11th April 2022

Data analysis report

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 was 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 included both a cross-sectional design and a cohort design.

3.2. Setting and study population

The study period was 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 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 were also included as paediatricians are part of primary care in Germany.

Children with unknown gender were not included in the study.

3.3. Variables

Please see Annex 2 for 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 were considered to have arterial hypertension from the first date of the diagnosis onwards. Children with a code for primary arterial hypertension were considered to have primary hypertension, and children with a code for secondary arterial hypertension were considered to have secondary hypertension. Where a diagnosis was not qualified as being either primary or secondary, it was assumed to be of primary aetiology. It was assumed that the same child can have both diagnoses.

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

3.4. Data sources

The study was 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 was used for the study.

3.5. Statistical analysis

3.5.1. Main statistical methods

A descriptive analysis of risk factors for arterial hypertension was carried in children 2-17 years with arterial hypertension during the study period, please see Tables 1a to 1c.

The yearly prevalence of arterial hypertension during the study period was calculated in children 2-17 years that were observable for at least one day during the year. Children with arterial hypertension during the year or with a history of arterial hypertension were included in the numerator, and the prevalence was 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 Tables 2a to 2c. In the IQVIA™ Disease Analyzer databases patients are 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 was calculated, please see Tables 3a to 3c This was done without requiring that the ARB was prescribed after the diagnosis of arterial hypertension as it was 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 was identified, and among these children the proportion of children with a diagnosis of arterial hypertension during the year or earlier was calculated, please see Tables 4a to 4c.

3.5.2. Sensitivity analysis

Descriptive analysis 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 were performed by the EMA researchers, using the IHD platform and SAS

3.6. Quality control

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

Standard operating procedures or internal process guidance were 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 undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis are either reviewed or checked via double coding.

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

4. Results

4.1. Descriptive data

4.1.1. Characteristics of children with arterial hypertension

In IQVIA™ Disease Analyzer Germany, a total of 13,656 children were identified that had a diagnosis of arterial hypertension before or between the years 2016 to 2021 please see Table 1a. Similarly, although during a longer time period between 1990 and May 2021, 252 children with arterial hypertension were identified in IMRD UK, please see Table 1b. In IQVIA™ Disease Analyzer France, 252 children with arterial hypertension were identified between 2016 and June 2021, please see Table 1c. Descriptive characteristics of the children with a diagnosis of arterial hypertension is provided in the tables. Please also see supplementary tables S1a and S1c in Annex 3 for the same analysis in IQVIA™ Disease Analyzer Germany and France, restricted to children that had a minimum of 365 days of observation at the time of the first arterial hypertension diagnosis.

Table 1a Characteristics of children 2-17 years with arterial hypertension (HT) between 2016 and June 2021 in IQVIA™ Disease Analyzer Germany by age at first HT diagnosis

	All N (%)	2-5 years at first HT diagnosis N (%)	6-12 years at first HT diagnosis N (%)	13-17 years at first HT diagnosis N (%)
Mean age at first HT diagnosis (SD)	12.13 (4.84)			
No. of children with HT diagnosis by age group at first HT diagnosis	13656	923	3338	8509
Primary HT[a] (%)	13586 (99.5 %)	909 (98.5 %)	3324 (99.6 %)	8473 (99.6 %)
Secondary HT[a] (%)	116 (0.8 %)	25 (2.7 %)	31 (0.9 %)	52 (0.6 %)

	All N (%)	2-5 years at first HT diagnosis N (%)	6-12 years at first HT diagnosis N (%)	13-17 years at first HT diagnosis N (%)
Risk factors				
Male gender (%)	8213 (60.1%)	534 (57.9 %)	1882 (56.4 %)	5307 (62.4 %)
Obesity (%)	4332 (31.7 %)	112 (12.1 %)	1300 (38.9 %)	2905 (34.1 %)
Diabetes mellitus type 1 and diabetes mellitus type 2[b] (%)	452 (3.3 %)	24 (2.6 %)	98 (2.9 %)	322 (3.8 %)
Potential causes of secondary hypertension				
Renal diseases (%)	895 (6.6 %)	156 (16.9 %)	287 (8.6 %)	329 (3.9 %)
Cardiovascular malformation (%)	100 (0.7 %)	13 (1.4 %)	38 (1.1 %)	38 (0.4 %)
Endocrine (%) [d]	1420 (10.4 %)	44 (4.8 %)	281 (8.4 %)	1075 (12.6 %)
Bronchopulmonary dysplasia (%)	50 (0.4 %)	9 (1.0 %)	<5 (0.1%)	5 (0.1 %)
Drug use [c]				
Glucocorticoids (%)	225 (1.6 %)	62 (6.7 %)	77 (2.3 %)	70 (0.8 %)
Beta-agonist (%)	683 (5.0 %)	93 (10.1 %)	174 (5.2 %)	354 (4.2 %)
Stimulants for ADHD (%)	240 (1.8 %)	0 (0.0 %)	66 (2.0 %)	174 (2.0 %)
Cyclosporine, tacrolimus (%)	18 (0.1 %)	9 (1.0 %)	6 (0.2 %)	<5 (0.0 %)
Tricyclic antidepressants (%)	6 (0.0 %)	<5 (0.1 %)	0 (0.0 %)	5 (0.1 %)
Atypical antipsychotics (%)	24 (0.2 %)	0 (0.0 %)	<5 (0.1 %)	21 (0.2 %)

a- identified through diagnosis codes; b-either a diagnosis code or treatment as a proxy; c–at least one prescriptions in the last 6 months; d-excluding diabetes mellitus. Numbers below n=5 have been suppressed.

Table 1b Characteristics of children 2-17 years with arterial hypertension (HT) from 1990 to May 2021 in IMRD (UK)

	All n(%)	2-5 years n(%)	6-12 years n(%)	13-17 years n(%)
Mean age at first HT diagnosis (SD)				
No. of children with HT diagnosis by age group at first HT diagnosis	252	29	76	147
Primary HT[a] (%)	238 (94.4%)	26 (89.7%)	72 (94.7%)	140 (95.2%)
Secondary HT[a] (%)	18 (7.1%)	<6 (13.8%)	6 (7.9%)	8 (5.4%)
Risk factors				
Male gender (%)	133 (52.8%)	18 (62.1%)	44 (57.9%)	71 (48.3%)
Obesity (%)	22 (8.7%)	<6 (6.9%)	6 (7.9%)	14 (9.5%)
Diabetes mellitus type 1 and diabetes mellitus type 2[b] (%)	29 (11.5%)	6 (20.7%)	<6 (5.3%)	19 (12.9%)
Potential causes of secondary hypertension				
Renal diseases (%)	43 (17.1%)	<6 (13.8%)	20 (26.3%)	19 (12.9%)
Cardiovascular malformation (%)	<6 (2.0%)	0 (0%)	<6 (2.6%)	<6 (2.0%)
Endocrine (%)	12 (4.8%)	<6 (6.9)	<6 (6.6)	<6 (3.4%)
Bronchopulmonary dysplasia (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Drug use [c]				
Glucocorticoids (%)	16 (6.3%)	<6 (3.4%)	<6 (5.3%)	11 (7.5%)
Beta-stimulants (%)	34 (13.5%)	<6 (10.3%)	14 (18.4%)	17 (11.6%)
Stimulants for ADHD (%)	7 (2.8%)	0 (0)	0 (0)	7 (4.8%)
Cyclosporine, tacrolimus (%)	<6 (1.2%)	0 (0)	<6 (2.6%)	<6 (0.7%)
Tricyclic antidepressants (%)	<6 (0.4%)	0 (0)	0 (0)	<6 (0.7%)
Atypical antipsychotics (%)	0 (0%)	0 (0)	0 (0)	0 (0)

a- identified through diagnosis codes; b-either a diagnosis code or treatment as a proxy; c–at least one prescriptions in the last 6 months

Table 1c Characteristics of children 2-17 years with arterial hypertension (HT) between 2016 and June 2021 in IQVIA™ Disease Analyzer France by age at first HT diagnosis

	All n(%)	2-5 years at first HT diagnosis n(%)	6-12 years at first HT diagnosis n(%)	13-17 years at first HT diagnosis n(%)
Mean age at first HT diagnosis (SD)	10.63 (5.29)			
No. of children with HT diagnosis by age group at first HT diagnosis	252	43	76	120
Primary HT[a] (%)	252 (100.0 %)	43 (100.0 %)	76 (100.0 %)	120 (100.0 %)
Secondary HT[a] (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Risk factors				
Male gender (%)	134 (53.2%)	20 (46.5 %)	41 (53.9 %)	66 (55.0 %)
Obesity (%)	13 (5.2 %)	<10 (-)	<10 (-)	10 (8.3 %)
Diabetes mellitus type 1 and diabetes mellitus type 2[b] (%)	<10 (-)	<10 (-)	0 (0.0 %)	<10 (-)
Potential causes of secondary hypertension				
Renal diseases (%)	<10 (-)	0 (0.0 %))	<10 (-)	<10 (-)
Cardiovascular malformation (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Endocrine (%) [d]	<10 (-)	<10 (-)	0 (0.0 %)	<10 (-)
Bronchopulmonary dysplasia (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Drug use [c]				
Glucocorticoids (%)	17 (6.7 %)	<10 (-)	<10 (-)	<10 (-)
Beta-agonists (%)	12 (4.8 %)	<10 (-)	<10 (-)	<10 (-)
Stimulants for ADHD (%)	<10 (-)	0 (0.0 %)	<10 (-)	<10 (-)
Cyclosporine, tacrolimus (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Tricyclic antidepressants (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Atypical antipsychotics (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)

a- identified through diagnosis codes; b-either a diagnosis code or treatment as a proxy; c–at least one prescriptions in the last 6 months; d-excluding diabetes mellitus. Numbers below n=10 have been suppressed.

4.1.2. Yearly prevalence of arterial hypertension

For the yearly prevalence of arterial hypertension per 100,000 years of observation in children 2-17 years between 2016 and 2020 in IQVIA™ Disease Analyzer Germany, IMRD UK and IQVIA™ Disease Analyzer France, please see Tables 2a to 2c below.

Table 2a Yearly prevalence of arterial hypertension in IQVIA™ Disease Analyzer Germany

Prevalence (95% confidence interval) per 100,000 patient-years				
Year	**All (2-17 years)**	**2-5 years**	**6-12 years**	**13-17 years**
2016	n=5238 619.11 (602.55 - 636.00)	n=357 143.01 (128.58 - 158.62)	n=1424 390.76 (370.80 - 411.51)	n=3457 1490.05 (1441.50 - 1539.79)
2017	n=5600 640.21 (623.76 - 657.20)	n=372 143.17 (129.01 - 158.46)	n=1523 407.61 (387.47 - 428.52)	n=3705 1536.72 (1488.36 - 1586.22)
2018	n=5736 660.23 (643.36 - 677.42)	n=410 157.08 (142.26 - 173.02)	n=1555 418.61 (398.14 - 439.85)	n=3771 1595.76 (1546.01 - 1646.67)
2019	n=5914 706.63 (688.86 - 724.74)	n=416 161.99 (146.82 - 178.30)	n=1603 452.62 (430.82 - 475.22)	n=3895 1723.75 (1670.93 - 1777.77)
2020	n=5671 783.11 (763.01 - 803.59)	n=416 188.18 (170.56 - 207.13)	n=1470 479.28 (455.20 - 504.30)	n=3785 1927.22 (1866.87 - 1988.99)

Table 2b Yearly prevalence of arterial hypertension in IMRD (UK)

Prevalence (95% confidence interval) per 100,000 patient-years				
Year	**All (2-17 years)**	**2-5 years**	**6-12 years**	**13-17 years**
2016	n=72 22.66 (17.99-28.53)	n=6 6.66 (3.05-14.53)	n=27 19.35 (13.30-28.16)	n=39 44.22 (32.35-60.44)
2017	n=92 28.02 (22.85-34.37)	n=14 15.62 (9.31-26.22)	n=31 20.77 (14.64-29.48)	n=47 52.55 (39.53-69.87)
2018	n=105 31.22 (25.79-37.79)	n=12 13.58 (7.77-23.74)	n=35 21.79 (15.67-30.30)	n=58 66.44 (51.41-85.87)
2019	n=118 34.44 (28.76-41.24)	n=17 19.79 (12.36-31.69)	n=44 26.79 (19.96-35.96)	n=57 61.63 (47.58-79.84)
2020	n=130 37.37 (31.47-44.37)	n=20 23.88 (15.46-36.89)	n=48 28.77 (21.70-38.13)	n=62 63.74 (49.73-81.69)

Table 2c Yearly prevalence of arterial hypertension in IQVIA™ Disease Analyzer France

Prevalence (95% confidence interval) per 100,000 patients observed for a year				
Year	**All (2-17 years)**	**2-5 years**	**6-12 years**	**13-17 years**
2016	n=87 51.47 (41.23 - 63.49)	n=12 25.46 (13.15 - 44.46)	n=26 35.15 (22.96-51.49)	n=49 102.28 (75.68-135.20)
2017	n=92 54.15 (43.66 - 66.41)	n=14 27.91 (14.86 - 47.73)	n=30 40.31 (27.20-57.54)	n=49 100.20 (74.14-132.45)
2018	n=89 53.11 (42.65 - 65.35)	n=12 26.34 (13.61 - 46.01)	n=38 51.63 (36.54-70.86)	n=39 80.55 (57.29-110.10)
2019	n=123 76.48 (63.57 - 91.24)	n=17 39.39 (22.95 - 63.06)	n=57 80.77 (61.18-104.63)	n=49 104.04 (76.98-137.52)
2020	n=92 76.20 (61.44 - 93.45)	n=12 47.44 (24.52 - 82.86)	n=40 70.78 (50.57-96.37)	n=40 102.78 (73.44-139.93)

4.1.3. Yearly proportion of children with arterial hypertension that received an ARB prescription during the year

For the yearly proportion of children 2-17 years with arterial hypertension that received any ARB prescription during the year, please see Tables 3a to 3c.

Table 3a Yearly proportion of children with arterial hypertension that had a prescription for an ARB in IQVIA™ Disease Analyzer Germany

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	1.5% (1.2-1.8%)	0.6% (0.2-2.0%)	1.3% (0.8-2.0%)	1.6% (1.3-2.1%)
2017	1.5% (1.3-1.9%)	1.3% (0.6-3.1%)	1.3% (0.9-2.0%)	1.6% (1.3-2.1%)
2018	1.3% (1.0-1.6%)	0.5% (0.1-1.8%)	0.8% (0.5-1.4%)	1.5% (1.2-2.0%)
2019	1.3% (1.0-1.6%)	1.0% (0.4-2.5%)	0.9% (0.6-1.5%)	1.5% (1.2-1.9%)
2020	1.5% (1.2-1.8%)	0.7% (0.3-2.1%)	1.0% (0.6-1.6%)	1.7% (1.4-2.2%)

Table 3b Yearly proportion of children with arterial hypertension that had a prescription for an ARB in IMRD (UK)

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	14.3 (7.7-24.9)	0 (0-40.8)	0 (0-13.4)	27.6 (15.2-44.6)
2017	12.7 (6.8-22.4)	0 (0-39.5)	0 (0-12.2)	24.1 (13.2-39.7)
2018	8.2 (4.0-16.0)	0 (0-30.8)	0 (0-12.3)	14.2 (7.1-26.5)
2019	8.3 (4.1-16.2)	0 (0-23.8)	3.3 (0.6-16.5)	14.4 (6.8-28.0)
2020	3.2 (1.1-9.0)	7.4 (1.3-32.4)	0 (0-9.6)	4.5 (1.2-15.0)

Table 3c Yearly proportion of children with arterial hypertension that had a prescription for an ARB in IQVIA™ Disease Analyzer France

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	5.7% (2.5-12.8%)	. (.-.)*	. (.-.)*	2.1% (0.4-10.7%)
2017	3.3% (1.1-9.2%)	. (.-.)*	. (.-.)*	4.1% (1.1-13.7%)
2018	3.4% (1.2-9.5%)	. (.-.)*	. (.-.)*	2.5% (0.5-13.2%)
2019	0.8% (0.1-4.5%)	. (.-.)*	. (.-.)*	2.0% (0.4-10.7%)
2020	2.2% (0.6-7.4%)	. (.-.)*	. (.-.)*	5.0% (1.4-16.5%)

* Error when calculating %

4.1.4. Yearly proportion of children with an ARB prescription during the year that had a diagnosis of arterial hypertension

Please see Tables 4a and 4c (not done for IMRD) for the yearly proportion of children with an ARB prescription during the year that had a diagnosis of arterial hypertension.

Table 4a Yearly proportion of children with a prescription for ARB during the year that had arterial hypertension during the year or earlier in IQVIA™ Disease Analyzer Germany

	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	42.5%	16.7%	33.3%	49.6%
2017	45.7%	50.0%	32.8%	52.1%
2018	39.5%	28.6%	22.4%	48.3%
2019	40.1%	30.8%	27.8%	46.4%
2020	46.1%	42.9%	29.8%	52.4%

Table 4c Yearly proportion of children with a prescription for an ARB during the year that had arterial hypertension during the year or earlier in IQVIA™ Disease Analyzer France

	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	1.5%	7.4%	1.5%	0.6%
2017	0.9%	0.0%	0.7%	1.3%
2018	0.9%	2.4%	0.7%	0.7%
2019	0.3%	0.0%	0.0%	0.7%
2020	0.7%	0.0%	0.0%	1.8%

4.2. Main results

Most children in all three databases that had a diagnosis of hypertension had received a diagnosis of presumed primary hypertension, and only a small proportion of children, had a diagnosis of secondary hypertension. The highest proportion of children with a diagnosis of secondary hypertension was identified in IMRD UK (7.1%) vs 0.8% in IQVIA™ Disease Analyzer Germany and 0.0% in IQVIA™ Disease Analyzer France).

Risk factors for hypertension in the children with a hypertension diagnosis varied between the three countries and databases, both in terms of history of diseases or conditions, and in terms of treatment with drugs that increase blood pressure. Male gender was more frequent in Germany (60.1%) compared to France (53.2%) or the UK (52.8%). Also, obesity was more frequently recorded in Germany (31.7% vs 8.7% in the UK and 5.2% in France) whereas diabetes mellitus was more frequently recorded in the UK (11.5% vs 3.3% in Germany and 3.2% in France). Other endocrine diseases besides diabetes mellitus were, however, more frequently recorded in Germany (10.4% vs 4.8% in the UK and 0.8% in France). Renal diseases were instead more frequently recorded in the UK (17.1% vs 6.6% in Germany and 1.2% in France) as were cardiovascular malformations (2.0% vs. 0.7% in Germany and 0.0% in France). Bronchopulmonary dysplasia was only recorded in Germany (0.4%).

In Germany, the most frequent treatments that increase blood pressure identified in patients with arterial hypertension were beta-agonists (5.0%), psychostimulants for ADHD (1.8%) and systemic corticosteroids (1.6%). Only a minor proportion of patients with arterial hypertension had received treatment with atypical antipsychotics (0.2%), cyclosporine or tacrolimus (0.1%) or tricyclic antidepressants (0.0%). In the UK, the most frequent treatments also included beta-agonists (13.5%), systemic corticosteroids (6.3%) and psychostimulants for ADHD (2.8%). However, a higher proportion of patients had received cyclosporine or tacrolimus (1.2%). A low proportion of patients (0.4%) received tricyclic antidepressants and no patient received atypical antipsychotics. In France, systemic corticosteroids (6.7%) were more frequent compared to beta-agonists (4.8%), and only 0.8% of

patients received psychostimulants for ADHD. No patient received cyclosporine or tacrolimus, tricyclic antidepressants or atypical antipsychotics.

Obesity seemed to be more frequent in older vs younger children with arterial hypertension. However, there was not a clear increase from age-group to age-group in France and Germany, but a difference between the youngest and the oldest age group was observed in all three databases (from 12.1% in 2-5 year olds to 34.1% in 13-17 year olds in Germany; from 6.9% in 2-5 year olds to 9.5% in 13-17 year olds in the UK; from 4.7% in 2-5 year olds to 8.3 % in 13-17 year olds in France).

Renal disease as a possible cause of arterial hypertension seemed to be observed less frequently in the oldest children 13-17 years compared to children 6-12 years, but there was no clear difference between age groups in France. Also, children 2-5 years had a lower frequency of renal disease compared to children 6-12 years in the UK, and no child 2-5 years of age in France had a recorded diagnosis of renal disease, but numbers were low.

Large differences, up to around 20-fold, were identified between the three databases in the yearly prevalence of a diagnosis of arterial hypertension in children 2-17 years. The highest prevalence was recorded in Germany (around 6-7.8 per 1000 children observed for one year) and the lowest prevalence was recorded in the UK (around 0.2-0.4 per 1000 children observed for one year). The prevalence in France was slightly higher compared to the UK (around 0.5-0.8 per 1000 children observed for one year). Prevalence seems to increase with increasing age, however this was not tested.

In children with a history of arterial hypertension, treatment with an ARB during the year was only observed in a minority of the children. The highest proportion of children with a history of arterial hypertension that received an ARB was observed in the UK (14.3%), followed by France (5.7%) and Germany (1.5%). It was difficult to estimate accurately this proportion in the two younger age groups due to small numbers of children with arterial hypertension.

In all children with a prescription for an ARB during the year, the proportion of children that had a history of arterial hypertension varied between the three databases. Up to 45.7% of children that received an ARB prescription during the year between 2016 and 2020 had a history of arterial hypertension compared to only 1.5% in France.

5. Discussion

5.1. Prevalence of arterial hypertension

Arterial hypertension in children younger than 16 years in Europe is diagnosed on the basis of the normal distribution of blood pressure in children in relation to sex, age and height, requiring an elevation to at least the 95th percentile on at least three separate occasions [1]. In children 16 years or older, hypertension is diagnosed based on blood pressure cut-offs in adults. Childhood hypertension is the strongest risk factor for hypertension during adulthood. Recently updated guidelines in America including the definition of arterial hypertension in children are not identical to European guidelines and result in a higher prevalence of hypertension compared to the European guidelines [2].

A systematic review of the global prevalence of hypertension in children has concluded that the prevalence of hypertension has increased between 1994 and 2018 and that prevalence was highest in children 14 years of age [3]. There was an overall prevalence around 4% and close to 1% for more severe hypertension (grade 2). Obesity was a risk factor strongly related to hypertension with a prevalence of hypertension of 15.3% in obese children compared to 1.9% in normal weight children.

In this study, the prevalence of arterial hypertension was lower than expected from other publications, and it was particularly low in the UK and France. As expected prevalence increased with increasing age. There are many possible reasons for the lower-than-expected prevalence. The likelihood of recording diagnoses and risk factors can be influenced by the health care system. For example, the completeness of recording of smoking, and of height and weight, varies significantly between different primary care settings despite the fact that this information is relevant for many conditions treated in primary care. We also found a low proportion of children with arterial hypertension that had subsequently a diagnosis of secondary hypertension. One possible reason for this could be that a diagnosis of secondary hypertension may require investigations in secondary care, and therefore a diagnosis of secondary hypertension is more likely to be made in a secondary care setting while the initial diagnosis of primary (or any) arterial hypertension in primary care might not be updated.

Prevalence could be also influenced by the existence of a bias in the population denominator. Whereas the IMRD database in the UK registers the population, the IQVIA™ Disease Analyzer databases in Germany and France only record patients that visit primary care. Excluding people not visiting health care can result in falsely elevated prevalence estimates.

5.2. Risk factors for arterial hypertension

In line with an underestimation of arterial hypertension this study could also have underestimated the proportion of risk factors in children with arterial hypertension. Furthermore, it is important to consider the possibility that the true proportion of risk factors in children with arterial hypertension depends on the severity of hypertension. Secondary hypertension is more likely in case of severe hypertension or early onset hypertension. It is possible that this study captured a more severe end of the spectrum.

Considering the importance of the health care system for the interpretation of the results in this study it might be more useful to consider the results within the same database individually rather than comparing across databases. Based on this reasoning, in Germany, obesity was the most frequently identified risk factor for hypertension in children except in the youngest children 2-5 years of age where renal disease was more frequently identified. Other endocrine diseases besides diabetes were also identified relatively frequently and increased with age. Use of drugs that increase blood pressure was relatively frequent in the youngest age group, particularly beta agonists and systemic corticosteroids. In the UK, renal disease was the most identified risk factor, with the highest frequency in children 6-12 years. Other conditions included diabetes with the highest frequency in the youngest age group, whereas obesity, which increased with increasing age, was slightly less frequently recorded. Secondary hypertension was also common with the highest frequency in children 2-5 years. Other endocrine disorders besides diabetes decreased with increasing age. Use of drugs that increase blood pressure was also frequent, especially beta-agonists in children 6-12 years and systemic corticosteroids in children 13-17 years. In France, risk factors were overall less frequently recorded. The most frequently recorded conditions were obesity with the highest frequency in children 13-17 years and diabetes with the highest frequency in children 2-5 years. The most frequently recorded drugs that increase blood pressure were systemic corticosteroids with the highest frequency in children 6-12 years and beta-agonists with the highest frequency in children 13-17 years.

5.3. ARB treatment in children with arterial hypertension

Only a limited proportion of children with a history of arterial hypertension received an ARB during a one-year time period. The proportion was highest in the UK and lowest in Germany. Other treatments for arterial hypertension were not investigated.

5.4. Arterial hypertension in children treated with ARBs

In France, a high proportion of children treated with an ARB had no recorded history of arterial hypertension. This finding might point to the possibility that children received ARB for arterial hypertension despite not recording the diagnosis in the history of the patient. Alternatively, the finding points to other diagnoses being the most frequently prescribed indications for ARBs in children in France.

5.5. 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 was also 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 leads 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.

6. Conclusion

The prevalence of arterial hypertension in children in this study was lower than expected from other publications. However, as expected, prevalence increased with increasing age and was highest in children 13-17 years and lowest in children 2-5 years. The risk factors for arterial hypertension were also generally less frequently observed than expected, except for obesity in Germany. Due to differences between health care systems, it was not possible to compare the frequency of risk factors in the three countries included in the study, and the distribution of risk factors across age groups was also not always consistent with the expected distribution.

The majority of children with a diagnosis of arterial hypertension did not receive an ARB during the period of a year between 2016 and 2020, and in France, only a small proportion of all children that received an ARB during the period of a year had a recorded diagnosis of arterial hypertension.

7. References

1. Lurbe, E., et al., *2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents.* J Hypertens, 2016. **34**(10): p. 1887-920.
2. Goulas, I., et al., *Comparison of the 2017 American Academy of Pediatrics with the fourth report and the 2016 European Society of Hypertension guidelines for the diagnosis of hypertension and the detection of left ventricular hypertrophy in children and adolescents: a systematic review and meta-analysis.* J Hypertens, 2022. **40**(2): p. 197-204.
3. Song, P., et al., *Global Prevalence of Hypertension in Children: A Systematic Review and Meta-analysis.* JAMA Pediatr, 2019. **173**(12): p. 1154-1163.

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

ICD 10 code	Description
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

ICD 10 code or EphMRA ATC code	Type of code	Description
E11.3	ICD 10	Type 2 diabetes mellitus, with ophthalmic complications
E11.4	ICD 10	Type 2 diabetes mellitus, with neurological complications
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

ICD 10 code or EphMRA ATC code	Type of code	Description
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
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

ICD 10 code	Description
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
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

ICD 10 code	Description
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
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

ICD 10 code	Description
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
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

ICD 10 code	Description
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
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]

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ICD 10 code or EphMRA ATC code	Type of code	Description
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
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
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 – Supplementary tables

Table S1a Characteristics of children 2-17 years with arterial hypertension (HT) between 2016 and June 2021 in IQVIA™ Disease Analyzer Germany by age at first HT diagnosis, restricted to children with at least one year of observation at the time of the first HT diagnosis.

	All (0-17 years at first HT diagnosis)	2-5 years at first HT diagnosis	6-12 years at first HT diagnosis	13-17 years at first HT diagnosis
Mean age at first HT diagnosis (SD)	12.85 (3.86)			
No. of children with HT diagnosis by age group at first HT diagnosis	9405	649	2510	6205
Primary HT[a] (%)	9368 (99.6 %)	642 (98.9 %)	2507 (99.9 %)	6179 (99.6 %)
Secondary HT[a] (%)	60 (0.6%)	12 (1.8 %)	12 (0.5 %)	35 (0.6 %)
Risk factors				
Male gender (%)	5672 (60.3%) %	364 (56.1 %)	1404 (55.9 %)	3885 (62.6 %)
Obesity (%)	3456 (36.7 %)	93 (14.3 %)	1042 (41.5 %)	2320 (37.4 %)
Diabetes mellitus type 1 and diabetes mellitus type 2[b] (%)	338 (3.6 %)	14 (2.2 %)	68 (2.7 %)	253 (4.1 %)
Potential causes of secondary hypertension				
Renal diseases (%)	536 (5.7 %)	109 (16.8 %)	181 (7.2 %)	238 (3.8 %)
Cardiovascular malformation (%)	74 (0.8 %)	11 (1.7 %)	29 (1.2 %)	33 (0.5 %)
Endocrine (%) [d]	1214 (12.9 %)	32 (4.9 %)	237 (9.4 %)	940 (15.1 %)
Bronchopulmonary dysplasia (%)	17 (0.2 %)	8 (1.2 %)	4 (0.2%)	5 (0.1 %)
Drug use [c]				
Glucocorticoids (%)	189 (2.0 %)	51 (7.9 %)	69 (2.7 %)	63 (1.0 %)
Beta-stimulants (%)	555 (5.9 %)	77 (11.9 %)	157 (6.3 %)	313 (5.0 %)
Stimulants for ADHD (%)	223 (2.4 %)	0 (0.0 %)	61 (2.4 %)	162 (2.6 %)
Cyclosporine, tacrolimus (%)	10 (0.2 %)	4 (1.4 %)	4 (0.2 %)	2 (0.0 %)
Tricyclic antidepressants (%)	5 (0.1 %)	0 (0.0 %)	0 (0.0 %)	5 (0.1 %)
Atypical antipsychotics (%)	18 (0.2 %)	0 (0.0 %)	2 (0.1 %)	16 (0.3 %)

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

Table S1c Characteristics of children 2-17 years with arterial hypertension (HT) between 2016 and June 2021 in IQVIA™ Disease Analyzer France by age at first HT diagnosis, restricted to children with at least one year of observation at the time of the first HT diagnosis.

	All (0-17 years at first HT diagnosis)	2-5 years at first HT diagnosis	6-12 years at first HT diagnosis	13-17 years at first HT diagnosis
Mean age at first HT diagnosis (SD)	11.07 (4.76)			
No. of children with HT diagnosis by age group at first HT diagnosis	170	31	53	86
Primary HT[a] (%)	170 (100.0 %)	31 (100.0 %)	53 (100.0 %)	86 (100.0 %)
Secondary HT[a] (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Risk factors				
Male gender (%)	89 (52.4%)	14 (45.2 %)	28 (52.8 %)	47 (54.7 %)
Obesity (%)	13 (7.6 %)	<10 (-)	<10 (-)	10 (11.6 %)
Diabetes mellitus type 1 and diabetes mellitus type 2[b] (%)	<10 (-)	<10 (-)	0 (0.0 %)	<10 (-)
Potential causes of secondary hypertension				
Renal diseases (%)	<10 (-)	0 (0.0 %))	<10 (-)	<10 (-)
Cardiovascular malformation (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Endocrine (%) [d]	<10 (-)	<10 (-)	0 (0.0 %)	0 (0.0 %)
Bronchopulmonary dysplasia (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Drug use [c]				
Glucocorticoids (%)	14 (8.2 %)	<10 (-)	<10 (-)	<10 (-)
Beta-stimulants (%)	10 (5.9 %)	<10 (-)	<10 (-)	<10 (-)
Stimulants for ADHD (%)	<10 (-)	0 (0.0 %)	<10 (-)	0 (0.0 %)
Cyclosporine, tacrolimus (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Tricyclic antidepressants (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Atypical antipsychotics (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)

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