

SAP for EHDEN HMB

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2023-07-20

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1 Background

This study is a continuation of a Bayer Heavy-menstrual bleed (HMB) study, which had been conducted internally. The second part of the HMB study sees it expand to the European Health Data and Evidence Network (EHDEN) aiming to characterize HMB across a network of European database who have had their data standardized to the OMOP CDM. Part 2 of the HMB study has a dedicated protocol, the purpose of this document is provide further details of part 2 of the analysis as supported by Odysseus Data Services.

2 Research Questions

- What are the characteristics of women diagnosed with HMB in terms of demographics, comorbidities, procedures, and comedication?
- What are the treatment patterns for HMB?
- What is the incidence of HMB across different countries and data sources?

3 Objectives

3.1 Primary Objectives

The primary objectives of this study are to:

- Describe demographics and baseline clinical characteristics of women of reproductive age diagnosed with HMB between 2000 and 2022 in a set of observational data from the EU.
- Describe treatment utilization and longitudinal treatment pathways of women of reproductive age diagnosed with HMB across different countries and data sources between the years 2000 and 2022 in a set of observational data from the EU.
- Estimate incidence of HMB among women between the ages of 11 to 55 between the years 2000 and 2022 in a set of observational data from the EU.

4 Study Design

This large-scale retrospective cohort study will be conducted across a network of European healthcare databases standardized to the OMOP CDM. Databases assessed in this study are either: a) Bayer data assests (CPRD GOLD and AURUM) or b) participating EHDEN data-partners. The final list of EHDEN data partners will be provided in the Data Sources section.

The study period will begin on January 1, 1999 (or earliest date of data availability following this date) and end at the latest date of data availability in each database. Persons involved in

this study must have a minimum of one-year prior observation in the database, therefore the indexing period will begin on January 1, 2000.

The study population for this study are women between the ages of 11 and 55 who have a first-time diagnosis of HMB, given that they have at least 365 days of continuous observation prior to the index date. More details of the study population are found in the study population section.

4.1 Study Population

The study population are women between the ages of 11 to 55 who with a diagnosis heavy-menstrual bleeding between the years 2000 and 2022. The index event of this cohort are women between the ages of 11 to 55 with a first-time diagnosis of heavy-menstrual bleeding. The index event of HMB must have occurred between the years 2000 and 2022. Women entering the HMB cohort must have a minimum of 365 days of prior observation. Women are excluded from the cohort if they have one of the following criteria:

- 1) Observation of a hysterectomy or bilateral ovariectomy
- 2) Observation of a menopause diagnosis
- 3) Observation of other gynecological bleeding (vaginal bleeding outside the menstrual cycle)

Women remain in the cohort and exit based on the end of continuous observation or observation of one of the following censoring criteria:

- 1) Death
- 2) Turning age 55 (indicating transition into natural menopause)
- 3) Observation of a hysterectomy or bilateral ovariectomy
- 4) Observation of a menopause diagnosis

4.2 Exposure Definition

In this study we wish to assess treatments used by women with HMB to alleviate symptoms. Thus we define two exposure definitions: a) lines of pharmacotherapy (drugs or combinations of drugs) prescribed to alleviate HMB and b) procedures performed to alleviate HMB.

4.2.1 Lines of pharmacotherapy

Our first exposure definition is women between the ages of 11 to 55 who have been prescribed a line of treatment between the years of 2000 and 2022 and have at least 365 days of prior observation. Lines of treatment can either be a single pharmacotherapy or a combination of 2 or more. The pharmacotherapies of interest are:

- Tranexamic acid (B02AA02)
- Progestin only regimens:
 - Medroxyprogesterone acetate (MPA) (G03AC06)
 - Oral norethindrone acetate (NETA) (G03DC02)
 - Desogestrel (G03AC09)
 - Etonogestrel implant (G03AC08)
- Non-steroidal anti-inflammatory drugs (NSAIDs) (M01A)
- Combined oral hormonal contraceptives
 - Dienogest and estradiol (G03AB08; sequential combinations)
 - Nomegestrol and estradiol (G03AA14; fixed combinations)
- Selective progesteron receptor modulators [Ulipristal acetate (G03AD02, G03XB02)]
- Danazol (G03XA01)
- Gonadotropin releasing hormone analogues (L02AE)
- Intrauterine devices (G02BA)
- Iron preparations (B03A)

We refer to these drug cohorts as drug eras, where an era is the span of time a person is considered continuously exposed to the same treatment. Eras are built by binding successive drug exposure events into a single duration where the person is inferred to be continuing use of that same treatment. We allow for a maximum of 30 days between drug exposure records to consider them part of the same era. This means that if there is a gap greater than 30 days between the same treatment, this would indicate two separate eras in the treatment history for the individual person. Persons may also exit the cohort either at the end of their drug era, the last available date in the database or from following censoring events, whichever occurs first:

- 1) Death
- 2) Turning age 55 (indicating transition into natural menopause)
- 3) Observation of a hysterectomy or bilateral ovariectomy
- 4) Observation of a menopause diagnosis

Combination treatments are defined as two or more drug eras that have an overlap of exposure for at least 30 days. This means if two drugs are taken on the same dates for at least 30 days they are considered a combination treatment. To “break” treatment combinations, at least 30 days of non-overlap must be observed either before or after the combination. A combination treatment is considered a separate line of treatment. To build the exposure definition we must align the drug eras to determine whether a treatment combination has occurred and adjust the cohort index date of the subsequent era if combinations are “broken” to determine each line of therapy eligible for the exposure definition. Lines of therapy, both single and combination treatments, are derived using the TreatmentPatterns package.

4.2.2 Procedures

Our second exposure definition is women between the ages of 11 to 55 who have had a procedure of interest between the years of 2000 and 2022. The procedures of interest are:

- Hysterectomy
- Endometrial ablation
- Uterine artery embolization (UAE)
- Myomectomy

The index event for the procedure cohort is a first time occurrence of one of the procedures of interest in the patient history. Women in the procedure cohort must have at least 365 days of prior observation. Women exit the cohort on the day of the procedure occurrence.

4.3 Outcome Definition

4.3.1 Heavy-menstrual Bleed

It is of interest to ascertain the overall and yearly incidence of HMB in each participating EU databases. We define the outcome for this incidence analysis to the target population defined in Section 4.1, women between the ages of 11 to 55 with first time diagnosis of HMB. The denominator for this incidence calculation will be women age 11 to 55 in the database who exit the cohort based on whether they have experienced one of the following events: turn age 55, observation of a menopause diagnosis, observation of a hysterectomy or observation of a bilateral ovariectomy.

4.3.2 Time to Discontinuation

For the women in the HMB cohort who have a line of pharmacotherapy exposure defined in Section 4.2.1, we define time discontinuation as the time between the start and end of the pharmacotherapy line. The end of a pharmacotherapy is derived from the exposure definition defined in Section 4.2.1 where a drug era ends either at the end of persistent exposure of the line of therapy, switch to a different line of therapy or observation of a censoring event: a) turning 55 years old, b) menopause c) hysterectomy or oophorectomy or d) death, whichever occurs first. A persistent exposure is defined as observation of multiple exposures to the same line of therapy within a maximum of 30 days from each other.

4.3.3 Time to Intervention

For women who in the HMB cohort who have a procedure exposure defined in Section 4.2.2, we define the time to intervention as the duration between the index date of the HMB cohort to the index date of the procedure exposure cohort. Surgical intervention is determined if women in the HMB cohort have a procedure exposure at some point between HMB diagnosis and the end of observation.

5 Data Sources

The datasources for this study include: a) Bayer OMOP assets and b) European databases that are part of EHDEN. All databases used in this study have been standardized to the OMOP CDM.

Table 1: Data Sources used in study

Name	Country	Type	Size	Availability	Description
CPRD AURM	UK	EHR	Number2008- 2010		Primary care data from a participating electronic system in England
CPRD AURM	UK	EHR	Number2008- 2010		Primary care data from across the UK

The above table will be expanded upon receiving information of the EHDEN participants.

6 Analysis Plan

6.1 Cohort Diagnostics

Prior to running any specific analysis, we will evaluate the HMB cohort using the OHDSI R package `CohortDiagnostics`. This package produces metrics such as cohort counts in the database, incidence rates (by calendar year, age and gender), time distributions, cohort attrition and breakdown of index events. Evaluation of these metrics helps ensure that the clinical cohort is indeed reliable in capturing HMB in the OMOP database.

6.2 Baseline Characteristics

We assess baseline characteristics based on an observation window of 365 to 1 days prior to the index date. Categorical covariates are reported using the count and percentage. Continuous covariates are reported using the median, 25th and 75th percentile.

Demographics

- Age at HMB diagnosis as 5-year categories
- Age at HMB diagnosis as continuous
- Race (if available)
- Ethnicity (if available)
- Year of HMB Diagnosis (per calendar year)

Comorbidity Scores

- BMI (if available) in following categories
 - Underweight ($< 18.5 \text{ kg/m}^2$)
 - Normal Weight ($18.5 - 24.9 \text{ kg/m}^2$)
 - Overweight ($25.0 - 29.9 \text{ kg/m}^2$)
 - Obese ($30.0 - 39.9 \text{ kg/m}^2$)
 - Morbidly obese ($> 40.0 \text{ kg/m}^2$)
- Charlston Comorbidity Score
- CHADs2Vasc

Concept-based

- Drug Era individual and rolled up to ATC2 Categories
- Condition Era individual and rolled up to ICD10 Chapters

Note: Concept-based covariates are based on prevalence concepts accumulated via **FeatureExtraction**. The roll-up is used for the table 1 report and the individual concepts are used to construct manhattan plots.

Cohort-based

- Conditions
 - Underlying Causes of HMB (individual)
 - * Uterine endometrial polyps
 - * Adenomyosis
 - * Uterine leiomyoma (fibroids) (subserous or intramural)
 - * Uterine malignancy and endometrial hyperplasia
 - * Coagulopathy / coagulation disorders

- * Ovulatory dysfunction (including hypothyroidism, polycystic ovary syndrome, adrenal disorders, hyperprolactinemia, hypothalamic disorders)
 - * Endometrial dysfunction
 - * Iatrogenic HMB
 - * Endometriosis
 - * Idiopathic menorrhagia
- Other Conditions
 - * Diabetes Mellitus
 - * Polycystic Ovary Syndrome (PCOS)
 - * Dysmenorrhea
 - * Pain
 - * Anemia
 - * Iron deficiency anemia
- Drugs
 - Antithrombotic Agents
 - Antidepressants
 - Tamoxifen
 - Antipsychotics
 - Gonadal Steroids
- Procedures
 - Endometrial ablation
 - Uterine artery embolization (UAE)
 - Myomectomy
 - Blood transfusion

6.3 Post-Index Utilization

We assess the prevalence of lines of therapy (defined in Section 4.2.1) and procedures (defined in Section 4.2.2) for women in the HMB cohort at time intervals of 0 days, 1 to 183 days, 184 to 365 days, 366 to 730 days, and 731 to 1825 days post index. Prevalence is defined as the number of persons who experienced the exposure during the time interval divided by the number of persons in the population at that time. We report the count and percentage for each line of therapy and procedure at each window.

6.4 Treatment Patterns

For each woman with HMB we determine the pattern of treatment lines (as defined in Section 4.2.1) over their entire history. Then we enumerate women within each unique sequence. Sequences with a count of less than 20 women are dropped from the analysis. The treatment

sequence results will be displayed using a sankey diagram, complemented by a summary table that shows the enumeration of each specific sequence.

6.5 Time to Event

Using the outcome definitions for time to discontinuation (Section 4.3.2) and time to intervention (Section 4.3.3), we will estimate the Kaplan-Meier (KM) curve for the treatment events specified in the post-index utilization section. From the KM we report the probability of survival at 183-, 365- and 730- days as well as the median, 25th and 75th percentile time to event. All of these statistics are reported with a corresponding two-sided 95% confidence interval. The time to discontinuation is calculated off of the treatment history table produced from the TreatmentPatterns package and then fit using the survival package. The time to intervention is calculated using the Characterization package from HADES.

6.6 Incidence Analysis

In this study we will calculate the incidence of the HMB cohort in a population of women age 11 to 55. Incidence is defined based on the following formula:

$$IR = \frac{\text{Number of new cases in time period}}{\text{Total person-time of the at risk population}} \times 1000$$

The incidence of HMB will be reported overall and per calendar year to show any variation over time. The incidence will be calculated using the CohortIncidence package from HADES.