11th March 2022

# Data analysis plan

Prevalence of primary and secondary arterial hypertension in children and treatment with angiotensin II receptor blockers

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# 1. Rationale and background

In the context of a regulatory procedure, it has been necessary to get recent data on the use of angiotensin II receptor blockers (ARBs) in children with arterial hypertension. In addition, it has been considered useful to obtain data on the prevalence of primary and secondary hypertension in children by age group, and to obtain data on risk factors for this disease that would help to understand if secondary causes of hypertension are more common in younger children below the age of 6 years compared to children 6 years or older.

The cause of primary or essential arterial hypertension is unknown. Secondary hypertension is diagnosed when a cause of the arterial hypertension is identified. Obesity, diabetes mellitus and sleep apnoea increase the risk of arterial hypertension in children [1]. Other causes or risk factors include chronic renal disease, certain endocrine disorders, cardiovascular malformation (coarctation of aorta, aortic stricture or stenosis), bronchopulmonary dysplasia and treatment with medicines that increase blood pressure, e.g. psychostimulants indicated for attention-deficit-hyperactivity disorder (ADHD), systemic corticosteroids, beta-2-agonists indicated for obstructive pulmonary disease, cyclosporine, tacrolimus or tricyclic antidepressants.

# 2. Research question and objectives

The objective of this study is to address the following research questions:

1. The number of children with arterial hypertension by age group (2-5 years, 6 to 12 years and 13-17 years), gender, and description of the risk factors for primary hypertension or potential causes of secondary hypertension
2. Yearly prevalence of arterial hypertension in the paediatric population age group
3. Yearly proportion of children with arterial hypertension treated with ARBs by age group
4. In children with arterial hypertension initiating ARB treatment between 2016 and 2019, the proportion of children with continued ARB prescriptions one year or more

# 3. Research methods

## 3.1. Study design

The study will include both a cross-sectional design and a cohort design.

## 3.2. Setting and study population

The study period will be January 2016 to June 2021 in the IQIVA™ Disease Analyzer France and Germany databases and from January 1990 to May 2021 for IMRD (UK). The population will included children aged 2-17 years during the study period and registered or treated by GPs. In IQVIA™ Disease Analyzer Germany children treated by paediatricians will also be included as paediatricians are part of primary care in Germany.

Children with unknown gender will not be included in the study.

## 3.3. Variables

Annex 2 provides the lists of codes for ARBs, arterial hypertension, primary hypertension, secondary hypertension, obesity or antiobesity treatment, diabetes mellitus or antidiabetic treatment, chronic renal disease and renal arterial and venous stricture, thrombosis or embolism (codes for chronic renal disease have been adapted from [2]), psychostimulants indicated for ADHD, beta-2-agonists indicated for asthma, endocrine disease (thyroid disease, Cushing disease, hyperaldosteronism, pheochromocytoma, hyperparathyroidism, treatment of hypothyroidism or hyperthyroidism), cardiovascular malformation (coarctation of aorta, aortic stricture or stenosis), bronchopulmonary dysplasia, systemic corticosteroid treatment, treatment with tricyclic antidepressants, treatment with cyclosporine or tacrolimus, and treatment with atypical antipsychotics.

Children with a code for arterial hypertension will be considered to have arterial hypertension from the first date of the diagnosis onwards. Children with a code for primary arterial hypertension will be considered to have primary hypertension, and children with a code for secondary arterial hypertension will be considered to have secondary hypertension. Where a diagnosis is not qualified as being either primary or secondary, it will be assumed to be of primary aetiology. It will be assumed that the same child can have both diagnoses.

Only ARB prescriptions after the initial arterial hypertension diagnosis will be considered in children with hypertension.

## 3.4. Data sources

The study will be conducted using databases in France (IQVIA™ Disease Analyzer France), Germany (IQVIA™ Disease Analyzer Germany) and the UK (IQVIA™ Medical Research Data - IMRD-UK). The version June 2021 of all three databases will be used for the study.

## 3.5. Statistical analysis

### 3.5.1. Main statistical methods

A descriptive analysis of risk factors for arterial hypertension will be carried in children 2-17 years with arterial hypertension during the study period, please see template table 1.

The yearly prevalence of arterial hypertension during the study period will be calculated in children 2-17 years that are observable for at least one day during the year. Children with arterial hypertension during the year or with a history of arterial hypertension will be included in the numerator, and the prevalence will be calculated as the number of children in the numerator per 100,000 children observed for a year (i.e. 100,000 person-years of observation), please see template table 2. In the IQVIA™ Disease Analyzer databases patients will be considered observable between their first and last visits to the practice.

Among yearly prevalent children with arterial hypertension, the proportion of children that also had a prescription for an ARB during the year will be calculated, please see template table 3. This will be done without requiring that the ARB be prescribed after the diagnosis of arterial hypertension as it will be assumed that any prescribing of an ARB during the same year as a diagnosis of arterial hypertension would be related to hypertension.

In addition, the yearly total number of children 2-17 years with an ARB prescription will be identified, and among these children the proportion of children with a diagnosis of arterial hypertension during the year or earlier will be calculated, please see template table 4.

### 3.5.2. Sensitivity analysis

The descriptive analysis will be redone in a cohort restricted to children that had a minimum of 365 days of observation at the time of the first arterial hypertension diagnosis.

Analyses will be performed by the EMA researchers, using the IHD platform and SAS

## 3.6. Quality control

The study will be conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance will be adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents will undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis will be either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

## 3.7. General limitations

The IQVIA™ Disease Analyzer France and Germany databases are based on primary care health visits. Patients are only identified uniquely within the same practice, and patients have free doctor's choice, which means that information about an individual patient can be patchy. Some patients might also be followed only for a short duration. It is important to consider this limitation, in particular the different lengths of observation time available for the assessment of risk factors, as this assessment is based on the existence of historical data in the patients. This limitation could lead to the erroneous assessment that a patient did not have a risk factor which would have been recorded in the data if the observation time had extended to the timepoint when that risk factor was diagnosed in the patient. For this reason, a sensitivity analysis restricted to patients with at least 365 days of observation at the time of the first arterial hypertension diagnosis will be undertaken.

This study is based on primary care data. Events that lead to hospitalization or require input from secondary care might therefore be incompletely recorded. Arterial hypertension might be incompletely recorded, and secondary hypertension might be under-recorded as a form of arterial hypertension due to incomplete capture of secondary causes. In Germany, physicians are required to record a diagnosis (reason for the consultation) at each visit, whereas in France, this is not required.

In the IQVIA™ Disease Analyzer databases, it is also important to take into account that patients are only observed when they visit the practice, and this in combination with the free doctor's choice might lead to an underestimation of the time that a person can be observed. If a person has visited a practice once, this person only contributes one day of observation if he or she continues to be healthy and doesn't require further visits to the practice. This can have a highly significant impact on the calculation of prevalence, which is based on the total observation time, as more than one visit is required to contribute more than one day of observation. The resulting underestimate of the number of subjects in the underlying population might then cause the prevalence of a condition to be overestimated.

# Annexes

# Annex 1 - Information on Databases and Healthcare systems included

**IQVIA™ Medical Research Data (IMRD) UK**

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

**IQVIA™ Disease Analyzer Germany**

IQVIA™ Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases

worldwide. IQVIA™ Disease Analyzer Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS Germany and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

**IQVIA™ Disease Analyzer France**

IQVIA™ Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2% of physicians and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). Some 99% of the French population is insured, but there are differences regarding level of coverage. IQVIA™ Disease Analyzer France includes around 1,000 GPs and represents more than 4,000,000 of patients and considered representative for the French population. This database used to be named IMS France and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

# Annex 2 - Codelists

EphMRA ATC codes for angiotensin receptor blockers

| EphMRA ATC code | Description |
|---|---|
| R03A2 | BETA-2-AGONISTEN.SYSTEM |
| R03A3 | BET2-AGON.LANGE WIRK INH |
| R03A4 | B2-AGONIST INH CRTE-ACT |
| R03E1 | BETA-2-AGON.+R3C INHAL. |
| R03F1 | ASS B2-AGON+CORTIC INH |

ICD 10 codes for arterial hypertension

| ICD 10 code | Description |
|---|---|
| H35.0 | Background retinopathy and retinal vascular changes |
| I10 | Essential (primary) hypertension |
| I11 | Hypertensive heart disease |
| I11.0 | Hypertensive heart disease with (congestive) heart failure |
| I11.9 | Hypertensive heart disease without (congestive) heart failure |
| I12 | Hypertensive renal disease |
| I12.0 | Hypertensive renal disease with renal failure |
| I12.9 | Hypertensive renal disease without renal failure |
| I13 | Hypertensive heart and renal disease |
| I13.0 | Hypertensive heart and renal disease with (congestive) heart failure |
| I13.1 | Hypertensive heart and renal disease with renal failure |
| I13.2 | Hypertensive heart and renal disease with both (congestive) heart failure and renal failure |
| I13.9 | Hypertensive heart and renal disease, unspecified |
| I15 | Secondary hypertension |
| I15.0 | Renovascular hypertension |
| I15.1 | Hypertension secondary to other renal disorders |
| I15.2 | Hypertension secondary to endocrine disorders |
| I15.8 | Other secondary hypertension |
| I15.9 | Secondary hypertension, unspecified |
| I67.4 | Hypertensive encephalopathy |
| N26 | Unspecified contracted kidney |
| O10 | Pre-existing hypertension complicating pregnancy, childbirth and the puerperium |
| O10.0 | Pre-existing essential hypertension complicating pregnancy, childbirth and the puerperium |
| O10.1 | Pre-existing hypertensive heart disease complicating pregnancy, childbirth and the puerperium |
| O10.2 | Pre-existing hypertensive renal disease complicating pregnancy, childbirth and the puerperium |
| O10.3 | Pre-existing hypertensive heart and renal disease complicating pregnancy, childbirth and the puerperium |
| O10.4 | Pre-existing secondary hypertension complicating pregnancy, childbirth and the puerperium |
| O10.9 | Unspecified pre-existing hypertension complicating pregnancy, childbirth and the puerperium |
| O11 | Pre-eclampsia superimposed on chronic hypertension |
| P29.2 | Neonatal hypertension |

ICD 10 codes for primary arterial hypertension

| ICD 10 code | Description |
|---|---|
| H35.0 | Background retinopathy and retinal vascular changes |
| I10 | Essential (primary) hypertension |
| I11 | Hypertensive heart disease |
| I11.0 | Hypertensive heart disease with (congestive) heart failure |
| I11.9 | Hypertensive heart disease without (congestive) heart failure |
| I12 | Hypertensive renal disease |
| I12.0 | Hypertensive renal disease with renal failure |
| I12.9 | Hypertensive renal disease without renal failure |
| I13 | Hypertensive heart and renal disease |
| I13.0 | Hypertensive heart and renal disease with (congestive) heart failure |
| I13.1 | Hypertensive heart and renal disease with renal failure |
| I13.2 | Hypertensive heart and renal disease with both (congestive) heart failure and renal failure |
| I13.9 | Hypertensive heart and renal disease, unspecified |
| I67.4 | Hypertensive encephalopathy |
| N26 | Unspecified contracted kidney |
| O10 | Pre-existing hypertension complicating pregnancy, childbirth and the puerperium |
| O10.0 | Pre-existing essential hypertension complicating pregnancy, childbirth and the puerperium |
| O10.1 | Pre-existing hypertensive heart disease complicating pregnancy, childbirth and the puerperium |
| O10.2 | Pre-existing hypertensive renal disease complicating pregnancy, childbirth and the puerperium |
| O10.3 | Pre-existing hypertensive heart and renal disease complicating pregnancy, childbirth and the puerperium |
| O10.4 | Pre-existing secondary hypertension complicating pregnancy, childbirth and the puerperium |
| O10.9 | Unspecified pre-existing hypertension complicating pregnancy, childbirth and the puerperium |
| O11 | Pre-eclampsia superimposed on chronic hypertension |
| P29.2 | Neonatal hypertension |

ICD 10 codes for secondary arterial hypertension

| ICD 10 code | Description |
|---|---|
| I15 | Secondary hypertension |
| I15.0 | Renovascular hypertension |
| I15.1 | Hypertension secondary to other renal disorders |
| I15.2 | Hypertension secondary to endocrine disorders |
| I15.8 | Other secondary hypertension |
| I15.9 | Secondary hypertension, unspecified |

ICD 10 codes for obesity and EphMRA ATC codes for antiobesity treatment

| ICD 10 code or EphMRA ATC code | Type of code | Description |
|---|---|---|
| E66 | ICD 10 | Obesity |
| E66.0 | ICD 10 | Obesity due to excess calories |
| E66.1 | ICD 10 | Drug-induced obesity |
| E66.2 | ICD 10 | Extreme obesity with alveolar hypoventilation |
| E66.8 | ICD 10 | Other obesity |
| E66.9 | ICD 10 | Obesity, unspecified |
| A08A0 | EphMRA ATC | ANTIOBESITY PREPARATIONS |

ICD 10 codes for diabetes and EphMRA ATC codes for antidiabetic treatment

| ICD 10 code or EphMRA ATC code | Type of code | Description |
|---|---|---|
| E10 | ICD 10 | Type 1 diabetes mellitus |
| E10.0 | ICD 10 | Type 1 diabetes mellitus, With coma |
| E10.1 | ICD 10 | Type 1 diabetes mellitus, With ketoacidosis |
| E10.2 | ICD 10 | Type 1 diabetes mellitus, With renal complications |
| E10.3 | ICD 10 | Type 1 diabetes mellitus, With ophthalmic complications |
| E10.4 | ICD 10 | Type 1 diabetes mellitus, With neurological complications |
| E10.5 | ICD 10 | Type 1 diabetes mellitus, With peripheral circulatory complications |
| E10.6 | ICD 10 | Type 1 diabetes mellitus, With other specified complications |
| E10.7 | ICD 10 | Type 1 diabetes mellitus, With multiple complications |
| E10.8 | ICD 10 | Type 1 diabetes mellitus, With unspecified complications |
| E10.9 | ICD 10 | Type 1 diabetes mellitus, Without complications |
| E11 | ICD 10 | Type 2 diabetes mellitus |
| E11.0 | ICD 10 | Type 2 diabetes mellitus, with coma |
| E11.1 | ICD 10 | Type 2 diabetes mellitus, with ketoacidosis |
| E11.2 | ICD 10 | Type 2 diabetes mellitus, with renal complications |
| E11.3 | ICD 10 | Type 2 diabetes mellitus, with ophthalmic complications |
| E11.4 | ICD 10 | Type 2 diabetes mellitus, with neurological complications |

| ICD 10 code or EphMRA ATC code | Type of code | Description |
|---|---|---|
| E11.5 | ICD 10 | Type 2 diabetes mellitus, with peripheral circulatory complications |
| E11.6 | ICD 10 | Type 2 diabetes mellitus, with other specified complications |
| E11.7 | ICD 10 | Type 2 diabetes mellitus, with multiple complications |
| E11.8 | ICD 10 | Type 2 diabetes mellitus, with unspecified complications |
| E11.9 | ICD 10 | Type 2 diabetes mellitus, without complications |
| E12 | ICD 10 | Malnutrition-related diabetes mellitus |
| E12.0 | ICD 10 | Malnutrition-related diabetes mellitus, with coma |
| E12.1 | ICD 10 | Malnutrition-related diabetes mellitus, with ketoacidosis |
| E12.2 | ICD 10 | Malnutrition-related diabetes mellitus, with renal complications |
| E12.3 | ICD 10 | Malnutrition-related diabetes mellitus, with ophthalmic complications |
| E12.4 | ICD 10 | Malnutrition-related diabetes mellitus, with neurological complications |
| E12.5 | ICD 10 | Malnutrition-related diabetes mellitus, with peripheral circulatory complications |
| E12.6 | ICD 10 | Malnutrition-related diabetes mellitus, with other specified complications |
| E12.7 | ICD 10 | Malnutrition-related diabetes mellitus, with multiple complications |
| E12.8 | ICD 10 | Malnutrition-related diabetes mellitus, with unspecified complications |
| E12.9 | ICD 10 | Malnutrition-related diabetes mellitus, without complications |
| E13 | ICD 10 | Other specified diabetes mellitus |
| E13.0 | ICD 10 | Other specified diabetes mellitus, with coma |
| E13.1 | ICD 10 | Other specified diabetes mellitus, with ketoacidosis |
| E13.2 | ICD 10 | Other specified diabetes mellitus, with renal complications |
| E13.3 | ICD 10 | Other specified diabetes mellitus, with ophthalmic complications |
| E13.4 | ICD 10 | Other specified diabetes mellitus, with neurological complications |
| E13.5 | ICD 10 | Other specified diabetes mellitus, with peripheral circulatory complications |
| E13.6 | ICD 10 | Other specified diabetes mellitus, with other specified complications |
| E13.7 | ICD 10 | Other specified diabetes mellitus, with multiple complications |
| E13.8 | ICD 10 | Other specified diabetes mellitus, with unspecified complications |
| E13.9 | ICD 10 | Other specified diabetes mellitus, without complications |
| E14 | ICD 10 | Unspecified diabetes mellitus |
| E14.0 | ICD 10 | Unspecified diabetes mellitus, with coma |
| E14.1 | ICD 10 | Unspecified diabetes mellitus, with ketoacidosis |
| E14.3 | ICD 10 | Unspecified diabetes mellitus, with ophthalmic complications |
| E14.4 | ICD 10 | Unspecified diabetes mellitus, with neurological complications |
| E14.5 | ICD 10 | Unspecified diabetes mellitus, with peripheral circulatory complications |
| E14.6 | ICD 10 | Unspecified diabetes mellitus, with other specified complications |
| E14.7 | ICD 10 | Unspecified diabetes mellitus, with multiple complications |
| E14.8 | ICD 10 | Unspecified diabetes mellitus, with unspecified complications |
| E14.9 | ICD 10 | Unspecified diabetes mellitus, without complications |
| A10C1 | EphMRA ATC | H INSUL+ANG FAST ACT |
| A10C2 | EphMRA ATC | H INSUL+ANG INTERMED ACT |
| A10C3 | EphMRA ATC | INSUL H+ANA INT OU PR+RA |
| A10C4 | EphMRA ATC | H INSUL+ANG INT+LONG ACT |
| A10C5 | EphMRA ATC | H INSUL+ANG LONG ACT |
| A10C9 | EphMRA ATC | AUT INSUL HUM+ANALOGUES |

| ICD 10 code or EphMRA ATC code | Type of code | Description |
|---|---|---|
| A10D0 | EphMRA ATC | ANIMAL INSULINS |
| A10E0 | EphMRA ATC | INSULIN DEVICES |
| A10H0 | EphMRA ATC | SULPHONYLUREA A-DIABS |
| A10J1 | EphMRA ATC | BIGUANIDE A-DIABS PLAIN |
| A10J2 | EphMRA ATC | BIGUANIDE & S-UREA COMBS |
| A10K1 | EphMRA ATC | GLITAZONE A-DIABS PLAIN |
| A10K2 | EphMRA ATC | GLITAZONE & S-UREA COMBS |
| A10K3 | EphMRA ATC | GLITAZONE & BIGUAN COMBS |
| A10L0 | EphMRA ATC | A-GLUCOSIDASE INH A-DIAB |
| A10M1 | EphMRA ATC | GLINIDE A-DIABS PLAIN |
| A10N1 | EphMRA ATC | DPP-IV INH A-DIAB PLAIN |
| A10N3 | EphMRA ATC | DPP-IV INH & BIGUAN COMB |
| A10P1 | EphMRA ATC | SGLT2-HEMM.ANTIDIAB.REIN |
| A10P3 | EphMRA ATC | SGLT2-HEMM+BIGUAN.KOMBI. |
| A10P5 | EphMRA ATC | SGLT2-HEMM+DPP-IV.HEMM.K |
| A10S0 | EphMRA ATC | GLP-1 AGONIST A-DIABS |
| A10X9 | EphMRA ATC | OTH DRG USED IN DIABETES |

ICD 10 codes for chronic renal disease

| ICD 10 code | Description |
|---|---|
| A18.1 | Tuberculosis of genitourinary system |
| B52.0 | Plasmodium malariae malaria with nephropathy |
| C64 | Malignant neoplasm of kidney, except renal pelvis |
| C68.9 | Malignant neoplasm: Urinary organ, unspecified |
| D30.0 | Benign neoplasm: Kidney |
| D41.0 | Neoplasm of uncertain or unknown behaviour: Kidney |
| D41.1 | Neoplasm of uncertain or unknown behaviour: Renal pelvis |
| D41.2 | Neoplasm of uncertain or unknown behaviour: Ureter |
| D59.3 | Haemolytic-uraemic syndrome |
| E10.2 | Type 1 diabetes mellitus, With renal complications |
| E11.2 | Type 2 diabetes mellitus, with renal complications |
| E13.2 | Other specified diabetes mellitus, with renal complications |
| E74.8 | Other specified disorders of carbohydrate metabolism |
| I12 | Hypertensive renal disease |
| I12.0 | Hypertensive renal disease with renal failure |
| I12.9 | Hypertensive renal disease without renal failure |
| I13 | Hypertensive heart and renal disease |
| I13.0 | Hypertensive heart and renal disease with (congestive) heart failure |
| I13.1 | Hypertensive heart and renal disease with renal failure |
| I13.2 | Hypertensive heart and renal disease with both (congestive) heart failure and renal failure |
| I13.9 | Hypertensive heart and renal disease, unspecified |

| ICD 10 code | Description |
|---|---|
| K76.7 | Hepatorenal syndrome |
| M10.3 | Gout due to impairment of renal function |
| M32.1 | Systemic lupus erythematosus with organ or system involvement |
| N01 | Rapidly progressive nephritic syndrome |
| N01.0 | Rapidly progressive nephritic syndrome, minor glomerular abnormality |
| N01.1 | Rapidly progressive nephritic syndrome, focal and segmental glomerular lesions |
| N01.2 | Rapidly progressive nephritic syndrome, diffuse membranous glomerulonephritis |
| N01.3 | Rapidly progressive nephritic syndrome, diffuse mesangial proliferative glomerulonephritis |
| N01.4 | Rapidly progressive nephritic syndrome, diffuse endocapillary proliferative glomerulonephritis |
| N01.5 | Rapidly progressive nephritic syndrome, diffuse mesangiocapillary glomerulonephritis |
| N01.6 | Rapidly progressive nephritic syndrome, dense deposit disease |
| N01.7 | Rapidly progressive nephritic syndrome, diffuse crescentic glomerulonephritis |
| N01.8 | Rapidly progressive nephritic syndrome, other |
| N01.9 | Rapidly progressive nephritic syndrome, unspecified |
| N02 | Recurrent and persistent haematuria |
| N02.0 | Recurrent and persistent haematuria, minor glomerular abnormality |
| N02.1 | Recurrent and persistent haematuria, focal and segmental glomerular lesions |
| N02.2 | Recurrent and persistent haematuria, diffuse membranous glomerulonephritis |
| N02.3 | Recurrent and persistent haematuria, diffuse mesangial proliferative glomerulonephritis |
| N02.4 | Recurrent and persistent haematuria, diffuse endocapillary proliferative glomerulonephritis |
| N02.5 | Recurrent and persistent haematuria, diffuse mesangiocapillary glomerulonephritis |
| N02.6 | Recurrent and persistent haematuria, dense deposit disease |
| N02.7 | Recurrent and persistent haematuria, diffuse crescentic glomerulonephritis |
| N02.8 | Recurrent and persistent haematuria, other |
| N02.9 | Recurrent and persistent haematuria, unspecified |
| N03 | Chronic nephritic syndrome |
| N03.0 | Chronic nephritic syndrome, minor glomerular abnormality |
| N03.1 | Chronic nephritic syndrome, focal and segmental glomerular lesions |
| N03.2 | Chronic nephritic syndrome, diffuse membranous glomerulonephritis |
| N03.3 | Chronic nephritic syndrome, diffuse mesangial proliferative glomerulonephritis |
| N03.4 | Chronic nephritic syndrome, diffuse endocapillary proliferative glomerulonephritis |
| N03.5 | Chronic nephritic syndrome, diffuse mesangiocapillary glomerulonephritis |
| N03.6 | Chronic nephritic syndrome, dense deposit disease |
| N03.7 | Chronic nephritic syndrome, diffuse crescentic glomerulonephritis |
| N03.8 | Chronic nephritic syndrome, other |
| N03.9 | Chronic nephritic syndrome, unspecified |
| N04 | Nephrotic syndrome |
| N04.0 | Nephrotic syndrome, minor glomerular abnormality |
| N04.1 | Nephrotic syndrome, focal and segmental glomerular lesions |
| N04.2 | Nephrotic syndrome, diffuse membranous glomerulonephritis |
| N04.3 | Nephrotic syndrome, diffuse mesangial proliferative glomerulonephritis |
| N04.4 | Nephrotic syndrome, diffuse endocapillary proliferative glomerulonephritis |
| N04.5 | Nephrotic syndrome, diffuse mesangiocapillary glomerulonephritis |
| N04.6 | Nephrotic syndrome, dense deposit disease |
| N04.7 | Nephrotic syndrome, diffuse crescentic glomerulonephritis |

| ICD 10 code | Description |
|---|---|
| N04.8 | Nephrotic syndrome, other |
| N04.9 | Nephrotic syndrome, unspecified |
| N05 | Unspecified nephritic syndrome |
| N05.0 | Unspecified nephritic syndrome, minor glomerular abnormality |
| N05.1 | Unspecified nephritic syndrome, focal and segmental glomerular lesions |
| N05.2 | Unspecified nephritic syndrome, diffuse membranous glomerulonephritis |
| N05.3 | Unspecified nephritic syndrome, diffuse mesangial proliferative glomerulonephritis |
| N05.4 | Unspecified nephritic syndrome, diffuse endocapillary proliferative glomerulonephritis |
| N05.5 | Unspecified nephritic syndrome, diffuse mesangiocapillary glomerulonephritis |
| N05.6 | Unspecified nephritic syndrome, dense deposit disease |
| N05.7 | Unspecified nephritic syndrome, diffuse crescentic glomerulonephritis |
| N05.8 | Unspecified nephritic syndrome, other |
| N05.9 | Unspecified nephritic syndrome, unspecified |
| N06 | Isolated proteinuria with specified morphological lesion |
| N06.0 | Isolated proteinuria with specified morphological lesion, minor glomerular abnormality |
| N06.1 | Isolated proteinuria with specified morphological lesion, focal and segmental glomerular lesions |
| N06.2 | Isolated proteinuria with specified morphological lesion, diffuse membranous glomerulonephritis |
| N06.3 | Isolated proteinuria with specified morphological lesion, diffuse mesangial proliferative glomerulonephritis |
| N06.4 | Isolated proteinuria with specified morphological lesion, diffuse endocapillary proliferative glomerulonephritis |
| N06.5 | Isolated proteinuria with specified morphological lesion, diffuse mesangiocapillary glomerulonephritis |
| N06.6 | Isolated proteinuria with specified morphological lesion, dense deposit disease |
| N06.7 | Isolated proteinuria with specified morphological lesion, diffuse crescentic glomerulonephritis |
| N06.8 | Isolated proteinuria with specified morphological lesion, other |
| N06.9 | Isolated proteinuria with specified morphological lesion, unspecified |
| N07 | Hereditary nephropathy, not elsewhere classified |
| N07.0 | Hereditary nephropathy, not elsewhere classified, minor glomerular abnormality |
| N07.1 | Hereditary nephropathy, not elsewhere classified, focal and segmental glomerular lesions |
| N07.2 | Hereditary nephropathy, not elsewhere classified, diffuse membranous glomerulonephritis |
| N07.3 | Hereditary nephropathy, not elsewhere classified, diffuse mesangial proliferative glomerulonephritis |
| N07.4 | Hereditary nephropathy, not elsewhere classified, diffuse endocapillary proliferative glomerulonephritis |
| N07.5 | Hereditary nephropathy, not elsewhere classified, diffuse mesangiocapillary glomerulonephritis |
| N07.6 | Hereditary nephropathy, not elsewhere classified, dense deposit disease |
| N07.7 | Hereditary nephropathy, not elsewhere classified, diffuse crescentic glomerulonephritis |
| N07.8 | Hereditary nephropathy, not elsewhere classified, other |
| N07.9 | Hereditary nephropathy, not elsewhere classified, unspecified |
| N08 | Glomerular disorders in diseases classified elsewhere |
| N08.0 | Glomerular disorders in infectious and parasitic diseases classified elsewhere |
| N08.1 | Glomerular disorders in neoplastic diseases |
| N08.2 | Glomerular disorders in blood diseases and disorders involving the immune mechanism |
| N08.3 | Glomerular disorders in diabetes mellitus |
| N08.4 | Glomerular disorders in other endocrine, nutritional and metabolic diseases |

| ICD 10 code | Description |
|---|---|
| N08.5 | Glomerular disorders in systemic connective tissue disorders |
| N08.8 | Glomerular disorders in other diseases classified elsewhere |
| N13.1 | Hydronephrosis with ureteral stricture, not elsewhere classified |
| N13.2 | Hydronephrosis with renal and ureteral calculous obstruction |
| N13.3 | Other and unspecified hydronephrosis |
| N14 | Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions |
| N14.0 | Analgesic nephropathy |
| N14.1 | Nephropathy induced by other drugs, medicaments and biological substances |
| N14.2 | Nephropathy induced by unspecified drug, medicament or biological substance |
| N14.3 | Nephropathy induced by heavy metals |
| N14.4 | Toxic nephropathy, not elsewhere classified |
| N15.0 | Balkan nephropathy |
| N15.8 | Other specified renal tubulo-interstitial diseases |
| N15.9 | Renal tubulo-interstitial disease, unspecified |
| N16 | Renal tubulo-interstitial disorders in diseases classified elsewhere |
| N16.0 | Renal tubulo-interstitial disorders in infectious and parasitic diseases classified elsewhere |
| N16.1 | Renal tubulo-interstitial disorders in neoplastic diseases |
| N16.2 | Renal tubulo-interstitial disorders in blood diseases and disorders involving the immune mechanism |
| N16.3 | Renal tubulo-interstitial disorders in metabolic diseases |
| N16.4 | Renal tubulo-interstitial disorders in systemic connective tissue disorders |
| N16.5 | Renal tubulo-interstitial disorders in transplant rejection |
| N16.8 | Renal tubulo-interstitial disorders in other diseases classified elsewhere |
| N17 | Acute renal failure |
| N17.0 | Acute renal failure with tubular necrosis |
| N17.1 | Acute renal failure with acute cortical necrosis |
| N17.2 | Acute renal failure with medullary necrosis |
| N17.8 | Other acute renal failure |
| N17.9 | Acute renal failure, unspecified |
| N18 | Chronic kidney disease |
| N18.1 | Chronic kidney disease, stage 1 |
| N18.2 | Chronic kidney disease, stage 2 |
| N18.3 | Chronic kidney disease, stage 3 |
| N18.4 | Chronic kidney disease, stage 4 |
| N18.5 | Chronic kidney disease, stage 5 |
| N18.9 | Chronic kidney disease, unspecified |
| N19 | Unspecified kidney failure |
| N25 | Disorders resulting from impaired renal tubular function |
| N25.0 | Renal osteodystrophy |
| N25.1 | Nephrogenic diabetes insipidus |
| N25.8 | Other disorders resulting from impaired renal tubular function |
| N25.9 | Disorder resulting from impaired renal tubular function, unspecified |
| N26 | Unspecified contracted kidney |
| O10.4 | Pre-existing secondary hypertension complicating pregnancy, childbirth and the puerperium |
| O12 | Gestational [pregnancy-induced] oedema and proteinuria without hypertension |
| O12.0 | Gestational oedema |

| ICD 10 code | Description |
|---|---|
| O12.1 | Gestational proteinuria |
| O12.2 | Gestational oedema with proteinuria |
| Q26.0 | Congenital stenosis of vena cava |
| Q26.1 | Persistent left superior vena cava |
| Q26.2 | Total anomalous pulmonary venous connection |
| Q26.3 | Partial anomalous pulmonary venous connection |
| Q61.0 | Congenital single renal cyst |
| Q61.1 | Polycystic kidney, autosomal recessive |
| Q61.2 | Polycystic kidney, autosomal dominant |
| Q61.3 | Polycystic kidney, unspecified |
| Q61.4 | Renal dysplasia |
| Q61.5 | Medullary cystic kidney |
| Q61.8 | Other cystic kidney diseases |
| R94.4 | Abnormal results of kidney function studies |
| I82.3 | Embolism and thrombosis of renal vein |
| I70.1 | Atherosclerosis of renal artery |
| N28.0 | Ischaemia and infarction of kidney |
| Q27.1 | Congenital renal artery stenosis |
| I15.0 | Renovascular hypertension |
| I15.1 | Hypertension secondary to other renal disorders |

Molecule names for psychostimulants indicated for ADHD

| EphMRA ATC code | Description | Molecule name |
|---|---|---|
| N06B0 | PSYCHOSTIMULANTS | Adrafinil |
| N06B0 | PSYCHOSTIMULANTS | Amfetaminil |
| N06B0 | PSYCHOSTIMULANTS | Dexamfetamine |
| N06B0 | PSYCHOSTIMULANTS | Fenetylline |
| N06B0 | PSYCHOSTIMULANTS | Lisdexamfetamine |
| N06B0 | PSYCHOSTIMULANTS | Methylphenidate |
| N06B0 | PSYCHOSTIMULANTS | Modafinil |
| N06B0 | PSYCHOSTIMULANTS | Pemoline |

EphMRA ATC codes for beta-2-agonists indicated for asthma

| EphMRA ATC code | Description |
|---|---|
| R03A2 | BETA-2-AGONISTEN.SYSTEM |
| R03A3 | BET2-AGON.LANGE WIRK INH |
| R03A4 | B2-AGONIST INH CRTE-ACT |
| R03E1 | BETA-2-AGON.+R3C INHAL. |
| R03F1 | ASS B2-AGON+CORTIC INH |

ICD 10 codes and EphMRA ATC codes for endocrine disease

| ICD 10 code or EphMRA ATC code | Type of code | Description |
|---|---|---|
| C74 | ICD 10 | Malignant neoplasm of adrenal gland |
| C74.0 | ICD 10 | Malignant neoplasm: Cortex of adrenal gland |
| C74.1 | ICD 10 | Malignant neoplasm: Medulla of adrenal gland |
| C74.9 | ICD 10 | Malignant neoplasm: Adrenal gland, unspecified |
| D35.0 | ICD 10 | Benign neoplasm: Adrenal gland |
| E00 | ICD 10 | Congenital iodine-deficiency syndrome |
| E00.0 | ICD 10 | Congenital iodine-deficiency syndrome, neurological type |
| E00.1 | ICD 10 | Congenital iodine-deficiency syndrome, myxoedematous type |
| E00.2 | ICD 10 | Congenital iodine-deficiency syndrome, mixed type |
| E00.9 | ICD 10 | Congenital iodine-deficiency syndrome, unspecified |
| E02 | ICD 10 | Subclinical iodine-deficiency hypothyroidism |
| E03 | ICD 10 | Other hypothyroidism |
| E03.0 | ICD 10 | Congenital hypothyroidism with diffuse goitre |
| E03.1 | ICD 10 | Congenital hypothyroidism without goitre |
| E03.2 | ICD 10 | Hypothyroidism due to medicaments and other exogenous substances |
| E03.3 | ICD 10 | Postinfectious hypothyroidism |
| E03.4 | ICD 10 | Atrophy of thyroid (acquired) |
| E03.5 | ICD 10 | Myxoedema coma |
| E03.8 | ICD 10 | Other specified hypothyroidism |
| E03.9 | ICD 10 | Hypothyroidism, unspecified |
| E05 | ICD 10 | Thyrotoxicosis [hyperthyroidism] |
| E05.0 | ICD 10 | Thyrotoxicosis with diffuse goitre |
| E05.1 | ICD 10 | Thyrotoxicosis with toxic single thyroid nodule |
| E05.2 | ICD 10 | Thyrotoxicosis with toxic multinodular goitre |
| E05.3 | ICD 10 | Thyrotoxicosis from ectopic thyroid tissue |
| E05.4 | ICD 10 | Thyrotoxicosis factitia |
| E05.5 | ICD 10 | Thyroid crisis or storm |
| E05.8 | ICD 10 | Other thyrotoxicosis |
| E05.9 | ICD 10 | Thyrotoxicosis, unspecified |
| E06 | ICD 10 | Thyroiditis |
| E06.0 | ICD 10 | Acute thyroiditis |
| E06.1 | ICD 10 | Subacute thyroiditis |
| E06.2 | ICD 10 | Chronic thyroiditis with transient thyrotoxicosis |
| E06.3 | ICD 10 | Autoimmune thyroiditis |
| E06.4 | ICD 10 | Drug-induced thyroiditis |
| E06.5 | ICD 10 | Other chronic thyroiditis |
| E06.9 | ICD 10 | Thyroiditis, unspecified |
| E21.0 | ICD 10 | Primary hyperparathyroidism |
| E21.1 | ICD 10 | Secondary hyperparathyroidism, not elsewhere classified |
| E21.2 | ICD 10 | Other hyperparathyroidism |
| E21.3 | ICD 10 | Hyperparathyroidism, unspecified |
| E24 | ICD 10 | Cushing syndrome |
| E24.0 | ICD 10 | Pituitary-dependent Cushing disease |

| ICD 10 code or EphMRA ATC code | Type of code | Description |
|---|---|---|
| E24.1 | ICD 10 | Nelson syndrome |
| E24.2 | ICD 10 | Drug-induced Cushing syndrome |
| E24.3 | ICD 10 | Ectopic ACTH syndrome |
| E24.4 | ICD 10 | Alcohol-induced pseudo-Cushing syndrome |
| E24.8 | ICD 10 | Other Cushing syndrome |
| E24.9 | ICD 10 | Cushing syndrome, unspecified |
| E27.0 | ICD 10 | Other adrenocortical overactivity |
| E27.5 | ICD 10 | Adrenomedullary hyperfunction |
| I15.2 | ICD 10 | Hypertension secondary to endocrine disorders |
| H03A0 | EphMRA ATC | THYROID PREPARATIONS |
| H03B0 | EphMRA ATC | ANTI-THYROID PREPARATIONS |
| H03C0 | EphMRA ATC | IODINE PREPARATIONS |

ICD 10 codes for cardiovascular malformation

| ICD 10 code | Description |
|---|---|
| Q25.1 | Coarctation of aorta |
| Q25.2 | Atresia of aorta |
| Q25.3 | Stenosis of aorta |

ICD 10 codes for bronchopulmonary dysplasia

| ICD 10 code | Description |
|---|---|
| P27.1 | Bronchopulmonary dysplasia originating in the perinatal period |

EphMRA ATC codes for systemic corticosteroids

| EphMRA ATC code | Description |
|---|---|
| H02A1 | INJ CORTICOSTEROIDS PLAIN |
| H02A2 | ORAL CORTICOSTEROID PLAIN |
| H02A3 | OTH SYS CORTICOSTERO PLN |
| H02B0 | COMB CORTICOSTEROIDS |
| R03D2 | CORTICOIDS, SYSTEMIC |

EphMRA ATC code and molecule names for tricyclic antidepressants

| EphMRA ATC code | Description | Molecule name |
|---|---|---|
| N06A9 | ANTIDEPRESSANTS ALL OTH | AMITRIPTYLINE |
| N06A9 | ANTIDEPRESSANTS ALL OTH | AMITRIPTYLINOXIDE |
| N06A9 | ANTIDEPRESSANTS ALL OTH | AMOXAPINE |
| N06A9 | ANTIDEPRESSANTS ALL OTH | CLOMIPRAMINE |
| N06A9 | ANTIDEPRESSANTS ALL OTH | DESIPRAMINE |

| EphMRA ATC code | Description | Molecule name |
|---|---|---|
| N06A9 | ANTIDEPRESSANTS ALL OTH | DIBENZEPIN |
| N06A9 | ANTIDEPRESSANTS ALL OTH | DOSULEPIN |
| N06A9 | ANTIDEPRESSANTS ALL OTH | DOXEPIN |
| N06A9 | ANTIDEPRESSANTS ALL OTH | IMIPRAMINE |
| N06A9 | ANTIDEPRESSANTS ALL OTH | LOFEPRAMINE |
| N06A9 | ANTIDEPRESSANTS ALL OTH | MAPROTILINE |
| N06A9 | ANTIDEPRESSANTS ALL OTH | NORTRIPTYLINE |
| N06A9 | ANTIDEPRESSANTS ALL OTH | OPIPRAMOL |
| N06A9 | ANTIDEPRESSANTS ALL OTH | TIANEPTINE |
| N06A9 | ANTIDEPRESSANTS ALL OTH | TRIMIPRAMINE |

EphMRA ATC code and molecule names for cyclosporine and tacrolimus

| EphMRA ATC code | Description | Molecule name |
|---|---|---|
| L04X0 | OTHER IMMUNOSUPPRESSANTS | CICLOSPORINE |
| L04X0 | OTHER IMMUNOSUPPRESSANTS | TACROLIMUS |

EphMRA ATC code and molecule names for atypical antipsychotics

| EphMRA ATC code | Description |
|---|---|
| N05A1 | ATYPICAL ANTIPSYCHOTICS |

# Annex 3 – Template tables for results

**Template table 1:** Characteristics of children 2-17 years with arterial hypertension (HT) by age at first HT diagnosis (per database)

| | All<br>N (%) | 2-5 years at first HT diagnosis<br>N (%) | 6-12 years at first HT diagnosis<br>N (%) | 13-17 years at first HT diagnosis<br>N (%) |
|---|---|---|---|---|
| Mean age at first HT diagnosis (SD) | | | | |
| No. of children with HT diagnosis by age group at first HT diagnosis | | | | |
| Primary HT[a] (%) | | | | |
| Secondary HT[a] (%) | | | | |
| **Risk factors** | | | | |
| Male gender (%) | | | | |
| Obesity (%) | | | | |
| Diabetes mellitus type 1 and diabetes mellitus type 2[b] (%) | | | | |
| **Potential causes of secondary hypertension** | | | | |
| Renal diseases (%) | | | | |
| Cardiovascular malformation (%) | | | | |
| Endocrine (%) [d] | | | | |
| Bronchopulmonary dysplasia (%) | | | | |
| Drug use [c]<br>Glucocorticoids (%)<br>Beta-agonist (%)<br>Stimulants for ADHD (%)<br>Cyclosporine, tacrolimus (%)<br>Tricyclic antidepressants (%)<br>Atypical antipsychotics (%) | | | | |

a- identified through diagnosis codes; b-either a diagnosis code or treatment as a proxy; c–at least one prescription in the last 6 months; d-excluding diabetes mellitus.

**Template table 2:** Yearly prevalence of arterial hypertension (per database)

| | Prevalence (95% confidence interval) per 100,000 patient-years | | | |
|---|---|---|---|---|
| **Year** | **All (2-17 years)** | **2-5 years** | **6-12 years** | **13-17 years** |
| **2016** | | | | |
| **2017** | | | | |
| **2018** | | | | |
| **2019** | | | | |
| **2020** | | | | |

**Template table 3:** Yearly proportion of children with arterial hypertension that had a prescription for an ARB (per database)

| | Percentage of children (no. of children with ARB/no. of children with HT) | | | |
|---|---|---|---|---|
| **Year** | **All (2-17 years)** | **2-5 years** | **6-12 years** | **13-17 years** |
| **2016** | | | | |
| **2017** | | | | |
| **2018** | | | | |
| **2019** | | | | |
| **2020** | | | | |

**Template table 4:** Yearly proportion of children with a prescription for ARB during the year that had arterial hypertension during the year or earlier (per database)

| | Percentage of children (no. of children with ARB and HT/no. of children with ARB) | | | |
|---|---|---|---|---|
| **Year** | **All (2-17 years)** | **2-5 years** | **6-12 years** | **13-17 years** |
| **2016** | | | | |
| **2017** | | | | |
| **2018** | | | | |
| **2019** | | | | |
| **2020** | | | | |