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Prescription of cardiovascular medication in children with congenital heart defects across six European Regions from 2000 to 2014: data from the EUROlinkCAT population-based cohort study

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ABSTRACT

Objectives Advances in surgical management strategies have substantially reduced fatality from congenital heart defects (CHD). Decreased infant mortality might be expected, consequentially to result in greater morbidity in older children due to complications later in childhood and adolescence. This study aims to evaluate the use of cardiovascular medication (CVM) as an indicator of disease burden in children born with CHD in the first 10 years of life.

Design Population-based cohort study.

Setting Six population-based registries from the European Surveillance of Congenital Anomalies (EUROCAT) network participated. Data from live born children with major congenital anomalies (CA) born from 2000 to 2014 were linked to prescription databases. Four groups of children were analysed: CA, CHD, severe CHD (sCHD) and ventricular septal defect (VSD) without sCHD. Live born children without CA were included as reference group.

Participants We obtained data on 61 038 children born with a CA, including 19 678 with CHD, 3392 with sCHD, 12 728 children with VSD without sCHD, and 1 725 496 reference children.

Results Children born with sCHD were the most likely to receive a CVM prescription (42.9%, 95% CI, 26.3 to 58.5) in the first year of life compared with 13.3% (6.7 to 22.0) of children with any CHD, 5.9% (3.7 to 8.7) of children with any CA and 0.1% (0.0 to 0.1) of reference children. Medication was less likely to be prescribed after the first year of life for sCHD; 18.8% (14.8 to 23.1) for children 1–4 years and 15.8% (12.0 to 20.1) 5–9 years. Children with sCHD were most likely to receive a diuretic (36.4%, 18.6 to 54.5), an antihypertensive (6.9%, 3.7 to 11.3) or a beta-blocker (5.5%, 2.9 to9.2).

Conclusion Almost half of all children with sCHD were prescribed CVM in their first year of life. For all four groups of children with anomalies, the proportion of children with a CVM prescription decreased with age.

Strengths and limitations of this study

- ► That this is a population-based study covering all children and not only those referred to tertiary hospitals for treatment.
- ► The study spans a 15-year period and covers six different European regions, and are thus able to include data on more than 1.7 million children.
- ► The use of reference children for comparison enables interpretation of the results for children with congenital anomalies in the context of results for unaffected children.
- ► A limitation of this study is the lack of information about hospital prescribed medication. As a consequence, the exposure to cardiovascular medication will be underestimated in this study.

INTRODUCTION

Congenital anomalies (CA) span a wide spectrum of diseases; from minor anomalies with minimal clinical significance, to severe malformations incompatible with life. It has been estimated that CA account for 1% of all deaths worldwide, ranking as the 23rd most prevalent cause of death for all age groups.[1] As children with CA tend to die within the first year of life, the burden in terms of years of life lost is high—and from this perspective CA are ranked 14th among the causes of death. As an example of this, CA were associated with about 40% of all infant deaths in Sweden and England from 2003 to 2012.[2] Advances in surgical management strategies and pharmacological treatment have substantially reduced fatality and as such, the

proportion of children born with a CA surviving beyond infancy is increasing.[3] This is the case both for CA in general, and also for specific subgroups such as congenital heart defects (CHD) which account for one-third of all CAs. Decreased infant mortality might be expected, consequentially to result in greater morbidity in older children due to complications later in childhood and adolescence.

Multiple studies have shown that a significant proportion of children with CHD have a decreased quality of life.[4] One factor that has been shown to negatively affect both the child's and mother's quality of life is taking daily medication, the effect of which appears independent of self-reported physical performance.[5] Similarly, among adults operated for coarctation of the aorta in childhood, their self-reported quality of life was significantly lower if they were receiving medication compared with age matched controls with similar exercise capacity who were likewise operated in childhood.[6] To the best of our knowledge, it is not well understood, why medication has a negative impact on quality of life. It is tempting to speculate that having to remember to take medication is a daily reminder of the disease and may trap patients in a vicious cycle of anxiety. In this context, it is notable that prescription of cardiovascular medication (CVM) to children in both Denmark and Norway has increased in the last 18 years—while the prevalence of CHD has remained constant.[7] Despite this finding, some authors have argued that there has been a state of nihilism in prescription of CVM to children with chronic heart failure so that medications known to be effective in adults are withheld from children.[8] As pointed out in the European Society of Cardiology (ESC) guidelines on management of Adults with CHD: 'The few available data on heart failure treatments (…) are often not conclusive and derived from small patient cohorts. As a consequence (…) recommendations are mostly based on clinical experience or position statements',[9] this is a problem that is even more pertinent for children with CHD. We have previously argued that with the paucity of data on both clinical effect of medication, which medication are being prescribed and to whom, it is 'difficult to argue a case of either under-treatment or over-treatment'.[7]

The aim of the EUROlinkCAT[10] project is to investigate the survival, morbidity and educational outcomes of children with specific CA for the first 10 years of their lives by linking births with CA in EUROCAT registries to electronic healthcare and education databases. The European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) started in 1979 and now includes 39 registries in 21 countries covering more than 29% of births in Europe.[11] In this paper, using data from six European regions covering a period of 15 years, we examine prescription of CVM (ie, antiarrhythmics, antihypertensives and diuretics) in the first 10 years of life for children with CA overall and for children with CHD, including severe Congenital Heart Defects (sCHD) and ventricular septal defect (VSD) without sCHD, compared with a cohort of reference children without CA.

METHODS

Study design

The study is a European, population-based linkage cohort study based on data from the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT)[12] linked with local prescription databases. As previously described in detail,[13] 13 population-based registries from the EUROCAT network planned to participate in this linkage study. Live born children with a major CA recorded in the EUROCAT registry born between 2000 (or the first year of the EUROCAT registry if later) and 2014 were included. Live born children without CA born during the same time-period and from the same population area covered by the registry were included as a reference group.

Information on prescriptions up to 10 years of age for all children were available by linking to local prescription databases. Data on medications were included from the year 2000 or the first birth year included in the study by each registry up to the end of 2015. Wales had information on prescriptions issued by the general practitioner (GP) for approximately 70% of Welsh GP practices that were part of the Secure Anonymised Information Linkage (SAIL) databank during the study period. The other five registries had information on prescriptions prescribed by a hospital doctor/GP that were dispensed by a pharmacy in their region. No registry had information on hospital inpatient prescribing. All registries used Anatomical Therapeutical Chemical (ATC) coding except for Wales. Wales used Read coding which was converted to ATC coding using a look-up table in SAIL. Details of the prescription databases are shown in table 1. The process of obtaining permissions for the study took longer than the 6 months expected when the study was planned, and eventually five registries could not contribute to the prescription study due to the difficulties in getting the approval. One registry did not have information on 7-digit ATC codes and was excluded from this part of the prescription studies and one registry withdrew from the EUROlinkCAT study due to COVID-19 response obligations. In total, data from six registries covering a population of more than 22 million people from five countries were included.

Time period of study

It was decided to restrict the study period to three time periods (2000–2004, 2005–2009 and 2010–2014). Only Denmark; Funen, Finland and Wales had prescription data from 2000.

Minimum number of prescriptions

For CVM, a child must have had at least one prescription to be classified as exposed to CVM.

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Table 1 Overview of the prescription databases from which data were extracted for the study

	Name of prescription database	Coverage	First year of birth	Source of prescriptions	Number of children				
					Reference population	Any CA (includes CHD)	CHD (includes sCHD)	sCHD	VSD without sCHD
Denmark: Funen	The Danish National Prescription Registry	All of Denmark	2000	Dispensed by pharmacy	72 355	1815	535	115	325
Finland	KELA Register on reimbursed medication (Social Insurance Institution)	All of Finland	2000	Dispensed by pharmacy	756 148	33 174	12 135	1763	8533
Italy: Emilia Romagna	AFT 'Pharmaceutical territorial assistance'	4 200 000	2008	Dispensed by pharmacy	250 832	5521	1534	379	940
Italy: Tuscany	AFT 'Pharmaceutical territorial assistance', FED 'Pharmaceutical hospital prescribing'. Prescription database only includes medications reimbursed by the national (or regional) health service	3 700 000	2008	Dispensed by pharmacy	16 844	3057	1095	213	737
Spain: Valencian Region	Regional prescription and dispensing database (GAIA)	5 million inhabitants	2010	Dispensed by pharmacy	223 760	4308	1380	267	695
UK: Wales	Secure Anonymised Information linkage (SAIL)	~70% of General Practitioner (GP) practices in Wales	2000	Prescribed by GP	405 555	13 165	3000	655	1500
Total number of children included		–		–	1 725 496	61 038	19 678	3392	12 728

AFT, Assistenza Farmaceutica Territoriale; CA, congenital anomaly; CHD, congenital heart defect; FED, Farmaci a Erogazione Diretta; KELA, Social Insurance Institution of Finland; sCHD, severe Congenital Heart Defect; VSD, ventricular septal defect.

Small numbers

Two registries (Denmark; Funen and Wales) have rules for releasing data with small numbers from their databases. In both registries, numbers less than five are not allowed. The rule also applies if the small number can be calculated from other numbers in the data tables. The SAIL databank (Wales) provided data to the EUROlinkCAT Central Results Repository based at Ulster University with the requirement that any individual results involving fewer than five people were not released.

Definitions of anomalies

Children with the below listed diagnoses were included in the study and divided into four groups according to the EUROCAT definitions:[14]

Congenital anomalies

All Q-codes in the ICD-10 diagnosis system (Finland and Italy used ICD-9 codes for part of the study period, only the ICD-10 codes are listed here), excluding minor anomalies according to EUROCAT exclusion criteria.[15] Finland and Italy used ICD-9 codes for part of the study period and therefore the equivalent ICD9 codes were included and excluded.

Congenital heart defects

Diagnosis Q20–Q26, excluding patent ductus arteriosus (PDA) (Q25.0) and peripheral pulmonary branch stenosis (Q25.6) if gestational age <37 weeks and persistent foramen ovale (Q21.11) for all gestational age groups.

Severe CHD

All diagnoses of common arterial truncus (Q20.0), transposition of great vessels (Q20.3), single ventricle (Q20.4), atrioventricular septal defect (Q21.2), tetralogy of fallot (Q21.3), pulmonary valve atresia (Q22.0), tricuspid atresia or stenosis (Q22.4), Ebstein's anomaly (Q22.5), hypoplastic right heart (Q22.6), aortic valve atresia or stenosis (Q23.0), hypoplastic left heart (Q23.4), coarctation of the aorta (Q25.1) and total anomalous pulmonary vein return (Q26.2). These CHD were classified as severe according to their perinatal mortality rate.[16]

VSD, excluding severe CHD

All types of VSD either isolated or associated with other CHD diagnosis, but excluding sCHD. The aim with this category was to provide an estimate for milder cases of CHD.

Classification of medication

Prescription databases categorise medication according to the WHO-based ATC classification, whereas clinical guidelines on prescription of antiarrhythmic medication from both the ESC and American Heart Association (AHA) are based on the Vaughan Williams classification (VWC).[17] We have chosen to classify antiarrhythmic medication according to the VWC (for comparison of the two systems refer to table 2). Antihypertensive medication and diuretics were classified according to the ATC system. In brief, this gave us the classification outlined below:

- VWC1: ATC codes C01BA (excluding C01BA51 and C01BA71), C01BB and C01BC.

Table 2 Comparison of the Vaughan Williams Classification (VWC) and the WHO-based Anatomical Therapeutical Classification (ATC)

Vaughan Williams	ATC codes	Examples	Mechanism of action
Class I	C01BA (Class Ia) C01BB (Class Ib) C01BC (Class Ic)	Procainamide Lidocaine Flecainide	Fast-sodium channel blockers
Class II	C07AA (non-selective) C07AB (selective) C07AG (alpha and betablockers)	Propranolol Atenolol Carvedilol	Beta-blockers
Class III	C01BD (Class III)	Amiodarone	Potassium channel blockers
Class IV	C08C C08D C08E C08G	Nifedipine	Calcium channel blockers
Class V	C01A C01EB	Digoxin Adenosine	Other mechanism of action

- VWC2: ATC codes C07A
- VWC3: ATC codes C01BD
- VWC5: ATC codes C01AA05
- Antihypertensives: ATC codes C08 and C09
- Diuretics: ATC codes C03

Calcium antagonists were grouped with antihypertensives due to small numbers.

Statistical methods

We estimated the proportion of children receiving a prescription within three age groups (<1 year, 1–4 years and 5–9 years) using Kaplan-Meier survival estimates to account for the censoring occurring especially in the older age groups. Three registries had no information on children over 6 years of age, as their prescription data started in 2008 (Italy: Emilia Romagna and Tuscany) and 2010 (Spain: Valencian region), and so they were excluded from the 5–9 years' analysis. The CIs for the KM survival analysis estimates were calculated by STATA (V.16) using the ln(-ln(S(t))) transformation. To obtain pooled estimates of these proportions across registries, random effects inverse-variance meta-analyses were performed using the ln(-ln(S(t))) transformation. For some anomaly groups and medications, no children received a prescription and the Kaplan Meier survival analysis did not provide estimates of the CI. Here, the upper CI was calculated using the exact binomial estimates with the number of children at the start of the age category as the denominator, the proportion of children with a prescription was estimated to be 0.1% and the lower 95% CI was calculated assuming symmetry on the ln(-ln(S(t)) scale.

Patient public involvement

The EUROlinkCAT project focusses on the lives of children with CAs in Europe during their first 10 years of life. As part of the project we have plans for dissemination and knowledge exchange with parents as described in detail on our webpage.[18]

RESULTS

Population characteristics

We obtained data from six EUROCAT registries spanning 15 birth years from 2000 to 2014. The reference population comprised 1 725 496 children without CA. In total 61 038 children with CA were included, of whom 19 678 had a CHD, including 3392 with sCHD and 12 728 with a VSD without sCHD (table 1). The percentage of children with valid identifications that could be linked to the prescription databases range from 85% (UK: Wales), 88% (Italy: Tuscany), 95% (Italy: Emilia-Romagna) to 100% (Spain: Valencia; Denmark: Funen; Finland).

Proportion of children with a prescription according to anomaly

The percentage of children with a CVM prescription correlated with severity of anomaly across all three age groups (table 3, figure 1). The percentage of children <1 year old receiving any CVM prescription was 0.1% (95% CI, 0.0 to 0.1) for reference children, 5.9% (95% CI, 3.7 to 8.7) for any CA, 13.3% (95% CI, 6.7 to 22.0) for children with CHD, 42.9% (95% CI, 26.3 to 58.5) for children with sCHD and 7.4% (95% CI, 3.5 to 13.2) for children with VSD without sCHD. Prescription rates correlated with severity of anomaly across all three age groups (table 3, figure 1). The same pattern of prescription was observed across all six European Regions, with no significant differences in overall prescription between regions.

Proportion of children with a prescription according to age

For the reference children, there was no significant changes with age (from 0.1% (95% CI, 0.0 to 0.1) to 0.2%, (95% CI, 0.0 to 0.2) across the three age groups). Among children with any CA, prescription was highest in the first year of life (5.9%, 95% CI, 3.7 to 8.7), and lower in the ensuing years with 3.1% (95% CI, 2.8 to 3.4) for ages 1–4 years and 2.3% (95% CI, 1.9 to 2.7) for ages 5–9 years. In CHD, it was 13.3% (95% CI, 6.7 to 22.0) for children <1 years, 5.9% (95% CI, 4.4 to 7.6) for ages 1–4 years and 3.7% (95% CI, 2.6 to 5.1) for ages 5–9 years. The same pattern with highest prescription in the first year of life and then declining prescription rates with age occurred in sCHD; 42.9% (95% CI, 26.3 to 58.5) in the first year, 18.8% (95% CI, 14.8 to 23.1) for ages 1–4 years and 15.8% (95% CI, 12.0 to 20.1) for ages 5–9 years (table 1, figure 1). For children born with a VSD without

Table 3 Percentage of children (95% CI) with any prescription according to age, anomaly and type of prescription

Anomaly	Age group (years)	Medication: Any cardiac medication % (95% CI)	Diuretics % (95% CI)	Antihyper-tensives % (95% CI)	VWC1 % (95% CI)	VWC2 % (95% CI)	VWC3 % (95% CI)	VWC5 % (95% CI)
Reference	<1	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
	1–4	0.1 (0.1 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
	5–9*	0.2 (0.1 to 0.4)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.1 (0.0 to 0.4)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Any CAs, (includes CHD)	<1	5.9 (3.7 to 8.7)	4.6 (2.5 to 7.7)	1.0 (0.5 to 1.7)	0.1 (0.0 to 0.2)	0.7 (0.5 to 1.0)	0.0 (0.0 to 0.1)	0.4 (0.1 to 1.1)
	1–4	3.1 (2.8 to 3.4)	2.0 (1.7 to 2.4)	1.1 (0.8 to 1.4)	0.1 (0.0 to 0.1)	0.6 (0.5 to 0.8)	0.0 (0.0 to 0.1)	0.2 (0.1 to 0.3)
	5–9*	2.3 (1.9 to 2.7)	0.9 (0.8 to 1.1)	1.2 (1.0 to 1.5)	0.0 (0.0 to 0.1)	0.7 (0.4 to 1.2)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.3)
CHD (includes sCHD)	<1	13.3 (6.7 to 22.0)	10.8 (4.7 to 19.8)	2.0 (0.8 to 4.0)	0.1 (0.0 to 0.5)	1.5 (0.8 to 2.7)	0.1 (0.0 to 0.2)	1.0 (0.3 to 2.7)
	1–4	5.9 (4.4 to 7.6)	4.1 (2.9 to 5.7)	1.9 (1.1 to 3.0)	0.1 (0.0 to 0.4)	1.2 (0.9 to 1.5)	0.1 (0.0 to 0.1)	0.4 (0.1 to 0.9)
	5–9*	3.7 (2.6 to 5.1)	1.9 (1.4 to 2.7)	1.7 (0.7 to 3.5)	0.1 (0.0 to 0.2)	1.3 (0.9 to 1.8)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.7)
sCHD	<1	42.9 (26.3 to 58.5)	36.4 (18.6 to 54.5)	6.9 (3.7 to 11.3)	0.3 (0.0 to 1.2)	5.5 (2.9 to 9.2)	0.2 (0.1 to 0.6)	3.2 (1.1 to 7.0)
	1–4	18.8 (14.8 to 23.1)	14.1 (10.8 to 17.8)	7.6 (5.3 to 10.4)	0.2 (0.0 to 0.6)	3.3 (2.1 to 5.0)	0.2 (0.1 to 0.4)	1.3 (0.7 to 2.2)
	5–9*	15.8 (12.0 to 20.1)	8.5 (7.1 to 10.1)	8.3 (4.2 to 14.1)	0.2 (0.0 to 0.7)	4.5 (3.4 to 5.8)	0.1 (0.0 to 0.4)	0.3 (0.0 to 1.8)
VSD, excluding severe CHD	<1	7.4 (3.5 to 13.2)	6.3 (2.7 to 11.9)	0.9 (0.3 to 2.4)	0.1 (0.0 to 0.3)	0.5 (0.3 to 0.7)	0.1 (0.0 to 0.1)	0.5 (0.1 to 1.9)
	1–4	2.6 (1.7 to 3.9)	1.9 (1.0 to 3.2)	0.4 (0.1 to 1.0)	0.1 (0.0 to 0.1)	0.4 (0.3 to 0.6)	0.1 (0.0 to 0.1)	0.2 (0.0 to 0.7)
	5–9*	0.9 (0.7 to 1.2)	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.5)	0.0 (0.0 to 0.1)	0.4 (0.1 to 1.1)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)

Please note that children with more than one major anomaly may be included in more than one congenital anomaly subgroup.
*Estimate for 5–9 years of age are based on only the three registries from Denmark, Finland and Wales.
CA, congenital anomaly; CHD, congenital heart defect; sCHD, severe Congenital Heart Defect; VSD, ventricular septal defects; VW1, Vaughan Williams class 1; VW2, Vaughan Williams class 2; VW3, Vaughan Williams class 3; VW5, Vaughan Williams class 5.

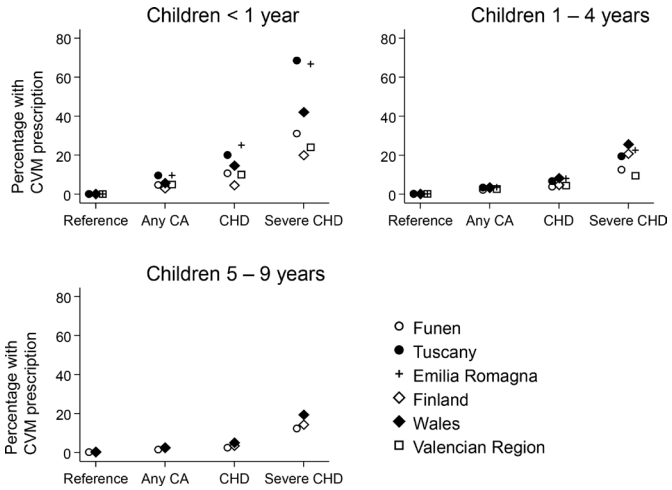

Figure 1 Percentage of children in each category receiving at least one prescription for any cardiovascular medication (CVM). Age in years above each panel. Data from six European Regions in the 15-year period from 2000 to 2014. CA, congenital anomaly; CHD, congenital heart defect; sCHD, severe Congenital Heart Defect. Please note children with more than one major anomaly may be included in more than one congenital anomaly subgroup (ie, sCHD is included in both CHD and CA).

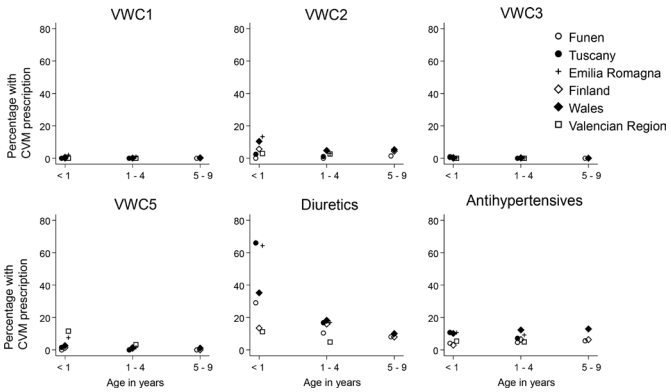

Figure 2 Percentage of children with severe Congenital Heart Defect (sCHD) receiving at least one prescription of six different pharmacological classes of CVM. Data from six European Regions from 2000 to 2014. VW1, Vaughan Williams class 1; VW2, Vaughan Williams class 2; VW3, Vaughan Williams class 3; VW5, Vaughan Williams class 5.

sCHD, the highest prescription rates were in the first year of life (7.4%, 95% CI, 3.5 to 13.2) and 2.6% (95% CI, 1.7 to 3.9) for 1–4 years and 0.9% (95% CI, 0.7 to 1.2) for 4–9 years (table 1).

Choice of medication classes in sCHD

Diuretics were the most frequently prescribed CVM in all three age groups, with 36.4% (95% CI, 18.6 to 54.5) in the first year of life, 14.1% (95% CI, 10.8 to 17.8) for ages 1–4 years and 8.5% (95% CI, 7.1 to 10.1) for ages 5–9 years. Listed in order of decreasing frequency of children receiving at least one prescription in their first year of life we found: antihypertensives 6.9% (95% CI, 3.7 to 11.3), VWC2 5.5% (95% CI, 2.9 to 9.2), VWC5 3.2% (95% CI, 1.1 to 7.0), VWC1 0.3 (95% CI, 0.0 to 1.2) and VWC3 0.2% (95% CI, 0.1 to 0.6). The same trends occurred for the two groups of older children, although with lower proportions of children overall receiving a prescription. The only exception to this was that antihypertensives remained fairly constant, 6.9% (95% CI, 3.7 to 11.3) for <1 years, 7.6% (95% CI, 5.3 to 10.4) for 1–4 years and 8.3% (95% CI, 4.2 to 14.1) for 5–9 years (table 3, figure 2).

Mean number of prescriptions per year

The mean number of prescriptions per 100 children per year were highest for children with sCHD<1 years of age at 91.1 (95% CI, 51.8 to 130.5). In all age groups and categories, the highest mean number of prescriptions were found for children with sCHD (table 4).

DISCUSSION

In the present study, we find that (i) prescription of CVM was associated with severity of CA, as the highest proportion of children receiving a CVM prescription in their first 10 years of life are children with sCHD, (ii) proportionally more children receive prescriptions of CVM in their first year of life for all subgroups of anomalies and (iii) diuretics and antihypertensives are the most frequently used CVM.

The most prevalent severe CHDs include atrioventricular septal defect (AVSD), TOF, transposition of the great arteries (TGA), double outlet right ventricle and hypoplastic left heart syndrome (HLHS).[19] Although the surgical strategy differs between defects (ie, complete operative correction in one procedure for AVSD vs staged repair in HLHS), complete surgical correction is recommended in all cases within the first year of life.[20–24] Although surgical repair is not without risk, results have improved substantially over the past 50 years and survival into adulthood is expected for almost all children born with CHD.[25] In the light of this; it seems reasonable that most CVM is given within the first year of life, either as a bridge to corrective surgery or in the postoperative period. In the present study, we do not have access to information regarding the indication for which the CVM was prescribed. However, the observation that the most frequently prescribed CVM in the first year of life is diuretics, appears to fit the picture of medication used as either a bridge to corrective surgery or use in the immediate postoperative phase. The use of diuretics in children ages 1–4 years and 5–9 years could reflect either chronic heart failure treatment or shorter courses given in relation to reoperations. Antihypertensives, including ACE inhibitors (ACEi), are widely used in paediatric heart failure,[26] despite lack of proven clinical efficacy.[27] The prescription of antihypertensives to children with sCHD might therefore well reflect a subset of children receiving ACEi treatment for chronic heart failure.

Because the subset of sCHD is included in the CHD group, it is not possible to accurately address how much of the CVM prescription in CHD is driven by the subset of sCHD. It is, however, possible to look at children with a

Table 4 Mean number of prescriptions per 100 children per year and the 95% CI

Anomaly	Age group (years)	Medication: Any cardiac medication n (95% CI)	Diuretics n (95% CI)	Antihyper- tensives % (95% CI)	VWC1 n (95% CI)	VWC2 n (95% CI)	VWC3 n (95% CI)	VWC5 n (95% CI)
Reference	<1	25.3 (12.7 to 38.0)	16.1 (7.4 to 24.7)	4.0 (2.1 to 5.9)	0.4 (0.0 to 0.7)	3.6 (1.8 to 5.3)	0.0 (0.0 to 0.0)	1.5 (0.7 to 2.2)
	1–4	9.3 (7.8 to 10.9)	3.5 (2.9 to 4.1)	3.1 (2.5 to 3.8)	0.1 (0.0 to 0.2)	1.3 (0.9 to 1.6)	0.0 (0.0 to 0.0)	0.3 (0.2 to 0.5)
	5–9*	7.9 (6.7 to 9.1)	1.3 (1.0 to 1.6)	4.2 (3.4 to 4.9)	0.0 (0.0 to 0.0)	1.3 (0.9 to 1.8)	0.0 (0.0 to 0.1)	0.6 (0.3 to 0.9)
Any CAs, (includes CHD)	<1	0.2 (0.1 to 0.3)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
	1–4	0.1 (0.1 to 0.2)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
	5–9*	0.2 (0.2 to 0.3)	0.0 (0.0 to 0.0)	0.1 (0.1 to 0.1)	0.0 (0.0 to 0.0)	0.1 (0.1 to 0.2)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
CHD (includes sCHD)	<1	53.3 (26.7 to 79.8)	35.1 (16.2 to 54.1)	7.8 (3.6 to 12.0)	1.2 (0.2 to 2.6)	7.9 (3.5 to 12.3)	0.1 (0.0 to 0.3)	3.4 (1.6 to 5.3)
	1–4	15.8 (12.9 to 18.7)	5.9 (4.5 to 7.3)	4.6 (3.6 to 5.7)	0.3 (0.1 to 0.5)	2.4 (1.8 to 3.0)	0.0 (0.0 to 0.0)	0.8 (0.5 to 1.1)
	5–9*	13.3 (10.8 to 15.8)	2.6 (2.0 to 3.3)	6.6 (5.1 to 8.1)	0.0 (0.0 to 0.1)	2.2 (1.7 to 2.7)	0.1 (0.0 to 0.2)	2.3 (1.2 to 3.5)
sCHD	<1	91.1 (51.8 to 130.5)	62.5 (32.9 to 92.1)	18.3 (9.2 to 27.4)	4.7 (1.0 to 8.4)	21.8 (9.9 to 33.7)	0.7 (0.1 to 1.3)	7.2 (3.3 to 11.2)
	1–4	43.9 (34.0 to 53.8)	20.7 (15.1 to 26.2)	17.5 (13.1 to 22.0)	0.5 (0.0 to 0.9)	5.8 (3.9 to 7.8)	0.1 (0.0 to 0.2)	4.1 (2.4 to 5.8)
	5–9*	49.0 (38.3 to 59.7)	12.7 (9.8 to 15.5)	28.0 (20.6 to 35.4)	0.2 (0.00 to 0.4)	6.9 (5.6 to 8.3)	0.6 (0.0 to 1.4)	5.6 (2.0 to 9.2)
VSD, excluding severe CHD	<1	24.4 (11.9 to 36.9)	19.0 (8.2 to 29.9)	3.9 (1.1 to 6.6)	0.2 (0.0 to 0.5)	1.0 (0.4 to 1.7)	0.5 (0.0 to 1.6)	0.9 (0.1 to 1.7)
	1–4	2.9 (1.8 to 3.9)	1.5 (0.9 to 2.1)	0.4 (0.2 to 0.7)	0.1 (0.0 to 0.4)	0.6 (0.3 to 0.8)	0.2 (0.0 to 0.5)	0.2 (0.0 to 0.5)
	5–9*	1.4 (0.9 to 1.8)	0.1 (0.0 to 0.2)	0.4 (0.2 to 0.6)	–	1.1 (0.8 to 1.4)	–	1.3 (0.0 to 3.1)

Please note that children with more than one major anomaly may be included in more than one congenital anomaly subgroup.
Blank cells (–) reflect too small numbers to report.
CA, congenital anomaly; CHD, congenital heart defect; sCHD, severe Congenital Heart Defect; VSD, ventricular septal defects; VW1, Vaughan Williams class 1; VW2, Vaughan Williams class 2; VW3, Vaughan Williams class 3; VW5, Vaughan Williams class 5.

diagnosis of VSD that had no sCHD diagnosis. This group will include both isolated VSD, but also those occurring in combination with other minor cardiac anomalies such as an ASD, PDA or pulmonary valve stenosis. The reported incidence of VSD in neonates is highly dependent on the quality/availability of imaging, as a large subset of muscular VSD will close spontaneously without ever causing symptoms.[28] Dependent on detection rates of asymptomatic cases, somewhere between 5% and 10% of isolated VSD cases will require surgical intervention.[29] In our data, we find that 7.4% (95% CI, 3.5 to 13.2) of the children in the VSD subgroup will receive a CVM prescription in their first year of life. It seems reasonable to assume that this is the subset that will require surgery.

Arrhythmias in CHD can either be caused by (i) the defect itself (ie, sinoatrial Wenckeback in TGA), (ii) an immediate postoperative complication (ie, junctional ectopic tachycardia) or (iii) arise as a late postoperative complication (most frequently atrial arrhythmias).[30] In Europe, the majority of centres used either flecanide (VWC1) or atenolol (VWC2) for the management of supraventricular arrhythmias.[31] In our population, VWC1 medication was rarely used, whereas VWC2 medication was more frequently prescribed. Although digoxin was recommended in the EHRA/AEPC-arrhythmia

Working group joint consensus statement,[30] when surveyed in the same year, no centres in Europe reported using it for paediatric arrythmias.[31] As can been seen from figure 2; VWC5 was used in both Emilia Romagna (Italy) and Valencian Region (Spain), this most likely reflects digoxin prescription for supraventricular arrhythmias. Very few prescriptions for VW3 (ie, amiodarone) were found in the present study. Guidelines suggest adding a VW3 class medication if treatment with a VW1 or VW2 does not achieve rhythm control. The low prescription rate of VW3 class medication might well reflect a tendency towards performing catheter ablation in patients where achieving rhythm control proves challenging,[31] rather than adding a second medication.

The main strength of this study is the population-based setting covering all children and not only those referred to tertiary hospitals for treatment.[26 31] Information is available on over 1.7 million children with potential to be linked from six European regions, in five countries covering both Northern and Southern Europe. In addition, the EUROCAT registries have a high level of case ascertainment and use standardised definitions and coding of CA to ensure consistency across Europe. The use of reference children for comparison enables interpretation of the results for children with CAs in the context of results for unaffected children. A limitation of this study is the lack of information about hospital prescribed medication. As a consequence, the exposure to CVM will be underestimated in this study. This will potentially have a bigger impact on children with more severe types of CHD as they are more likely to have a hospital admission. A second limitation is that not all children could be linked to the prescription databases due to, for example, invalid identification numbers. In tree regions, we were able to link 100% of children, but in the tree other regions, we were unable to link 5%–14% of children. A third limitation is that the data from Wales are based on prescription by the GP, rather than on pharmacy dispensed medication, this may overestimate the true amount due to medications being prescribed but never collected. We had intended to analyse data to see if there was a change in prescription rates over time in the three age groups. However, as some centres did not include data before 2008 or 2010, hence too few children were available in the older age categories. A recent study from Denmark and Norway found that prescription of CVM (measured as Defined Daily Doses) to children doubled during the study period from 1999 to 2016.[7] Information on DDD was not extracted from the prescription databases for this study, because the use of DDD in studies on children is problematic. The dose for children is always calculated individually, at the time of prescribing, based on the actual weight or body surface area of the child. The hospital databases only have the weight of the child at birth and even with the actual weight at time of dispensation, the comparisons of prescribed dose for children would be too uncertain. We therefore looked at individual prescription, which in our opinion, provides a better reflection of the medication burden. Another way to attempt to quantify the burden of medication is to look at the mean number of prescriptions which for instance for children with sCHD<1 years of age is 91 prescriptions per 100 children. Although this gives an indication of the burden, it is not possible to directly infer the length of treatment from this number. How long a given prescriptions is used will depend both on the prescribed package size and the weight (and height) of the child, information which is not available in the databases.

In conclusion, we show that a large proportion of children with sCHD receive more CVM through their first 10 years of life. For all children with CHD, sCHD or VSD without sCHD, the largest proportions of children receiving a CVM prescription are found in their first year of life, and then declined with advancing age. For children without CA, the proportion of prescribed CVM is very low. The most frequently prescribed medications are diuretics and antihypertensives.

The burden of disease for children with CHD and sCHD includes the need for daily medications, but also other important aspects of the disease burden such as hospitalisations, length of stay and number of surgeries should be studied.

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