)	14 (3.35%)	7 (1.54%)	317 (15.87%)	307 (16.17%)
Diuretics	373 (12.29%)	348 (11.45%)	14 (3.35%)	15 (3.3%)	404 (20.23%)	335 (17.65%)
Drugs for acid related disorders	594 (19.57%)	522 (17.18%)	36 (8.61%)	33 (7.27%)	1007 (50.43%)	971 (51.16%)
Drugs for obstructive airway diseases	102 (3.36%)	70 (2.3%)	15 (3.59%)	12 (2.64%)	264 (13.22%)	272 (14.33%)
Drugs used in diabetes	140 (4.61%)	214 (7.04%)	6 (1.44%)	21 (4.63%)	214 (10.72%)	309 (16.28%)
Immunosuppressants	27 (0.89%)	14 (0.46%)	32 (7.66%)	20 (4.41%)	17 (0.85%)	17 (0.9%)
Lipid modifying agents	260 (8.56%)	346 (11.39%)	10 (2.39%)	32 (7.05%)	414 (20.73%)	507 (26.71%)
Opioids	286 (9.42%)	257 (8.46%)	48 (11.48%)	50 (11.01%)	598 (29.94%)	495 (26.08%)
Psycholeptics	111 (3.66%)	93 (3.06%)	48 (11.48%)	50 (11.01%)	693 (34.7%)	425 (22.39%)
Psychostimulants	<5	0 (0%)	0 (0%)	0 (0%)	16 (0.8%)	19 (1%)

Table 5. Number and % of pre-specified medication use among individuals in Cohort 1 at time windows prior to index date, by sex

	IQVIA DA Germany				CDWBordeaux				SIDIAP			
	30 to 1 days prior		365 to 31 days prior		30 to 1 days prior		365 to 31 days prior		30 to 1 days prior		365 to 31 days prior	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Agents acting on the renin-angiotensin system	621 (20.45 %)	685 (22.54 %)	770 (25.36 %)	840 (27.64 %)	7 (1.67 %)	5 (1.1%)	16 (3.83 %)	21 (4.63 %)	668 (33.45 %)	719 (37.88 %)	714 (35.75 %)	767 (40.41 %)
Antibacterials for systemic use	116 (3.82 %)	90 (2.96 %)	506 (16.67 %)	393 (12.93 %)	8 (1.91 %)	9 (1.98 %)	10 (2.39 %)	18 (3.96 %)	298 (14.92 %)	281 (14.81 %)	798 (39.96 %)	690 (36.35 %)
Antidepressants	164 (5.4%)	86 (2.83 %)	251 (8.27 %)	144 (4.74 %)	5 (1.2%)	<5	7 (1.67 %)	6 (1.32 %)	471 (23.59 %)	214 (11.28 %)	517 (25.89 %)	236 (12.43 %)
Antiepileptics	89 (2.93 %)	72 (2.37 %)	116 (3.82 %)	109 (3.59 %)	5 (1.2%)	<5	<5	<5	259 (12.97 %)	200 (10.54 %)	310 (15.52 %)	203 (10.7 %)
Antiinflammatory and antirheumatic products	220 (7.25 %)	230 (7.57 %)	625 (20.59 %)	567 (18.66 %)	6 (1.44 %)	<5	6 (1.44 %)	<5	451 (22.58 %)	395 (20.81 %)	872 (43.67 %)	723 (38.09 %)
Antineoplastic agents	16 (0.53 %)	10 (0.33 %)	39 (1.28 %)	18 (0.59 %)	7 (1.67 %)	7 (1.54 %)	5 (1.2%)	6 (1.32 %)	49 (2.45 %)	52 (2.74 %)	66 (3.3%)	52 (2.74 %)
Antipsoriatics	0 (0%)	<5	0 (0%)	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	<5	9 (0.47 %)	<5	9 (0.47 %)
Antithrombotic agents	187 (6.16 %)	245 (8.06 %)	254 (8.37 %)	323 (10.63 %)	16 (3.83 %)	10 (2.2%)	12 (2.87 %)	24 (5.29 %)	325 (16.27 %)	358 (18.86 %)	309 (15.47 %)	308 (16.23 %)
Beta blocking agents	491 (16.17 %)	476 (15.66 %)	606 (19.96 %)	587 (19.32 %)	<5	11 (2.42 %)	9 (2.15 %)	22 (4.85 %)	299 (14.97 %)	285 (15.02 %)	303 (15.17 %)	292 (15.38 %)
Calcium channel blockers	273 (8.99 %)	244 (8.03 %)	345 (11.36 %)	343 (11.29 %)	5 (1.2%)	6 (1.32 %)	11 (2.63 %)	10 (2.2%)	323 (16.17 %)	318 (16.75 %)	337 (16.88 %)	323 (17.02 %)
Diuretics	361 (11.89 %)	320 (10.53 %)	427 (14.06 %)	387 (12.73 %)	6 (1.44 %)	11 (2.42 %)	9 (2.15 %)	22 (4.85 %)	432 (21.63 %)	359 (18.91 %)	457 (22.88 %)	377 (19.86 %)
Drugs for acid related disorders	474 (15.61 %)	396 (13.03 %)	657 (21.64 %)	568 (18.69 %)	12 (2.87 %)	8 (1.76 %)	13 (3.11 %)	26 (5.73 %)	1000 (50.08 %)	952 (50.16 %)	1069 (53.53 %)	909 (47.89 %)
Drugs for obstructive airway diseases	111 (3.66 %)	70 (2.3%)	249 (8.2%)	191 (6.28 %)	<5	<5	<5	6 (1.32 %)	297 (14.87 %)	301 (15.86 %)	486 (24.34 %)	443 (23.34 %)
Drugs used in diabetes	150 (4.94 %)	219 (7.21 %)	200 (6.59 %)	290 (9.54 %)	<5	<5	<5	7 (1.54 %)	216 (10.82 %)	314 (16.54 %)	223 (11.17 %)	315 (16.6 %)
Immunosuppressants	25 (0.82 %)	13 (0.43 %)	41 (1.35 %)	23 (0.76 %)	<5	<5	<5	6 (1.32 %)	18 (0.9%)	17 (0.9%)	19 (0.95 %)	18 (0.95 %)

Lipid modifying agents	290 (9.55 %)	370 (12.18 %)	363 (11.96 %)	479 (15.76 %)	<5	9 (1.98 %)	6 (1.44 %)	20 (4.41 %)	432 (21.63 %)	520 (27.4 %)	476 (23.84 %)	549 (28.93 %)
Opioids	240 (7.91 %)	202 (6.65 %)	326 (10.74 %)	269 (8.85 %)	17 (4.07 %)	9 (1.98 %)	16 (3.83 %)	15 (3.3%)	610 (30.55 %)	512 (26.98 %)	722 (36.15 %)	508 (26.77 %)
Psycholeptics	115 (3.79 %)	83 (2.73 %)	208 (6.85 %)	142 (4.67 %)	14 (3.35 %)	16 (3.52 %)	21 (5.02 %)	26 (5.73 %)	718 (35.95 %)	456 (24.03 %)	841 (42.11 %)	545 (28.71 %)
Psychostimulants	<5	<5	5 (0.16 %)	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (1%)	21 (1.11 %)	42 (2.1%)	28 (1.48 %)

Table 6. Number and % of pre-specified medication use among individuals in Cohort 1 at time windows post index date, by sex

	IQVIA DA Germany					
	1 to 30 days post		1 to 90 days post		1 to 365 days post	
	Female	Male	Female	Male	Female	Male
Agents acting on the renin-angiotensin system	655 (21.57%)	725 (23.86%)	707 (23.29%)	795 (26.16%)	803 (26.45%)	886 (29.15%)
Antibacterials for systemic use	195 (6.42%)	218 (7.17%)	321 (10.57%)	336 (11.06%)	614 (20.22%)	605 (19.91%)
Antidepressants	256 (8.43%)	127 (4.18%)	285 (9.39%)	154 (5.07%)	367 (12.09%)	219 (7.21%)
Antiepileptics	124 (4.08%)	104 (3.42%)	146 (4.81%)	137 (4.51%)	209 (6.88%)	203 (6.68%)
Antiinflammatory and antirheumatic products	246 (8.1%)	277 (9.11%)	336 (11.07%)	337 (11.09%)	521 (17.16%)	498 (16.39%)
Antineoplastic agents	20 (0.66%)	16 (0.53%)	28 (0.92%)	21 (0.69%)	43 (1.42%)	36 (1.18%)
Antipsoriatics	0 (0%)	<5	0 (0%)	<5	0 (0%)	<5
Antithrombotic agents	257 (8.47%)	302 (9.94%)	305 (10.05%)	368 (12.11%)	372 (12.25%)	452 (14.87%)
Beta blocking agents	540 (17.79%)	520 (17.11%)	601 (19.8%)	590 (19.41%)	681 (22.43%)	678 (22.31%)
Calcium channel blockers	309 (10.18%)	292 (9.61%)	359 (11.82%)	325 (10.69%)	427 (14.06%)	384 (12.64%)
Diuretics	418 (13.77%)	399 (13.13%)	480 (15.81%)	471 (15.5%)	573 (18.87%)	585 (19.25%)
Drugs for acid related disorders	680 (22.4%)	612 (20.14%)	767 (25.26%)	712 (23.43%)	921 (30.34%)	860 (28.3%)
Drugs for obstructive airway diseases	123 (4.05%)	99 (3.26%)	159 (5.24%)	145 (4.77%)	257 (8.47%)	224 (7.37%)
Drugs used in diabetes	174 (5.73%)	253 (8.33%)	195 (6.42%)	283 (9.31%)	225 (7.41%)	310 (10.2%)
Immunosuppressants	29 (0.96%)	16 (0.53%)	35 (1.15%)	21 (0.69%)	48 (1.58%)	27 (0.89%)
Lipid modifying agents	296 (9.75%)	387 (12.73%)	333 (10.97%)	432 (14.22%)	387 (12.75%)	494 (16.26%)
Opioids	365 (12.02%)	351 (11.55%)	437 (14.39%)	415 (13.66%)	549 (18.08%)	517 (17.01%)
Psycholeptics	163 (5.37%)	130 (4.28%)	205 (6.75%)	166 (5.46%)	303 (9.98%)	252 (8.29%)
Psychostimulants	<5	0 (0%)	<5	<5	<5	5 (0.16%)

Table 6 (continued). Number and % of pre-specified medication use among individuals in Cohort 1 at time windows post index date, by sex

	CDWBordeaux					
	1 to 30 day post		1 to 90 day post		1 to 365 day post	
	Female	Male	Female	Male	Female	Male
Agents acting on the renin-angiotensin system	63 (15.07%)	80 (17.62%)	70 (16.75%)	87 (19.16%)	82 (19.62%)	103 (22.69%)
Antibacterials for systemic use	100 (23.92%)	121 (26.65%)	121 (28.95%)	140 (30.84%)	149 (35.65%)	159 (35.02%)
Antidepressants	44 (10.53%)	33 (7.27%)	54 (12.92%)	38 (8.37%)	63 (15.07%)	51 (11.23%)
Antiepileptics	29 (6.94%)	41 (9.03%)	33 (7.89%)	51 (11.23%)	41 (9.81%)	67 (14.76%)
Antiinflammatory and antirheumatic products	12 (2.87%)	24 (5.29%)	15 (3.59%)	30 (6.61%)	22 (5.26%)	33 (7.27%)
Antineoplastic agents	203 (48.56%)	193 (42.51%)	227 (54.31%)	235 (51.76%)	246 (58.85%)	254 (55.95%)
Antipsoriatics	0 (0%)	<5	0 (0%)	<5	0 (0%)	<5
Antithrombotic agents	116 (27.75%)	150 (33.04%)	127 (30.38%)	164 (36.12%)	146 (34.93%)	189 (41.63%)
Beta blocking agents	54 (12.92%)	69 (15.2%)	61 (14.59%)	72 (15.86%)	74 (17.7%)	87 (19.16%)
Calcium channel blockers	54 (12.92%)	59 (13%)	57 (13.64%)	66 (14.54%)	68 (16.27%)	82 (18.06%)
Diuretics	64 (15.31%)	62 (13.66%)	68 (16.27%)	74 (16.3%)	80 (19.14%)	90 (19.82%)
Drugs for acid related disorders	111 (26.56%)	115 (25.33%)	123 (29.43%)	134 (29.52%)	140 (33.49%)	155 (34.14%)
Drugs for obstructive airway diseases	35 (8.37%)	32 (7.05%)	41 (9.81%)	41 (9.03%)	56 (13.4%)	64 (14.1%)
Drugs used in diabetes	17 (4.07%)	44 (9.69%)	17 (4.07%)	49 (10.79%)	21 (5.02%)	52 (11.45%)
Immunosuppressants	99 (23.68%)	95 (20.93%)	110 (26.32%)	119 (26.21%)	119 (28.47%)	133 (29.3%)
Lipid modifying agents	28 (6.7%)	59 (13%)	30 (7.18%)	60 (13.22%)	40 (9.57%)	67 (14.76%)
Opioids	99 (23.68%)	109 (24.01%)	114 (27.27%)	123 (27.09%)	133 (31.82%)	145 (31.94%)
Psycholeptics	114 (27.27%)	126 (27.75%)	127 (30.38%)	141 (31.06%)	157 (37.56%)	167 (36.78%)
Psychostimulants	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 6 (continued). Number and % of pre-specified medication use among individuals in Cohort 1 at time windows post index date, by sex

	SIDIAP					
	1 to 30 days post		1 to 90 days post		1 to 365 days post	
	Female	Male	Female	Male	Female	Male
Agents acting on the renin-angiotensin system	649 (32.5%)	684 (36.04%)	668 (33.45%)	704 (37.09%)	732 (36.65%)	743 (39.15%)
Antibacterials for systemic use	368 (18.43%)	363 (19.13%)	593 (29.69%)	561 (29.56%)	1104 (55.28%)	1043 (54.95%)
Antidepressants	483 (24.19%)	234 (12.33%)	539 (26.99%)	258 (13.59%)	658 (32.95%)	373 (19.65%)
Antiepileptics	283 (14.17%)	231 (12.17%)	353 (17.68%)	310 (16.33%)	503 (25.19%)	522 (27.5%)
Antiinflammatory and antirheumatic products	432 (21.63%)	382 (20.13%)	525 (26.29%)	455 (23.97%)	775 (38.81%)	668 (35.19%)
Antineoplastic agents	68 (3.41%)	70 (3.69%)	93 (4.66%)	93 (4.9%)	155 (7.76%)	134 (7.06%)
Antipsoriatics	<5	10 (0.53%)	<5	10 (0.53%)	<5	11 (0.58%)
Antithrombotic agents	460 (23.03%)	507 (26.71%)	559 (27.99%)	624 (32.88%)	710 (35.55%)	791 (41.68%)
Beta blocking agents	307 (15.37%)	294 (15.49%)	324 (16.22%)	309 (16.28%)	370 (18.53%)	371 (19.55%)
Calcium channel blockers	340 (17.03%)	326 (17.18%)	364 (18.23%)	355 (18.7%)	408 (20.43%)	404 (21.29%)
Diuretics	460 (23.03%)	389 (20.5%)	531 (26.59%)	461 (24.29%)	669 (33.5%)	572 (30.14%)
Drugs for acid related disorders	1148 (57.49%)	1133 (59.69%)	1264 (63.29%)	1240 (65.33%)	1425 (71.36%)	1383 (72.87%)
Drugs for obstructive airway diseases	310 (15.52%)	303 (15.96%)	379 (18.98%)	354 (18.65%)	560 (28.04%)	534 (28.13%)
Drugs used in diabetes	228 (11.42%)	322 (16.97%)	243 (12.17%)	332 (17.49%)	261 (13.07%)	356 (18.76%)
Immunosuppressants	18 (0.9%)	18 (0.95%)	19 (0.95%)	18 (0.95%)	25 (1.25%)	25 (1.32%)
Lipid modifying agents	418 (20.93%)	523 (27.56%)	435 (21.78%)	530 (27.92%)	475 (23.79%)	561 (29.56%)
Opioids	714 (35.75%)	609 (32.09%)	801 (40.11%)	702 (36.99%)	980 (49.07%)	872 (45.94%)
Psycholeptics	755 (37.81%)	495 (26.08%)	854 (42.76%)	578 (30.45%)	1020 (51.08%)	765 (40.31%)
Psychostimulants	17 (0.85%)	20 (1.05%)	25 (1.25%)	26 (1.37%)	37 (1.85%)	39 (2.05%)

Table 7. Number and % of pre-specified medication use among individuals in Cohort 1 at index date, by age group

	IQVIA DA Germany			CDWBordeaux			SIDIAP		
	45 to 59 years	60 to 69 years	>=70 years	45 to 59 years	60 to 69 years	>=70 years	45 to 59 years	60 to 69 years	>=70 years
Agents acting on the renin-angiotensin system	140 (12.97%)	296 (20.32%)	808 (24.63%)	<5	<5	13 (3.08%)	97 (14.56%)	279 (32.25%)	935 (45.34%)
Antibacterials for systemic use	45 (4.17%)	70 (4.8%)	115 (3.51%)	<5	6 (2.34%)	39 (9.24%)	56 (8.41%)	84 (9.71%)	244 (11.83%)
Antidepressants	59 (5.47%)	66 (4.53%)	171 (5.21%)	<5	<5	12 (2.84%)	82 (12.31%	141 (16.3%)	423 (20.51%)
Antiepileptics	20 (1.85%)	37 (2.54%)	124 (3.78%)	5 (2.92%)	6 (2.34%)	18 (4.27%)	73 (10.96%	103 (11.91%)	258 (12.51%)
Antiinflammatory and antirheumatic products	106 (9.82%)	101 (6.93%)	192 (5.85%)	5 (2.92%)	<5	<5	169 (25.38%)	178 (20.58%)	274 (13.29%)
Antineoplastic agents	7 (0.65%)	5 (0.34%)	20 (0.61%)	26 (15.2%)	60 (23.44%)	49 (11.61%)	9 (1.35%)	18 (2.08%)	65 (3.15%)
Antipsoriatics	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	<5	<5	7 (0.34%)
Antithrombotic agents	29 (2.69%)	69 (4.74%)	350 (10.67%)	<5	19 (7.42%)	67 (15.88%)	90 (13.51%)	170 (19.65%)	439 (21.29%)
Beta blocking agents	82 (7.6%)	217 (14.89%)	636 (19.38%)	0 (0%)	7 (2.73%)	23 (5.45%)	47 (7.06%)	121 (13.99%)	402 (19.5%)
Calcium channel blockers	48 (4.45%)	102 (7%)	373 (11.37%)	<5	5 (1.95%)	15 (3.55%)	42 (6.31%)	133 (15.38%)	445 (21.58%)
Diuretics	59 (5.47%)	135 (9.27%)	526 (16.03%)	<5	5 (1.95%)	23 (5.45%)	44 (6.61%)	101 (11.68%)	590 (28.61%)
Drugs for acid related disorders	198 (18.35%)	223 (15.31%)	608 (18.53%)	6 (3.51%)	17 (6.64%)	45 (10.66%)	248 (37.24%	445 (51.45%)	1246 (60.43%)
Drugs for obstructive airway diseases	26 (2.41%)	40 (2.75%)	100 (3.05%)	<5	8 (3.12%)	16 (3.79%)	53 (7.96%)	98 (11.33%)	370 (17.94%)
Drugs used in diabetes	40 (3.71%)	93 (6.38%)	217 (6.61%)	0 (0%)	7 (2.73%)	20 (4.74%)	41 (6.16%)	125 (14.45%)	352 (17.07%)
Immunosuppressants	8 (0.74%)	6 (0.41%)	26 (0.79%)	13 (7.6%)	24 (9.38%)	12 (2.84%)	7 (1.05%)	9 (1.04%)	16 (0.78%)
Lipid modifying agents	46 (4.26%)	127 (8.72%)	431 (13.14%)	<5	8 (3.12%)	32 (7.58%)	78 (11.71%	228 (26.36%)	610 (29.58%)
Opioids	71 (6.58%)	123 (8.44%)	344 (10.48%)	14 (8.19%)	24 (9.38%)	56 (13.27%)	164 (24.62%	268 (30.98%)	638 (30.94%)
Psycholeptics	27 (2.5%)	34 (2.33%)	139 (4.24%)	14 (8.19%)	25 (9.77%)	56 (13.27%)	171 (25.68%	262 (30.29%)	660 (32.01%)
Psychostimulants	0 (0%)	0 (0%)	<5	0 (0%)	0 (0%)	0 (0%)	<5	<5	27 (1.31%)

Table 8. Number and % of pre-specified medication use among individuals in Cohort 1 at time windows prior to index date, by age group

	IQVIA DA Germany						CDWBordeaux*			
	30 to 1 days prior	**365 to 31 days prior**	**30 to 1 days prior**	**365 to 31 days prior**	**30 to 1 days prior**	**365 to 31 days prior**	**30 to 1 days prior**	**365 to 31 days prior**	**30 to 1 days prior**	**365 to 31 days prior**
	45 to 59 years	45 to 59 years	60 to 69 years	60 to 69 years	>=70 years	>=70 years	60 to 69 years	60 to 69 years	>=70 years	>=70 years
Agents acting on the renin-angiotensin system	140 (12.97%)	174 (16.13%)	300 (20.59%)	370 (25.39%)	857 (26.12%)	1052 (32.06%)	<5	7 (2.73%)	5 (1.18%)	26 (6.16%)
Antibacterials for systemic use	27 (2.5%)	176 (16.31%)	46 (3.16%)	203 (13.93%)	120 (3.66%)	458 (13.96%)	5 (1.95%)	8 (3.12%)	9 (2.13%)	16 (3.79%)
Antidepressants	37 (3.43%)	79 (7.32%)	53 (3.64%)	76 (5.22%)	147 (4.48%)	216 (6.58%)	<5	<5	6 (1.42%)	10 (2.37%)
Antiepileptics	21 (1.95%)	32 (2.97%)	23 (1.58%)	40 (2.75%)	115 (3.51%)	149 (4.54%)	<5	<5	5 (1.18%)	<5
Antiinflammatory and antirheumatic products	114 (10.57%)	255 (23.63%)	108 (7.41%)	289 (19.84%)	209 (6.37%)	586 (17.86%)	<5	<5	0 (0%)	<5
Antineoplastic agents	6 (0.56%)	12 (1.11%)	<5	11 (0.75%)	16 (0.49%)	34 (1.04%)	<5	<5	7 (1.66%)	6 (1.42%)
Antipsoriatics	<5	<5	0 (0%)	0 (0%)	0 (0%)	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Antithrombotic agents	22 (2.04%)	41 (3.8%)	64 (4.39%)	86 (5.9%)	342 (10.42%)	445 (13.56%)	8 (3.12%)	10 (3.91%)	14 (3.32%)	22 (5.21%)
Beta blocking agents	79 (7.32%)	107 (9.92%)	222 (15.24%)	257 (17.64%)	659 (20.09%)	818 (24.93%)	<5	6 (2.34%)	12 (2.84%)	23 (5.45%)
Calcium channel blockers	40 (3.71%)	50 (4.63%)	97 (6.66%)	130 (8.92%)	378 (11.52%)	505 (15.39%)	<5	6 (2.34%)	5 (1.18%)	12 (2.84%)
Diuretics	56 (5.19%)	66 (6.12%)	118 (8.1%)	133 (9.13%)	506 (15.42%)	612 (18.65%)	<5	8 (3.12%)	13 (3.08%)	21 (4.98%)
Drugs for acid related disorders	136 (12.6%)	196 (18.16%)	172 (11.81%)	263 (18.05%)	542 (16.52%)	726 (22.13%)	<5	11 (4.3%)	10 (2.37%)	23 (5.45%)
Drugs for obstructive airway diseases	19 (1.76%)	78 (7.23%)	42 (2.88%)	113 (7.76%)	114 (3.47%)	232 (7.07%)	0 (0%)	<5	<5	7 (1.66%)
Drugs used in diabetes	39 (3.61%)	49 (4.54%)	97 (6.66%)	123 (8.44%)	230 (7.01%)	313 (9.54%)	<5	<5	<5	7 (1.66%)
Immunosuppressants	7 (0.65%)	12 (1.11%)	7 (0.48%)	13 (0.89%)	22 (0.67%)	36 (1.1%)	5 (1.95%)	<5	<5	<5

Lipid modifying agents	54 (5%)	68 (6.3%)	146 (10.02%)	176 (12.08%)	458 (13.96%)	593 (18.07%)	<5	9 (3.52%)	7 (1.66%)	16 (3.79%)
Opioids	71 (6.58%)	88 (8.16%)	90 (6.18%)	117 (8.03%)	276 (8.41%)	379 (11.55%)	6 (2.34%)	9 (3.52%)	10 (2.37%)	14 (3.32%)
Psycholeptics	20 (1.85%)	40 (3.71%)	33 (2.26%)	66 (4.53%)	139 (4.24%)	232 (7.07%)	7 (2.73%)	11 (4.3%)	13 (3.08%)	24 (5.69%)
Psychostimulants	0 (0%)	0 (0%)	<5	<5	<5	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Results for the age group 45-59 years were excluded for CDWBordeaux because of the small number of individuals in this age group and database.

Table 8 (continued). Number and % of pre-specified medication use among individuals in Cohort 1 at time windows prior to index date, by age group

	SIDIAP					
	30 to 1 days prior	**365 to 31 days prior**	**30 to 1 days prior**	**365 to 31 days prior**	**30 to 1 days prior**	**365 to 31 days prior**
	45 to 59 years	45 to 59 years	60 to 69 years	60 to 69 years	>=70 years	>=70 years
Agents acting on the renin-angiotensin system	107 (16.07%)	113 (16.97%)	291 (33.64%)	305 (35.26%)	982 (47.62%)	1055 (51.16%)
Antibacterials for systemic use	84 (12.61%)	179 (26.88%)	128 (14.8%)	333 (38.5%)	344 (16.68%)	901 (43.7%)
Antidepressants	85 (12.76%)	95 (14.26%)	144 (16.65%)	165 (19.08%)	441 (21.39%)	475 (23.04%)
Antiepileptics	71 (10.66%)	73 (10.96%)	109 (12.6%)	121 (13.99%)	269 (13.05%)	311 (15.08%)
Antiinflammatory and antirheumatic products	212 (31.83%)	320 (48.05%)	232 (26.82%)	402 (46.47%)	362 (17.56%)	765 (37.1%)
Antineoplastic agents	10 (1.5%)	9 (1.35%)	20 (2.31%)	25 (2.89%)	70 (3.39%)	82 (3.98%)
Antipsoriatics	<5	<5	<5	<5	6 (0.29%)	9 (0.44%)
Antithrombotic agents	76 (11.41%)	51 (7.66%)	154 (17.8%)	109 (12.6%)	438 (21.24%)	445 (21.58%)
Beta blocking agents	48 (7.21%)	47 (7.06%)	122 (14.1%)	119 (13.76%)	409 (19.84%)	424 (20.56%)
Calcium channel blockers	44 (6.61%)	43 (6.46%)	133 (15.38%)	125 (14.45%)	460 (22.31%)	489 (23.71%)
Diuretics	46 (6.91%)	42 (6.31%)	111 (12.83%)	119 (13.76%)	630 (30.55%)	668 (32.4%)
Drugs for acid related disorders	245 (36.79%)	238 (35.74%)	430 (49.71%)	432 (49.94%)	1243 (60.28%)	1268 (61.49%)
Drugs for obstructive airway diseases	64 (9.61%)	99 (14.86%)	113 (13.06%)	196 (22.66%)	400 (19.4%)	590 (28.61%)
Drugs used in diabetes	41 (6.16%)	39 (5.86%)	127 (14.68%)	127 (14.68%)	357 (17.31%)	367 (17.8%)
Immunosuppressants	8 (1.2%)	7 (1.05%)	9 (1.04%)	11 (1.27%)	16 (0.78%)	17 (0.82%)
Lipid modifying agents	79 (11.86%)	82 (12.31%)	235 (27.17%)	249 (28.79%)	633 (30.7%)	689 (33.41%)
Opioids	168 (25.23%)	161 (24.17%)	267 (30.87%)	287 (33.18%)	664 (32.2%)	762 (36.95%)
Psycholeptics	179 (26.88%)	199 (29.88%)	278 (32.14%)	317 (36.65%)	690 (33.46%)	825 (40.01%)
Psychostimulants	<5	<5	<5	8 (0.92%)	31 (1.5%)	55 (2.67%)

Table 9. Number and % of pre-specified medication use among individuals in Cohort 1 at time windows post index date, by age group

	IQVIA DA Germany								
	1 to 30 days post	1 to 90 days post	1 t to 365 days post	1 to 30 days post	1 to 90 days post	1 to 365 days post	1 to 30 days post	1 to 90 days post	1 to 365 days post
	45 to 59 years	45 to 59 years	45 to 59 years	60 to 69 years	60 to 69 years	60 to 69 years	>=70 years	>=70 years	>=70 years
Agents acting on the renin-angiotensin system	155 (14.37%)	168 (15.57%)	199 (18.44%)	315 (21.62%)	344 (23.61%)	385 (26.42%)	896 (27.31%)	974 (29.69%)	1087 (33.13%)
Antibacterials for systemic use	77 (7.14%)	121 (11.21%)	253 (23.45%)	108 (7.41%)	161 (11.05%)	284 (19.49%)	206 (6.28%)	340 (10.36%)	607 (18.5%)
Antidepressants	70 (6.49%)	81 (7.51%)	109 (10.1%)	81 (5.56%)	95 (6.52%)	131 (8.99%)	195 (5.94%)	225 (6.86%)	300 (9.14%)
Antiepileptics	21 (1.95%)	29 (2.69%)	51 (4.73%)	47 (3.23%)	63 (4.32%)	101 (6.93%)	157 (4.79%)	187 (5.7%)	254 (7.74%)
Antiinflammatory and antirheumatic products	126 (11.68%)	156 (14.46%)	238 (22.06%)	124 (8.51%)	160 (10.98%)	244 (16.75%)	236 (7.19%)	308 (9.39%)	465 (14.17%)
Antineoplastic agents	6 (0.56%)	10 (0.93%)	12 (1.11%)	5 (0.34%)	8 (0.55%)	16 (1.1%)	24 (0.73%)	30 (0.91%)	50 (1.52%)
Antipsoriatics	<5	<5	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Antithrombotic agents	41 (3.8%)	66 (6.12%)	88 (8.16%)	90 (6.18%)	110 (7.55%)	144 (9.88%)	422 (12.86%)	489 (14.9%)	582 (17.74%)
Beta blocking agents	98 (9.08%)	110 (10.19%)	142 (13.16%)	236 (16.2%)	265 (18.19%)	295 (20.25%)	717 (21.85%)	806 (24.57%)	910 (27.74%)
Calcium channel blockers	54 (5%)	64 (5.93%)	83 (7.69%)	116 (7.96%)	131 (8.99%)	156 (10.71%)	429 (13.08%)	487 (14.84%)	570 (17.37%)
Diuretics	66 (6.12%)	72 (6.67%)	94 (8.71%)	155 (10.64%)	181 (12.42%)	225 (15.44%)	594 (18.1%)	695 (21.18%)	835 (25.45%)
Drugs for acid related disorders	228 (21.13%)	262 (24.28%)	317 (29.38%)	264 (18.12%)	303 (20.8%)	394 (27.04%)	706 (21.52%)	818 (24.93%)	963 (29.35%)
Drugs for obstructive airway diseases	28 (2.59%)	47 (4.36%)	79 (7.32%)	54 (3.71%)	85 (5.83%)	126 (8.65%)	134 (4.08%)	164 (5%)	257 (7.83%)
Drugs used in diabetes	51 (4.73%)	55 (5.1%)	62 (5.75%)	103 (7.07%)	116 (7.96%)	131 (8.99%)	266 (8.11%)	299 (9.11%)	333 (10.15%)
Immunosuppressants	9 (0.83%)	12 (1.11%)	15 (1.39%)	7 (0.48%)	9 (0.62%)	18 (1.24%)	28 (0.85%)	34 (1.04%)	40 (1.22%)
Lipid modifying agents	54 (5%)	61 (5.65%)	81 (7.51%)	141 (9.68%)	162 (11.12%)	187 (12.83%)	483 (14.72%)	536 (16.34%)	607 (18.5%)
Opioids	92 (8.53%)	110 (10.19%)	152 (14.09%)	162 (11.12%)	185 (12.7%)	234 (16.06%)	453 (13.81%)	544 (16.58%)	661 (20.15%)
Psycholeptics	38 (3.52%)	44 (4.08%)	67 (6.21%)	50 (3.43%)	62 (4.26%)	104 (7.14%)	200 (6.1%)	257 (7.83%)	369 (11.25%)
Psychostimulants	0 (0%)	<5	<5	0 (0%)	<5	<5	<5	<5	<5

Table 9 (continued). Number and % of pre-specified medication use among individuals in Cohort 1 at time windows post index date, by age group

	CDWBordeaux								
	1 to 30 days post	1 to 90 days post	1 t to 365 days post	1 to 30 days post	1 to 90 days post	1 to 365 days post	1 to 30 days post	1 to 90 days post	1 to 365 days post
	45 to 59 years	45 to 59 years	45 to 59 years	60 to 69 years	60 to 69 years	60 to 69 years	>=70 years	>=70 years	>=70 years
Agents acting on the renin-angiotensin system	12 (7.02%)	13 (7.6%)	17 (9.94%)	32 (12.5%)	35 (13.67%)	43 (16.8%)	96 (22.75%)	106 (25.12%)	122 (28.91%)
Antibacterials for systemic use	34 (19.88%)	42 (24.56%)	47 (27.49%)	50 (19.53%)	60 (23.44%)	76 (29.69%)	132 (31.28%)	153 (36.26%)	179 (42.42%)
Antidepressants	10 (5.85%)	12 (7.02%)	14 (8.19%)	13 (5.08%)	17 (6.64%)	24 (9.38%)	51 (12.09%)	60 (14.22%)	73 (17.3%)
Antiepileptics	11 (6.43%)	13 (7.6%)	14 (8.19%)	13 (5.08%)	20 (7.81%)	27 (10.55%)	44 (10.43%)	49 (11.61%)	63 (14.93%)
Antiinflammatory and antirheumatic products	9 (5.26%)	12 (7.02%)	12 (7.02%)	13 (5.08%)	16 (6.25%)	21 (8.2%)	12 (2.84%)	15 (3.55%)	20 (4.74%)
Antineoplastic agents	86 (50.29%)	105 (61.4%)	115 (67.25%)	151 (58.98%)	173 (67.58%)	184 (71.88%)	144 (34.12%)	168 (39.81%)	183 (43.36%)
Antipsoriatics	0 (0%)	0 (0%)	0 (0%)	<5	<5	<5	<5	<5	<5
Antithrombotic agents	31 (18.13%)	38 (22.22%)	43 (25.15%)	61 (23.83%)	67 (26.17%)	74 (28.91%)	168 (39.81%)	180 (42.65%)	211 (50%)
Beta blocking agents	8 (4.68%)	10 (5.85%)	10 (5.85%)	25 (9.77%)	25 (9.77%)	32 (12.5%)	90 (21.33%)	98 (23.22%)	118 (27.96%)
Calcium channel blockers	6 (3.51%)	7 (4.09%)	10 (5.85%)	33 (12.89%)	35 (13.67%)	40 (15.62%)	71 (16.82%)	78 (18.48%)	95 (22.51%)
Diuretics	5 (2.92%)	9 (5.26%)	11 (6.43%)	25 (9.77%)	28 (10.94%)	32 (12.5%)	96 (22.75%)	105 (24.88%)	127 (30.09%)
Drugs for acid related disorders	33 (19.3%)	41 (23.98%)	43 (25.15%)	53 (20.7%)	61 (23.83%)	74 (28.91%)	136 (32.23%)	151 (35.78%)	173 (41%)
Drugs for obstructive airway diseases	10 (5.85%)	14 (8.19%)	21 (12.28%)	16 (6.25%)	21 (8.2%)	33 (12.89%)	39 (9.24%)	45 (10.66%)	63 (14.93%)
Drugs used in diabetes	<5	<5	<5	17 (6.64%)	18 (7.03%)	19 (7.42%)	43 (10.19%)	46 (10.9%)	51 (12.09%)
Immunosuppressants	49 (28.65%)	60 (35.09%)	62 (36.26%)	70 (27.34%)	80 (31.25%)	91 (35.55%)	62 (14.69%)	75 (17.77%)	84 (19.91%)
Lipid modifying agents	6 (3.51%)	6 (3.51%)	6 (3.51%)	21 (8.2%)	21 (8.2%)	27 (10.55%)	60 (14.22%)	63 (14.93%)	73 (17.3%)
Opioids	37 (21.64%)	46 (26.9%)	48 (28.07%)	50 (19.53%)	59 (23.05%)	69 (26.95%)	115 (27.25%)	126 (29.86%)	154 (36.49%)
Psycholeptics	42 (24.56%)	47 (27.49%)	60 (35.09%)	53 (20.7%)	62 (24.22%)	80 (31.25%)	133 (31.52%)	147 (34.83%)	172 (40.76%)

Table 9 (continued). Number and % of pre-specified medication use among individuals in Cohort 1 at time windows post index date, by age group

	SIDIAP								
	1 to 30 days post	1 to 90 days post	1 t to 365 days post	1 to 30 days post	1 to 90 days post	1 to 365 days post	1 to 30 days post	1 to 90 days post	1 to 365 days post
	45 to 59 years	45 to 59 years	45 to 59 years	60 to 69 years	60 to 69 years	60 to 69 years	>=70 years	>=70 years	>=70 years
Agents acting on the renin-angiotensin system	99 (14.86 %)	110 (16.52 %)	123 (18.47 %)	283 (32.72 %)	293 (33.87 %)	334 (38.61 %)	944 (45.78 %)	959 (46.51 %)	1006 (48.79%)
Antibacterials for systemic use	113 (16.97 %)	184 (27.63 %)	409 (61.41 %)	168 (19.42 %)	288 (33.29 %)	543 (62.77 %)	412 (19.98 %)	628 (30.46 %)	1089 (52.81%)
Antidepressants	91 (13.66 %)	104 (15.62 %)	149 (22.37 %)	155 (17.92 %)	172 (19.88 %)	233 (26.94 %)	456 (22.11 %)	504 (24.44 %)	620 (30.07%)
Antiepileptics	93 (13.96 %)	124 (18.62 %)	215 (32.28 %)	118 (13.64 %)	162 (18.73 %)	279 (32.25 %)	290 (14.06 %)	359 (17.41 %)	499 (24.2%)
Antiinflammatory and antirheumatic products	203 (30.48 %)	237 (35.59 %)	345 (51.8%)	228 (26.36 %)	267 (30.87 %)	381 (44.05 %)	331 (16.05 %)	407 (19.74 %)	602 (29.19%)
Antineoplastic agents	14 (2.1%)	17 (2.55%)	29 (4.35%)	28 (3.24%)	37 (4.28%)	62 (7.17%)	94 (4.56%)	129 (6.26%)	193 (9.36%)
Antipsoriatics	<5	<5	<5	<5	<5	<5	7 (0.34%)	7 (0.34%)	8 (0.39%)
Antithrombotic agents	163 (24.47 %)	229 (34.38 %)	301 (45.2%)	258 (29.83 %)	328 (37.92 %)	413 (47.75 %)	516 (25.02 %)	591 (28.66 %)	742 (35.98%)
Beta blocking agents	50 (7.51%)	55 (8.26%)	69 (10.36 %)	128 (14.8%)	133 (15.38 %)	160 (18.5%)	418 (20.27 %)	439 (21.29 %)	504 (24.44%)
Calcium channel blockers	48 (7.21%)	63 (9.46%)	89 (13.36 %)	144 (16.65 %)	152 (17.57 %)	180 (20.81 %)	469 (22.74 %)	498 (24.15 %)	535 (25.95%)
Diuretics	56 (8.41%)	72 (10.81 %)	107 (16.07 %)	142 (16.42 %)	175 (20.23 %)	242 (27.98 %)	645 (31.28 %)	738 (35.79 %)	880 (42.68%)
Drugs for acid related disorders	333 (50%)	388 (58.26 %)	470 (70.57 %)	538 (62.2%)	603 (69.71 %)	686 (79.31 %)	1351 (65.52 %)	1444 (70.03 %)	1571 (76.19%)
Drugs for obstructive airway diseases	63 (9.46%)	81 (12.16 %)	146 (21.92 %)	112 (12.95 %)	143 (16.53 %)	235 (27.17 %)	421 (20.42 %)	489 (23.71 %)	662 (32.1%)
Drugs used in diabetes	45 (6.76%)	49 (7.36%)	55 (8.26%)	133 (15.38 %)	139 (16.07 %)	151 (17.46 %)	366 (17.75 %)	380 (18.43 %)	402 (19.5%)

Immunosuppressants	7 (1.05%)	7 (1.05%)	11 (1.65%)	9 (1.04%)	9 (1.04%)	12 (1.39%)	17 (0.82%)	18 (0.87%)	23 (1.12%)
Lipid modifying agents	83 (12.46%)	91 (13.66%)	107 (16.07%)	235 (27.17%)	239 (27.63%)	250 (28.9%)	618 (29.97%)	629 (30.5%)	671 (32.54%)
Opioids	217 (32.58%)	255 (38.29%)	319 (47.9%)	330 (38.15%)	370 (42.77%)	444 (51.33%)	746 (36.18%)	839 (40.69%)	1040 (50.44%)
Psycholeptics	191 (28.68%)	219 (32.88%)	298 (44.74%)	300 (34.68%)	342 (39.54%)	436 (50.4%)	719 (34.87%)	819 (39.72%)	984 (47.72%)
Psychostimulants	<5	5 (0.75%)	9 (1.35%)	<5	6 (0.69%)	13 (1.5%)	29 (1.41%)	34 (1.65%)	46 (2.23%)

Appendix III: Supplementary figures

Figure 1. Frequency of use of cancer treatment class from 1 to 30 days after diagnosis, by sex

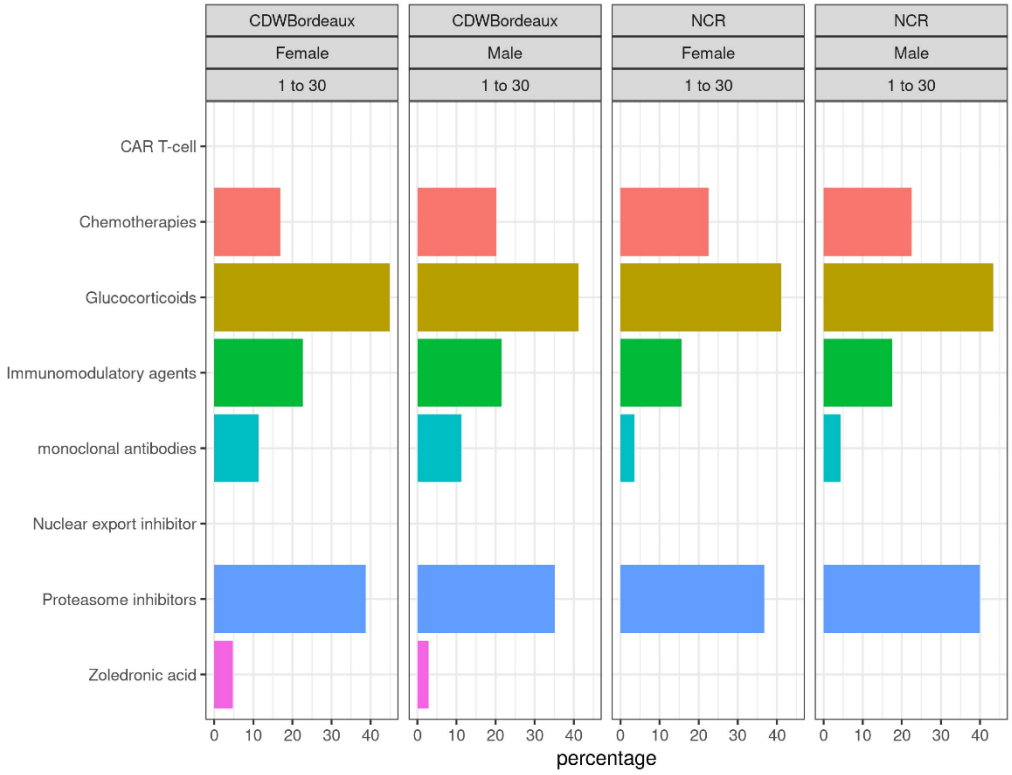


Figure 2. Frequency of use of cancer treatment class from 1 to 90 days after diagnosis, by sex

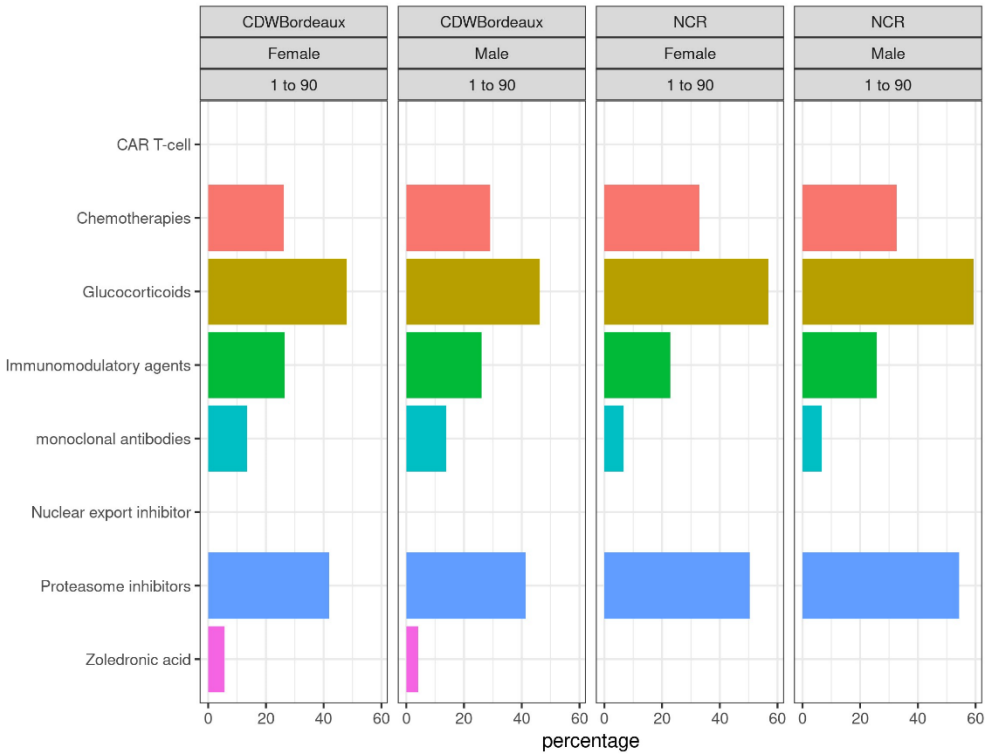


Figure 3. Frequency of use of cancer treatment class from 1 to 365 days after diagnosis, by sex

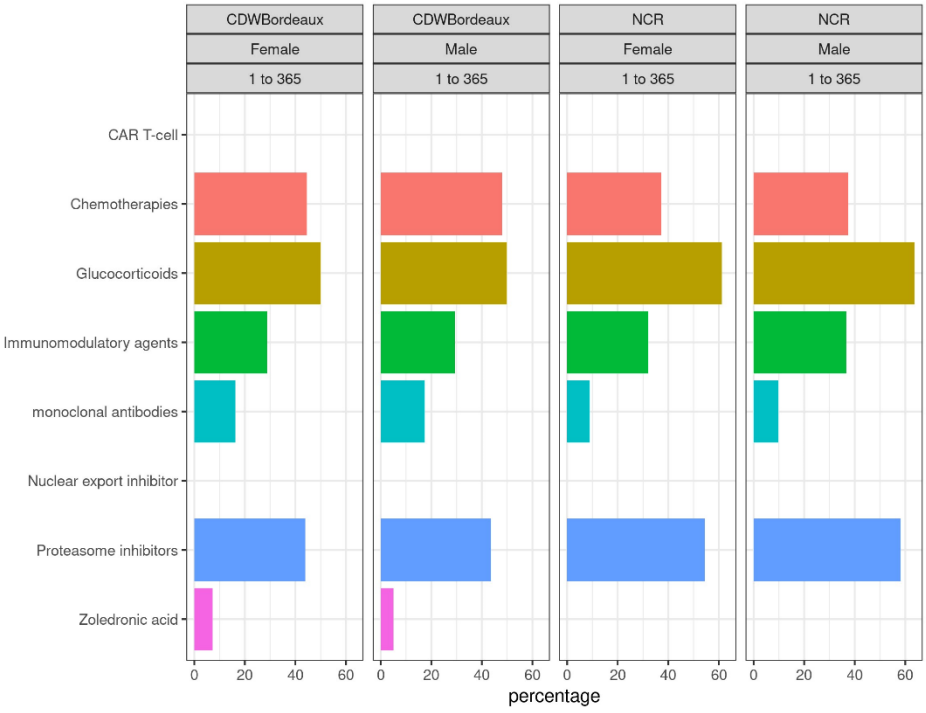


Figure 4. Frequency of use of cancer treatment class from 1 to 30 days after diagnosis, by age (at diagnosis) group

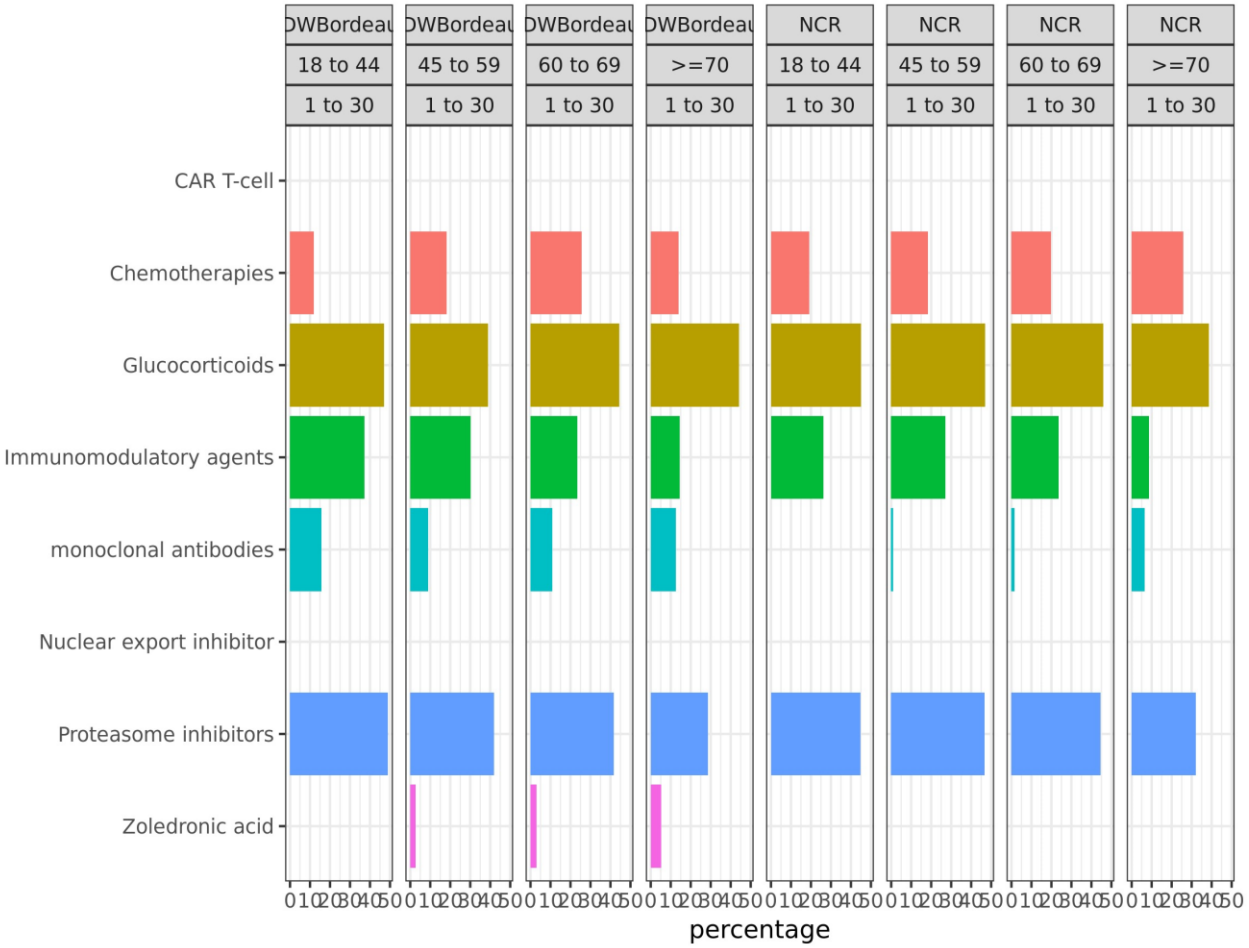


Figure 5. Frequency of use of cancer treatment class from 1 to 90 days after diagnosis, by age (at diagnosis) group

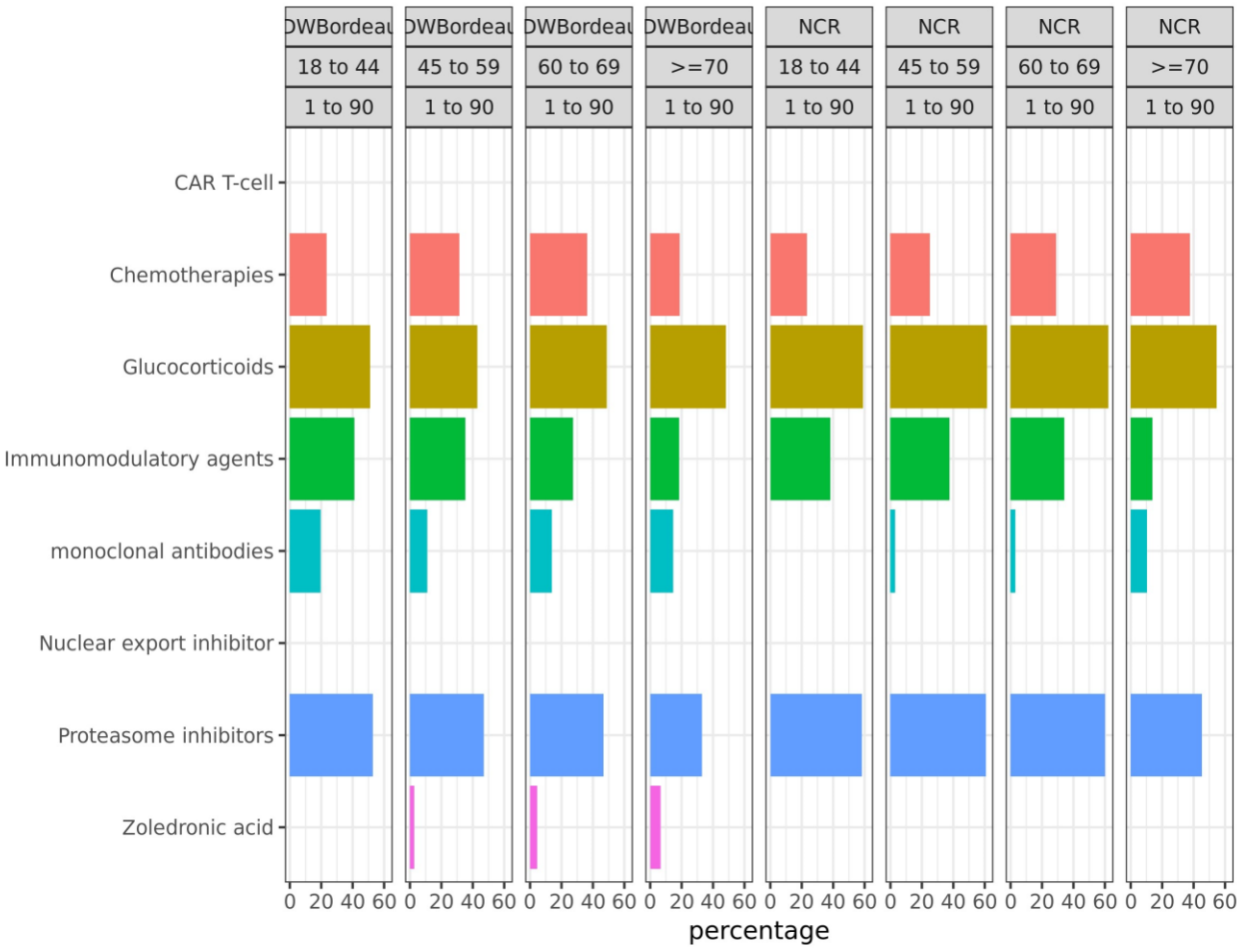


Figure 6. Frequency of use of cancer treatment class from 1 to 365 days after diagnosis, by age (at diagnosis) group