Risk stratification in transposition of the great arteries

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Publication date
2021

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High burden of drug therapy in adult congenital heart disease: polypharmacy as marker of morbidity and mortality

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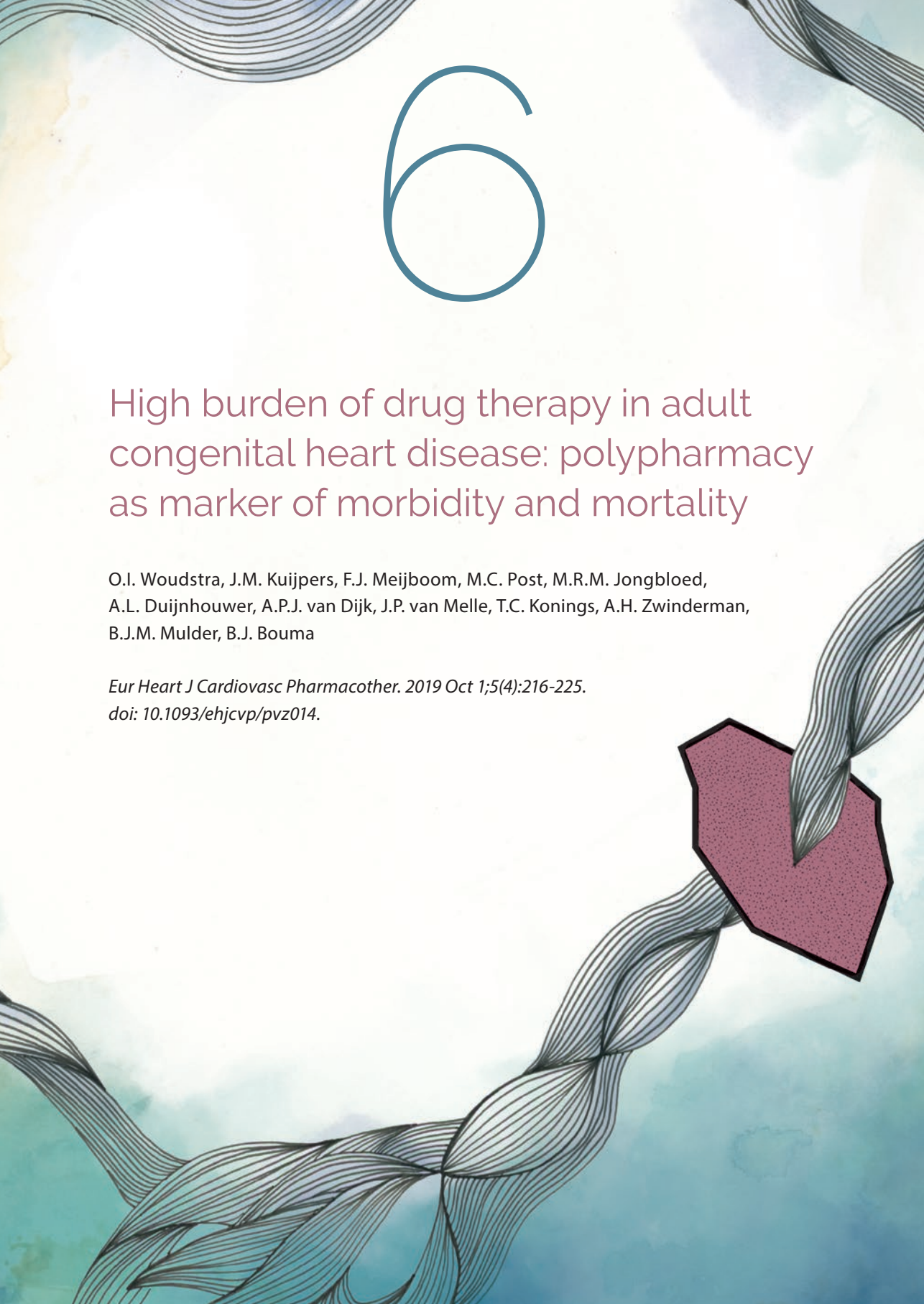
Eur Heart J Cardiovasc Pharmacother. 2019 Oct 1;5(4):216-225.
doi: 10.1093/ehjcvp/pvz014.



ABSTRACT

Aims

To assess medication use in adult congenital heart disease (ACHD) patients compared to the age- and sex-matched general population, identify patterns of pharmacotherapy, and analyze associations between pharmacotherapy and adverse outcomes in ACHD.

Methods and Results

Data of 14,138 ACHD patients from the CONCOR-registry (aged 35 [IQR 24-48] years, 49% male) and age- and sex-matched referents (1:10-ratio) were extracted from the Dutch Dispensed Drug Register for the years 2006-2014. ACHD patients had more cardiovascular and non-cardiovascular drugs than referents (median 3 vs 1, $p < 0.001$). Polypharmacy, defined as ≥ 5 dispensed drug types yearly, was present in 30% of ACHD and 15% of referents (OR = 2.47 [95% CI 2.39-2.54]). Polypharmacy was independently associated with female sex (OR = 1.92 [95% CI 1.88-1.96]), older age (for men: OR = 2.3/10years [95% CI 2.2-2.4], for women: OR = 1.6/10years [95% CI 1.5-1.6]; $p_{interaction} < 0.001$), and ACHD severity (mild: OR = 2.51 [95% CI 2.40-2.61], moderate: OR = 3.22 [95% CI 3.06-3.40], severe: OR = 4.87 [95% CI 4.41-5.38]). Cluster analysis identified three subgroups with distinct medication patterns; a "*low medication use*" group (8-year cumulative survival: 98%), and a "*cardiovascular*" and "*comorbidity*" group with lower survival (92% and 95%, respectively). Cox regression revealed a strong association between polypharmacy and mortality (HR = 3.94 [95% CI 3.22-4.81]), corrected for age, sex and defect severity. Polypharmacy also increased the risk of hospitalization for adverse drug events (HR = 4.58 [95% CI 2.04-10.29]).

Conclusion

Both cardiovascular and non-cardiovascular medication use is high in ACHD with twice as much polypharmacy compared to the matched general population. Patients with polypharmacy had a 4-fold increased risk of mortality and adverse drug events. Recognition of distinct medication patterns can help identify patients at highest risk. Drug regimens need repeating evaluation to assess the appropriateness of all prescriptions. More high-quality studies are needed to improve ACHD care with more evidence-based pharmacotherapy.

INTRODUCTION

The adult congenital heart disease (ACHD) population is still growing and aging[1,2]. Healthcare utilization is high, and drugs are more often prescribed in ACHD than in controls[3,4]. Unlike other cardiovascular areas, evidence for drug therapy in ACHD is based on scarce clinical data and remains mostly empiric[5]. Whether current pharmacological practice is efficient and safe in the long-term therefore remains questionable, but needs to be elucidated as drug therapy is increasingly used to address late complications. Pharmacological treatment in ACHD may start at a young age and may cumulate into chronic use of multiple medications. In elderly, it is known that the concurrent use of multiple medications, polypharmacy, is common (~50%)[6] and it is generally accepted that increased drug therapy is associated with adverse outcomes, such as adverse drug events (ADE), hospitalizations, and death[7]. However, data on polypharmacy in ACHD are lacking. This study therefore assessed medication use and polypharmacy in ACHD in comparison to the age- and sex-matched general population. Furthermore, we aimed to identify patterns of medication use in ACHD, and to analyze the association between polypharmacy and adverse outcomes in ACHD.

METHODS

Study population and data collection

This cohort study linked data of patients from the CONCOR-registry[8], which includes adults (aged ≥ 18 years) with congenital heart disease (CHD), to the national Dispensed Drug Register (DDR) of Statistics Netherlands (www.cbs.nl). For all Dutch residents, the DDR contains all dispensed outpatient drugs reimbursed by the compulsory basic Dutch health insurance. Drugs are classified following the Anatomical Therapeutic Chemical (ATC) classification (Supplementary table 1), which classifies drugs at five levels according to the organ/system on which they act (1st) and their therapeutic (2nd), pharmacological (3rd), and chemical properties (4th and 5th level)[9]. In the DDR, drugs are aggregated per person per year at the 3rd level of the ATC classification. Thus, specific drugs and their duration, timing, and daily doses within this one-year window cannot be extracted. Receiving a specific drug is coded as dichotomous value for a full year, regardless of the amount of drugs dispensed. We therefore defined polypharmacy using the cumulative concept[10] as ≥ 5 different drug types per calendar year, at the therapeutic (2nd) level of the ATC classification, to correct for changes in pharmacological classes.

Patients were matched with randomly selected age- and sex-matched reference subjects from the general population (1:10-ratio) to gain insight in the increase in medication use in ACHD compared to normal for these generally young persons (for details, see Supplementary methods and Supplementary figure 1). Subjects were followed from 2006 or CONCOR-inclusion until 2014 or death, using survival data from

the national Cause of Death Register (CDR), which includes International Classification of Diseases (ICD) tenth revision coded causes of all deaths in Dutch citizens. From CONCOR, we obtained date of birth, inclusion date, sex, and main CHD, classified into mild, moderate, and severe CHD according to a much used consensus-based classification where proposed level of care and survival prospects differ per severity (Supplementary table 2)[11,12].

Additionally, data on hospitalizations for ADE were collected via the Dutch Hospital Discharge Register (HDR) for the years 2006-2012. The HDR contains person-linked discharge records of Dutch hospital admissions, including ICD-9 coded diagnoses and dates of admission. We defined hospitalizations for ADE as admissions with ICD-9 codes 960-979 (poisoning by drugs, medicinal and biological substances) as main diagnosis. The CDR was subsequently reviewed for ADE as cause of death in all patients (ICD-10 codes T36-T50).

CONCOR was approved by the ethics boards of all participating centers[8] and complies with the declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using RStudio V.1.0.153 (RStudio Team, Boston, MA, USA) and SPSS V.22 (IBM, Armonk, NY, USA). Data are summarized as n (%), mean ± SD, and median (interquartile range [IQR]). Two-sided p-values of < 0.05 were considered statistically significant.

Drug use was described as percentage of years with dispensed drugs during the studied period. Generalized estimating equations with exchangeable working correlation and robust variance estimators were used to calculate odds ratios (ORs) for specific drugs and polypharmacy during the study in patients vs matched referents, to determine whether sex, age, and CHD severity were independently associated with the presence of polypharmacy, and to plot predicted probability of polypharmacy by age in subsets per CHD severity. We performed subgroup analyses based on CHD type, sex, and age. A sensitivity analysis excluding sex hormones was performed to analyze the influence of oral contraceptives on the difference in polypharmacy between the sexes. We also performed sensitivity analysis excluding non-chronic drug types (including antibiotics, full list in supplementary table 3) to test whether the cumulative definition of polypharmacy represented concurrent and continuous medication well.

To identify subgroups of patients with distinct patterns of medication relating to diseases of different organ systems, we used an unbiased machine learning approach. Of each patient, we determined whether drugs of the different anatomical classes of the ATC classification (1st level, Supplementary table 1) were used at year of inclusion. Hierarchical clustering was performed with the hclust and heatmap functions in R, using binary distance to calculate the dissimilarity matrix. The optimal number of clusters was estimated by maximizing the gap statistic using the gap method[13]. Differences between clusters were compared using χ^2 and ANOVA tests. Survival was assessed using Kaplan-

Meier analysis and compared between clusters using Cox hazard regression, adjusted for age, sex, and CHD severity.

For survival analyses, we excluded patients who were included in 2014 or died in their year of inclusion, because the yearly aggregated data required follow-up starting the following year. Cumulative survival for patients with and without polypharmacy at inclusion was assessed per CHD using Kaplan-Meier curves. Associations between polypharmacy and all-cause mortality were analyzed using multivariable Cox regression adjusted for age, sex, and CHD severity, with polypharmacy as time-varying factor. Interaction terms were used to analyze differences between CHD severities, and between ACHD patients and referents. Similarly, Cox hazards regression was used to analyze whether polypharmacy was associated with hospitalizations for ADE in ACHD patients.

RESULTS

In total, 14,138 ACHD patients (aged 35 [IQR 24-48] years, 49% male, 34% moderate and 9% severe CHD) were followed for 8 (IQR 5-9) years (baseline characteristics in Supplementary table 4). Overall, 96,835 person-years of patients and 982,563 person-years of referents were analyzed.

Common drugs

Table 1 shows the most commonly dispensed drugs. ACHD patients had higher use of cardiovascular drugs than referents, with highest use of antithrombotics (27% vs 6% in referents, OR = 5.83 [95% CI 5.60-6.07]), β-blockers (24% vs 6%, OR = 4.43 [95% CI 4.26-4.61]) and renin-angiotensin-aldosterone-system (RAAS) inhibitors (21% vs 7%, OR = 3.32 [95% CI 3.17-3.47]) (Table 1A).

Remarkably, most non-cardiovascular drugs were also used more frequently in ACHD, especially systemic antibiotics (38% vs 20%, OR = 2.45 [95% CI 2.40-2.51]), drugs for acid related disorders (15% vs 10%, OR = 1.60 [95% CI 1.54-1.66]) and drugs for obstructive airway disease (10% vs 7% OR = 1.57 [95% CI 1.50-1.65]) (Table 1B). Patients more commonly used drugs for thyroid disease than referents (3.8% vs 2.0%, OR = 1.83 [95% CI 1.66-2.01]), especially patients with complete atrioventricular septal defects (OR = 15.69 [95% CI 9.53-25.83]) who often had Down syndrome (142 of 214 patients (67%)). Antiepileptics also were more common (2.8% vs 1.5%, OR = 1.84 [95% CI 1.68-2.02]), particularly in patients with transposition of the great arteries (OR = 4.58 [95% CI 2.87-7.33]) or a functionally univentricular heart (UVH) (OR = 4.52 [95% CI 2.21-9.22]).

Table 1: Dispensed drugs.

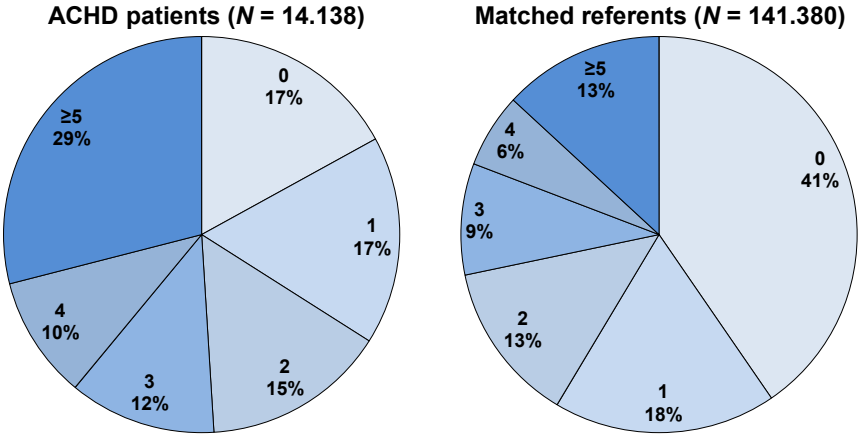
	ACHD patients n person-years = 96,835 %	Matched referents n person-years = 982,563 %	OR (95% CI)
A. Cardiovascular drugs			
Antithrombotics* (e.g. vitamin K antagonists, NOACs, platelet aggregation inhibitors)	26.5	5.4	5.83 (5.60-6.07)
β-blockers*	23.7	6.3	4.43 (4.26-4.61)
RAAS inhibitors*	21.2	6.9	3.32 (3.17-3.47)
Diuretics*	11.4	3.8	3.23 (3.07-3.40)
Lipid modifiers* (e.g. statins)	10.3	6.7	1.48 (1.39-1.56)
Calcium channel blockers*	6.1	2.6	2.17 (2.03-2.33)
Antiarrhythmics*	5.8	0.4	12.30 (11.23-13.47)
Other antihypertensives*	1.4	0.3	5.95 (5.14-6.90)
Antihemorrhagics* (e.g. vitamin K, coagulation factors)	1.0	0.2	6.30 (5.61-7.05)
Cardiac vasodilators* (e.g. nitrates)	0.3	0.2	1.72 (1.31-2.24)
B. Non-cardiovascular drugs used in >10% of ACHD			
Systemic antibiotics*	37.8	19.7	2.45 (2.40-2.51)
Anti-inflammatory and antirheumatic products (e.g. NSAIDs, excluding aspirin)	17.3	17.3	1.01 (0.98-1.03)
Drugs for acid related disorders* (e.g. PPIs and antacids)	15.1	10.3	1.60 (1.54-1.66)
Dermatological corticosteroids*	13.6	10.6	1.33 (1.29-1.37)
Sex hormones* (e.g. oral hormonal contraceptives)	11.2	8.6	1.33 (1.27-1.38)
Drugs for obstructive airway diseases* (includes inhalants (adrenergics, corticosteroids) and systemic adrenergics)	10.3	6.9	1.57 (1.50-1.65)
Analgesics* (e.g. opioids, aspirin)	10.2	6.7	1.58 (1.52-1.65)
Ophtalmologicals* (topical ocular drugs)	10.2	7.5	1.40 (1.35-1.46)

Use of cardiovascular medication (A) and the most common non-cardiovascular medication (B) in ACHD patients compared to the use in matched referents from the general population. Drugs are presented according to the therapeutic classes of the Anatomical Therapeutic Chemical classification (Supplementary table 1). *: Significant at the p<0.001 level. Abbreviations: ACHD, adult congenital heart disease; CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; OR, odds ratio; RAAS, renin-angiotensin-aldosterone-system.

Polypharmacy

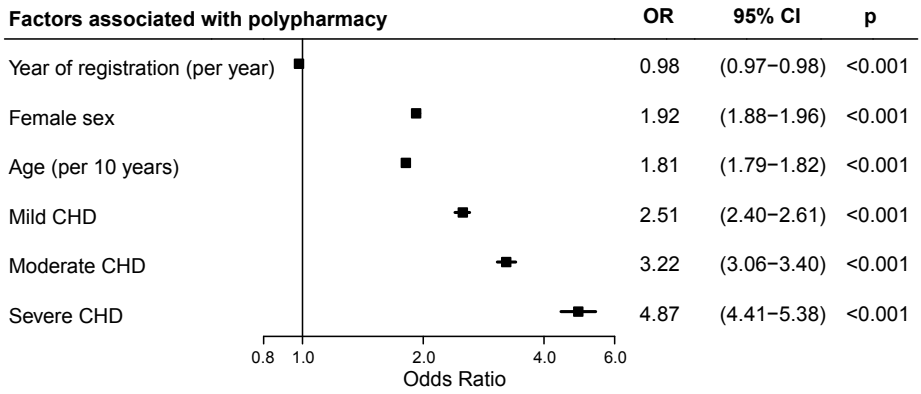
ACHD patients had a median of three different dispensed drugs at year of inclusion, compared to a median of one in reference subjects ($p < 0.001$) (Figure 1). Twice as little patients were free of dispensed drugs at inclusion compared to referents (17% vs 40%, $p < 0.001$) (Most common drugs in polypharmacy: Supplementary table 5).

Figure 1: Amount of different drugs types at inclusion in adult congenital heart disease (ACHD) patients and matched referents.



Mean prevalence of polypharmacy during the study was 30% in ACHD compared to 15% in referents (OR = 2.47 [95% CI 2.39-2.54]). Polypharmacy was independently associated with older age, female sex, and CHD severity (mild: OR = 2.51 [95% CI 2.40-2.61], moderate: OR = 3.22 [95% CI 3.06-3.40], severe: OR = 4.87 [95% CI 4.41-5.38]) (Figure 2). It was particularly present in patients with a UVH (44%, OR = 8.54 [95% CI 6.62-11.02]), with many cardiovascular drugs indicating high cardiac morbidity, and in patients with Marfan syndrome (45%, OR = 4.60 [95% CI 3.98-5.31]), with notable use of cardiovascular drugs, ocular medication (18%, OR = 2.61 [95% CI 2.20-3.11]), and analgesics(16%, OR = 2.55 [95% CI 2.16-3.01]), reflecting ocular and skeletal problems (e.g. scoliosis) often seen in these syndromic patients.

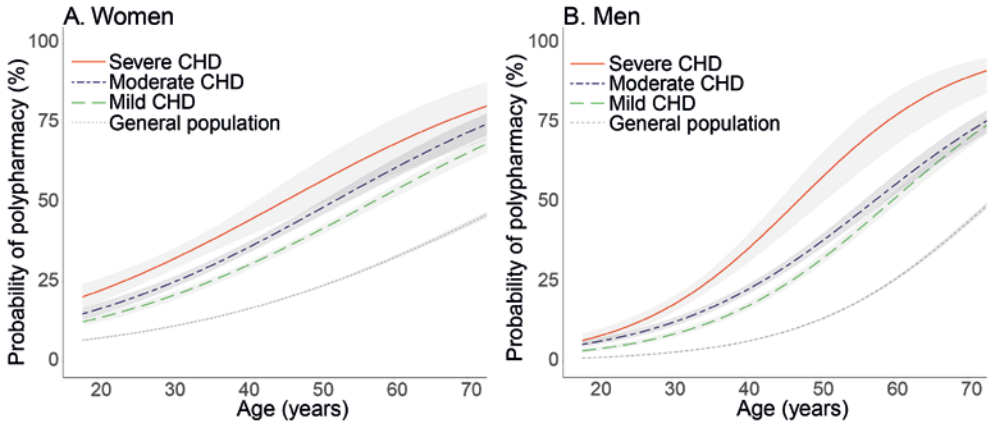
Figure 2: Factors associated with polypharmacy.



Factors independently associated with polypharmacy in the entire cohort, showing odds ratios (OR) for polypharmacy during the study period. Abbreviations: CHD, congenital heart defect.

Even in mild CHD, polypharmacy was already as common in 45-year old female and 50-year old male patients as in 65-year old persons from the general population (Figure 3). Already 48% of patients with severe CHD had polypharmacy at the age of 45 years, a proportion only seen for persons aged ≥ 70 in the general population.

Figure 3: Probability of polypharmacy by age and gender.



Predicted probability of polypharmacy for women (A) and men (B) by age, stratified for congenital heart defect (CHD) severity, compared to age- and sex-matched referents.

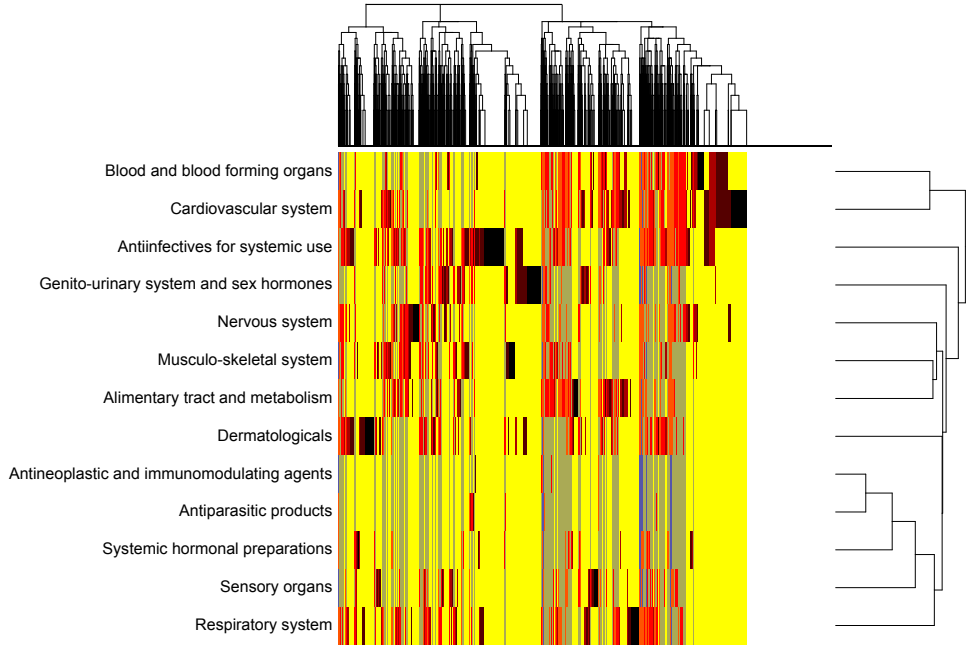
Overall, polypharmacy was more common in women than men (OR = 1.92 [95% CI 1.88-1.96]). It was already present in 24% of female patients aged < 40 years (vs 12% of female referents aged < 40 years), with high use of antibiotics (41%) and sex hormones including contraceptives (31%). Even after exclusion of sex hormones, polypharmacy prevalence remained higher in women (OR = 1.88 [95% CI 1.74-1.78]). In men, polypharmacy was less common at young age, but showed a steep incline with age (OR = 2.3/10years [95% CI 2.2-2.4], for women: OR = 1.6/10years [95% CI 1.5-1.6]; $p_{interaction} < 0.001$); 40% of male patients aged > 40 years had polypharmacy (vs 19% of male referents aged > 40 years), with high use of antithrombotics (46%) and renin-angiotensin-aldosterone-system inhibitors (23%). These sex- and age-specific differences were seen both in patients and referents.

Mean prevalence of polypharmacy was still 25% in ACHD compared to 12% in matched referents (OR = 2.39 [95% CI 2.32-2.48]) when non-therapeutic and non-chronic drugs were excluded for sensitivity analysis.

Patterns of medication use

The phenotype heat map created by hierarchical clustering of medication used in ACHD demonstrated heterogeneity among patients (Figure 4). The use of drugs acting on the cardiovascular and blood & blood forming organs (mainly antithrombotics) seemed to co-occur most.

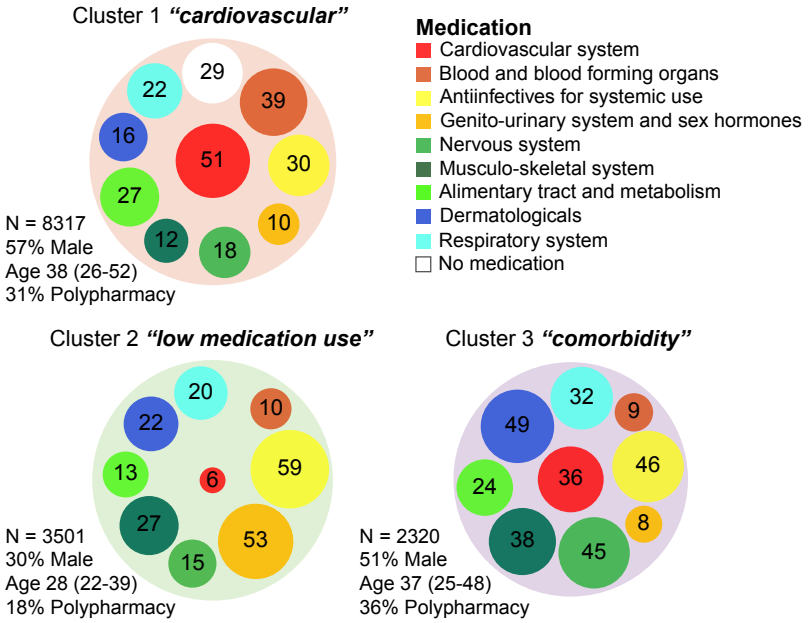
Figure 4: Medication phenotype heatmap of adults with congenital heart disease.



Columns represent individual patients and *rows* represent independent phenotypes of dispensed drugs aggregated at the anatomical level of the Anatomical Therapeutic Chemical classification. Red indicates increased value, yellow intermediate, and blue decreased value of a drug. White columns represent 2,409 patients with zero drugs.

The analysis arrived at three clusters as the optimal number to reflect phenotypic variability (Supplementary figure 2). The clusters differed significantly (Supplementary table 6). As shown in figure 5, cluster 1 (n = 8,317) had the highest proportion of patients with drugs acting on the cardiovascular and blood & blood forming systems. This "*cardiovascular*" cluster was the oldest and had most patients with severe CHD (10%) and left sided lesions (e.g. bicuspid aortic valve: 11%). Cluster 2 (n = 3,501) mainly contained patients using anti-infectives and genito-urinary medication (sex hormones), but relative low use of other drugs, with polypharmacy in only 18% of patients. This "*low medication use*" cluster contained young, mainly female (70%) patients, mostly with mild defects (61%). In cluster 3 (n = 2,320), the "*comorbidity*" cluster, many patients used extra-cardiac medication. It had the highest proportion of patients with polypharmacy (36%) and genetic syndromes (7%).

Figure 5: Clinical characteristics and medication use at inclusion stratified by phenogroup.



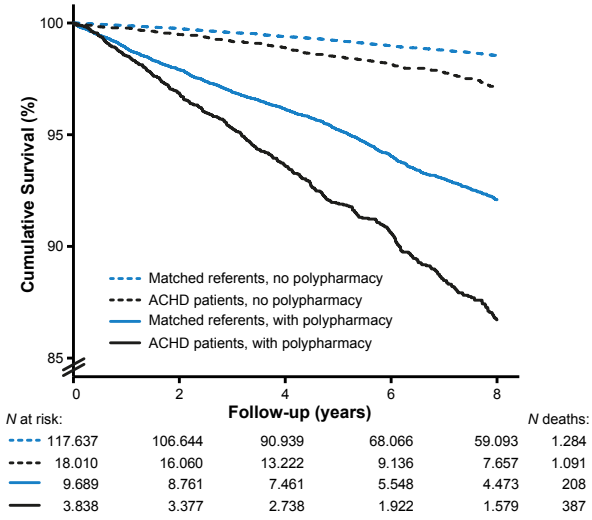
Numbers represent the percentage of patients per subgroup with medication for the different organ systems used at year of inclusion.

After eight years of follow-up, cumulative survival was 92% in the "*cardiovascular*" cluster, 98% in the "*low medication use*" cluster and 95% in the "*comorbidity*" cluster. Corrected for age, sex, and CHD severity, survival was better for the "*low medication use*" versus "*cardiovascular*" cluster (HR = 0.50 [95% CI 0.37-0.78], $p < 0.001$), but, despite the distinct medication patterns, did not differ between the " *comorbidity*" and "*cardiovascular*" cluster (HR = 0.89 [95% CI 0.71-1.11], $p = 0.31$).

Polypharmacy and outcome

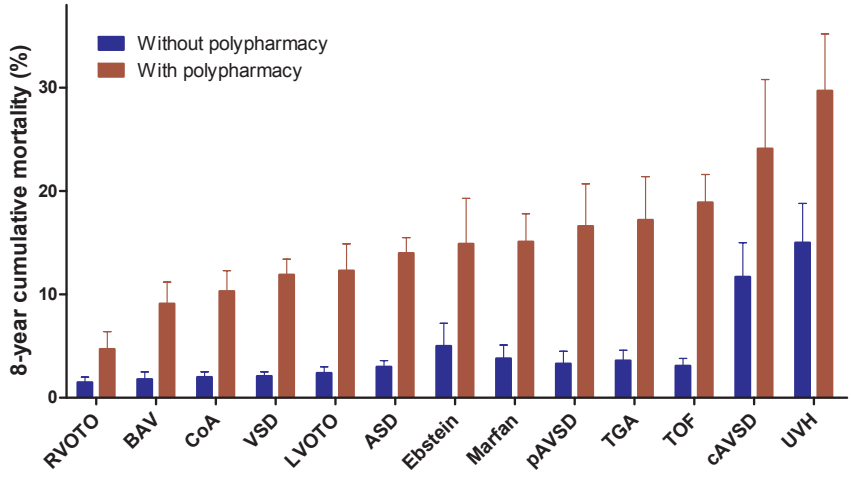
Survival analyses included 13,527 patients and 135,647 referents. During 7 (IQR 5-8) years, 595 patients (4%) and 2,375 referents (2%) died (Figure 6). Eight-year mortality was higher in patients with polypharmacy at inclusion compared to those without polypharmacy (Figure 7). Corrected for age, sex, and defect severity, polypharmacy during the study was strongly associated with all-cause mortality in ACHD (HR = 3.94 [95% CI 3.22-4.81]). The age- and sex-adjusted association was similar between the CHD severities ($p_{interaction} = 0.96$ for moderate and $p_{interaction} = 0.70$ for severe CHD compared to mild CHD) and was significantly stronger in ACHD patients than in referents ($p_{interaction} < 0.001$).

Figure 6: Kaplan-Meier survival curve of adult congenital heart disease (ACHD) patients and matched referents with and without polypharmacy at inclusion.



N at risk:						*N* deaths:
117.637	106.644	90.939	68.066	59.093	1.284
18.010	16.060	13.222	9.136	7.657	1.091
9.689	8.761	7.461	5.548	4.473	208
3.838	3.377	2.738	1.922	1.579	387

Figure 7: Eight-year cumulative mortality for patients with and without polypharmacy at inclusion per congenital heart defect.



Abbreviations: ASD, atrial septal defect; BAV, bicuspid aortic valve; cAVSD, complete atrioventricular septal defect; CoA, coarctation of the aorta; Ebstein, Ebstein's anomaly; LVOTO, left ventricular outflow tract obstruction; pAVSD, partial atrioventricular septal defect; RVOTO, right ventricular outflow tract obstruction; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH, functionally univentricular heart; VSD, ventricular septal defect.

A total of 10,015 ACHD patients were uniquely identified in the HDR between 2005-2012. During a median of 5 (IQR 3-6) years, 21 ACHD patients were hospitalized for an adverse drug event (ADE). Increasing drug amounts were associated with ADE (HR = 1.20/dispensed drug [95% CI 1.10-1.32]). Patients with polypharmacy were at markedly higher risk of hospitalization for an ADE compared to patients without polypharmacy (HR = 4.03 [95% CI 1.67-9.73]). None of the patients that died during the study had ADE as cause of death.

DISCUSSION

This study shows that ACHD patients not only use more cardiovascular medication than the general population, but also use more extra-cardiac drugs, cumulating into polypharmacy in 30% of the patients compared to only 15% of referents. The study identified distinct medication patterns, which differed by age, sex, and CHD. Furthermore, patients with polypharmacy had an almost 4-fold higher risk of all-cause mortality and almost 5-fold higher risk of hospitalizations for ADE.

Recently, ACHD investigators have stressed the need for more evidence regarding drug therapy in this growing population[5]. Trials investigating safety and efficacy of drugs in ACHD often remain small[14,15]. The existing pool of evidence in this area therefore only grows slowly and remains largely empiric. Some epidemiologic studies have identified common drugs in ACHD cohorts[4,16]. However, this study is the first to investigate polypharmacy and its associations with clinical characteristics and outcome in ACHD. Furthermore, this is the largest study comparing medication use in ACHD to the general population.

Previous studies focusing on other chronic conditions, such as diabetes mellitus, chronic kidney disease, and chronic heart failure, have shown comparably high odds for polypharmacy of these diseases[17,18]. Compared to these populations, ACHD patients are special due to their young age and lifelong disease which may involve both cardiac and extra-cardiac comorbidities. Polypharmacy in 15% of the age-matched referents may seem high, but is close to other findings using cumulative definitions of polypharmacy during a one-year period[19]. Not surprisingly, polypharmacy risk in our study increased with increasing CHD severity, which involves more cardiovascular complications requiring medical intervention[16,20].

Apart from common use of cardiovascular drugs, use of many non-cardiovascular drugs was increased in ACHD. Previous research showed increased prevalence of drugs related to asthma and epilepsy in patients who underwent surgery for a CHD as children[4]. Especially in patients with genetic syndromes, extra-cardiac comorbidities are common[4,21]. In our cohort we saw increased use of a large range of drugs, including drugs for acid-related disorders, dermatologicals, and sex hormones. This indicates high

prevalence of extra-cardiac comorbidities in the ACHD population. Contra-indications for pregnancy are more common in women with cardiovascular disease[22] and may explain a higher preventive use of oral contraceptives in ACHD.

Interestingly, polypharmacy was even increased in mild CHD and at young age, reflecting decreased health even in these mildly affected patients. Alternatively, the increase in medication use may originate from intensive surveillance that facilitates early diagnosis and treatment[3]. The particularly higher prevalence of polypharmacy in female compared to male ACHD patients at young age is in line with general sex differences that depend on differences including prevalence of morbidities and adverse drug effects, need for anticonceptives, and a lower likelihood to seek preventive healthcare in men[23].

Cluster analysis revealed three distinct patterns of medication use in ACHD, described as "*cardiovascular*", "*low medication use*", and " *comorbidity*" patterns. Cluster analysis based on phenotypical data has been used previously to identify distinct subgroups within other heterogeneous populations[24,25]. This unbiased approach makes it possible to identify patterns regardless of assumptions about clinical correlations. The identification of such distinct subgroups could be used to help target therapies and trials in heterogeneous syndromes such as ACHD. Clinical trials are prone to select patients without marked comorbidity, but concurrent use of different drugs is important to identify due to increased risk of drug-drug interactions and ADE[26,27]. This may be most crucial in the *comorbidity* subgroup.

This study showed, without implying causality, that patients with polypharmacy had a 4-fold higher mortality risk (HR = 3.94), independent of age, sex and defect severity. Furthermore, risk of hospitalization for adverse drug events was nearly 5 times higher in patients with polypharmacy (HR = 4.58). Interestingly, polypharmacy in the ACHD population was more associated with mortality than in the general population. Patients with polypharmacy may be sicker (needing therapy) than referents with polypharmacy (who e.g. often have statins as prevention). Whether an increased amount of drugs is an independent risk factor or a mere measure of poor health and multimorbidity, remains to be elucidated[6,7]. Polypharmacy may enhance risk of adverse drug events, including bleeding due to antithrombotics[28], and increased amounts of drugs correlate with hospitalizations for adverse drug reactions[26,27]. Notably, drugs often prescribed in ACHD, especially anticoagulants, are among the drugs most commonly causing ADE related emergency department visits and hospitalizations[29,30]. Benefits of prescribing may outweigh the risks of ADE, but evidence of beneficial effects of many therapies in ACHD is still limited[5]. In elderly, guidelines with criteria to start and stop certain drugs have been established to minimize inappropriate prescribing[31] and it has been suggested that deprescribing to reduce inappropriate polypharmacy can reduce mortality without harm[32,33].

Clinical implications

The remarkably high prevalence of polypharmacy in ACHD shows that experience with managing polypharmacy is needed in the efficient management of these patients. Physicians should carefully judge drug indications in ACHD, especially as pharmacotherapy is often based on low-level evidence extrapolated from non-ACHD studies or small studies involving heterogeneous ACHD patients. Long-term use of some medication, e.g. amiodarone, may be suboptimal due to side effects[5]. Occasionally, withdrawal of longstanding therapy with only weak indications might be an option. Trials that examine efficacy and safety of drug therapy in ACHD are warranted and the effects of longstanding polypharmacy in these patients needs to be studied further to enhance guidelines on the management of this complex population.

Methodological issues

These data from national administrative databases enable insightful comparisons with the general population. Automated data collection limits recall bias seen in questionnaires and data on dispensed drugs provide more accurate information on actual drug consumption than medical records, as these prescriptions have been filled. However, actual drug consumption may be overestimated, as we have no data on compliance. Non-compliance is of importance because it is associated with mortality and increases with treatment intensity and duration[34,35], although compliance in the Netherlands is reported to be high (> 80%)[36].

The lack of clinical detail inherent to administrative data introduces indication bias, as no information on drug indications, comorbidities, and functional status are available. We used the consensus-based severity classification to subdivide patients with different risks. However, mortality risk may vary within specific CHDs due to late complications, such as pulmonary hypertension in patients with septal defects. Therefore, these data do not provide information about individual patients, but give insight on a population level. Furthermore, appropriateness of polypharmacy is not assessed and associations with mortality have to be interpreted with caution, as polypharmacy may mark high-risk patients with multimorbidity.

Other limitations inherent to the dataset include unavailability of data on over-the-counter medication, and data on treatment duration, daily doses, and specific distributed drugs. Our cumulative measures of polypharmacy may overestimate the prevalence of simultaneous pharmacotherapy, due to inclusion of successive and non-chronic drugs in the observed time frame. We limited this by aggregating drugs by therapeutic class, correcting for switches in pharmacological class. Such cumulative definitions of polypharmacy are common and give comparable, clinically relevant, and as reliable results as other measures of polypharmacy[10,19,37].

Conclusion

In conclusion, ACHD patients used both more cardiovascular and non-cardiovascular medication compared to the general population, with polypharmacy in 30% of ACHD versus just 15% of referents. Polypharmacy was even common in mild CHD at young ages. We identified different medication patterns, that could be taken into account to help target therapies and trials in this heterogeneous population. As patients with polypharmacy had a four-fold higher risk of death and adverse drug events, daily clinical care of ACHD patients must include regular evaluation of their medication regimen, particularly in case of polypharmacy. Further clinical trials to investigate risks and benefits of pharmacotherapy remain needed to come to more evidence-based treatment in this population.

Acknowledgements

The authors thank all CONCOR participants, Lia Engelfriet, and Sylvia Mantels. This work was carried out in the context of the Parelsnoer Institute (part of and funded by the Dutch Federation of University Medical Centers). Results are based on calculations by the Amsterdam UMC – University of Amsterdam, using non-public microdata from Statistics Netherlands, which are accessible for statistical and scientific research under certain conditions.

Funding

This work was supported by the Dutch Heart Foundation [CVON 2014-18 project CONCOR-genes] and the Amsterdam University Fund [8532].

Conflict of interest

B.J.M.M. and B.J.B. report grants from Actelion Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer, and Daiichi Sankyo outside this work.

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Supplementary table 1: Coding of drug classes according to the Anatomical Therapeutic Chemical (ATC) classification system.

ATC code		Description	Includes the following (3rd or 4th level of ATC classification)	ATC code		Description	Includes the following (3rd or 4th level of ATC classification)
1st	2nd			1st	2nd		
A		**Alimentary tract and metabolism**		**C**		**Cardiovascular system**	
A	01	Stomatological preparations	Local oral treatments	C	01	Cardiac therapy	Cardiac glycosides (i.a. digitalis), antiarrhythmics, cardiac vasodilators (i.a. nitrates)
A	02	Drugs for acid related disorders	Antacids and drugs for peptic ulcer disease (i.a. proton-pump inhibitors)	C	02	Antihypertensives	Antiadrenergic agents
A	03	Drugs for functional gastrointestinal disorders	Antispasmodics, anticholinergics	C	03	Diuretics	Thiazides, sulfonamides, potassium-sparing diuretics
A	04	Antiemetics & antinauseants		C	04	Peripheral vasodilators	
A	05	Bile and liver therapy		C	05	Vasoprotectors	Local treatment of hemorrhoids and varices
A	06	Drugs for constipation		C	07	Beta blocking agents	
A	07	Antidiarrheals, intestinal antiinflammatory/ antiinfective agents		C	08	Calcium channel blockers	
A	08	Antiobesity preparations excl. diet products		C	09	Agents acting on renin-angiotensin system	ACE inhibitors, angiotensin II receptor blockers
A	09	Digestives, incl. enzymes		C	10	Lipid modifying agents	i.a. Statins
A	10	Drugs used in diabetes	Insulines, blood glucose lowering drugs	**D**		**Dermatologicals**	
A	11	Vitamins		D	01	Antifungals for dermatological use	
A	12	Mineral supplements	i.a. potassium, calcium	D	02	Emollients and protectives	
A	14	Anabolic agents for systemic use		D	03	Preparations for treatment of wounds and ulcers	
A	16	Other alimentary tract and metabolism products	Amino acids, enzymes	D	04	Antipruritics, incl. antihistamines, anaestetics, etc.	
B		**Blood and blood forming organs**		D	05	Antipsoriatics	
B	01	Antithrombotic agents	Platelet aggregation inhibitors, anticoagulants (vitamin K antagonists, non-vitamin K antagonists)	D	06	Antibiotics and chemotherapeutics for dermatoligical use	
B	02	Antihemorrhagics	i.a. vitamin K, other coagulation factors	D	07	Corticosteroids, dermatiological preparations	
B	03	Antianemic preparations	Iron preparation, vitamin B12 and folic acid	D	08	Antiseptics and disinfectants	
B	05	Blood substitutes and perfusion solutions		D	09	Medicated dressings	
B	06	Other hematological agents		D	10	Anti-acne preparations	
				D	11	Other dermatological preparations	
G		**Genito urinary system and sex hormones**		**M**		**Musculo-skeletal system**	
G	01	Gynaecological antiinfectives and antiseptics		M	01	Anti-inflammatory and antirheumatic products	Non-steroidal anti-inflammatory drugs (NSAIDs), excluding aspirin

ATC code 1st	2nd	Description	Includes the following (3rd or 4th level of ATC classification)
G	02	Other gynaecologicals	Uterotonics, intrauterine contraceptives
G	03	Sex hormones and modulators of the genital system	Hormonal contraceptives, androgens, estrogens, progesterons
G	04	Urologicals	i.a. drugs used in prostatic hypertrophy
H		**Systemic hormonal preparations, excl. sex hormones and insulins**	
H	01	Pituary and hypothalamic hormones and analogues	
H	02	Corticosteroids for systemic use	
H	03	Thyroid therapy	Thyroid hormones, antithyroid drugs iodine therapy
H	04	Pancreatic hormones	Glucagon
H	05	Calcium homeostasis	Parathyroid hormones, anti-parathyroid drugs
J		**Antiinfectives for systemic use**	
J	01	Antibacterials for systemic use	
J	02	Antimycotics for systemic use	
J	04	Antimycobacterials	
J	05	Antivirals for systemic use	
J	06	Immune sera and immunoglobulins	
J	07	Vaccines	
L		**Antineoplastic and immunomodulating agents**	
L	01	Antineoplastic agents	
L	02	Endocrine therapy	
L	03	Immunostimulants	
L	04	Immunosuppressants	
M	02	Topical products for joint and muscular pain	
M	03	Muscle relaxants	
M	04	Antigout preparations	
M	05	Drugs for treatment of bone disease	Bisphosphonates
M	09	Other drugs for disorders of the musculo-skeletal system	
N		**Nervous system**	
N	01	Anesthetics	
N	02	Analgesics	Opioids, aspirin, antimigraine drugs
N	03	Antiepileptics	
N	04	Anti-parkinson drugs	
N	05	Psycholeptics	Antipsychotics, anxiolytics, hypnotics, sedatives
N	06	Psychoanaleptics	Antidepressants, psychostimulants, anti-dementia drugs
N	07	Other nervous system drugs	Parasympathicomimetics, drugs used in addictive disorders, antivertigo preparations
P		**Antiparasitic products, insecticides and repellents**	
P	01	Antiprotozoals	
P	02	Anthelmintics	
P	03	Ectoparasiticides, incl. scabicides, insecticides and repellents	

ATC code		Description	Includes the following (3rd or 4th level of ATC classification)
1st	2nd		
R		**Respiratory system**	
R	01	Nasal preparations	Topical and systemic nasal decongestants
R	02	Throat preparations	Local antiseptics, antibiotics, anesthetics
R	03	Drugs for obstructive airway diseases	Inhalants (adrenergics, corticosteroids), systemic adrenergics
R	05	Cough and cold preparations	
R	06	Antihistamines for systemic use	
R	07	Other respiratory system products	
S		**Sensory organs**	
S	01	Ophtalmologicals	Local ocular drugs including anti-infectives, antiallergics, corticosteroids, antiglaucoma drugs
S	02	Otologicals	Ear drops including anti-infectives, corticosteroids, analgesics
S	03	Ophtalmological and otological preparations	
V		**Various**	
V	01	Allergens	
V	03	All other therapeutic products	i.a. drugs for treatment of hyperkalemia, hypoglycaemia, antidotes
V	04	Diagnostic agents	
V	06	General nutrients	
V	07	All other non-therapeutic products	i.a. plasters, diluting agents
V	08	Contrast media	
V	09	Diagnostic radiopharmaceuticals	
V	10	Therapeutic radiopharmaceuticals	
V	20	Surgical dressings	

First and second level of the Anatomical Therapeutic Chemical classification code.
Abbreviations: ACE, angiotensin converting enzyme; ATC, anatomical therapeutic chemical; i.a.; among others.

SUPPLEMENTARY METHODS:

Derivation of the full study cohort

CONCOR patients

For this study, CONCOR was linked to the Municipal Personal Records Database (MPRD) of Statistics Netherlands. The MPRD is a longitudinal registry containing all registered Dutch residents since 1995. CONCOR patients were identified in the MPRD by Statistics Netherlands using full postal code (4 digits, 2 letters), sex, and birthdate as the linkage key. Patients thus uniquely identifiable got an identification number, corresponding to unique persons in the Dispensed Drug Register (DDR) and Cause of Death Register (CDR). Data of the DDR and CDR were available for the years 2006-2014.

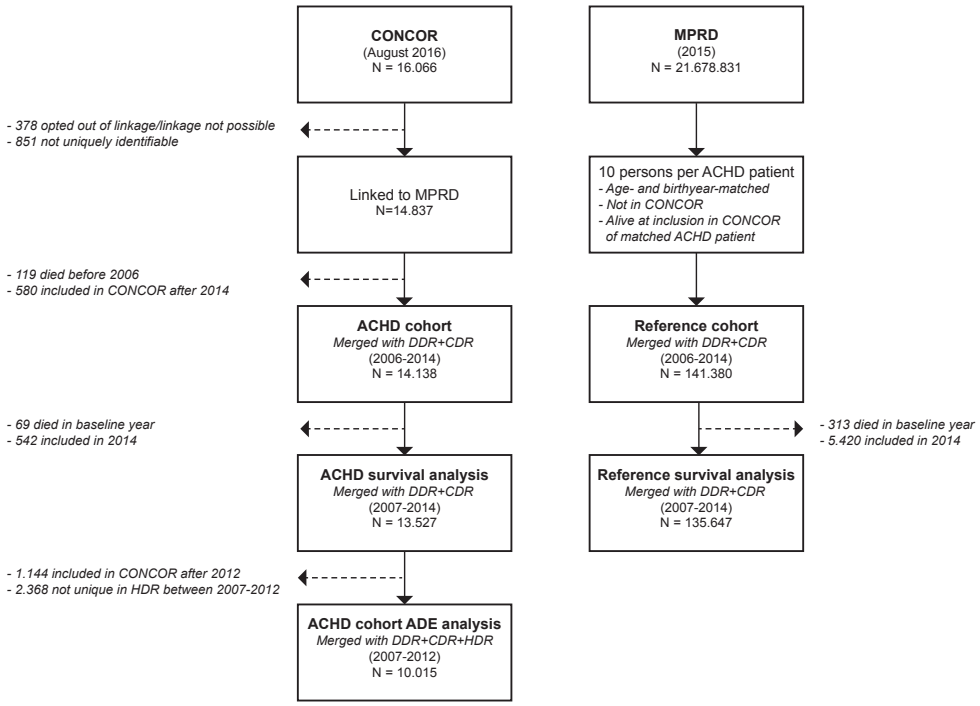
Supplementary figure 1 shows the derivation of the study cohort. Of 16,066 patients included in CONCOR at time of linkage, 378 (2.4%) had opted out of, or had no registered postal code for linkage to external registries; 851 (5.3%) were not unique on the MPRD linkage key. Of the 14,837 patients successfully linked to the MPRD, 119 had died before 2006 and 580 were included after 2014. The ACHD cohort for medication analyses therefore consisted of 14,138 patients. For survival analyses, an additional 611 patients were excluded (see Methods section in the manuscript).

Additionally, the Hospital Discharge Register (HDR) was used for analyses on hospitalizations for adverse drug events (ADE). Data of the HDR were available for the years 2007-2012. In the HDR, MPRD-unique persons may lose unicity on the linkage key at any time in the study-period, as the HDR is linked to the MPRD using 4-digit postal code, sex and birthdate. A total of 10,015 patients were included in analyses regarding hospitalizations for ADE.

Matched reference subjects

For every ACHD patient, ten sex- and birthyear-matched persons from the MPRD were selected to create an age- and sex-matched reference cohort from the general Dutch population (Supplementary figure 1). Exclusion criteria for referents included being included in the CONCOR-registry, having died before inclusion of the matched ACHD patient, and having emigrated during follow-up of the matched ACHD patient. For referents fulfilling any of the exclusion criteria, new referents were randomly selected from the MPRD until ten referents per patient were available.

Supplementary figure 1: Derivation of the ACHD and reference cohorts.



Abbreviations: ACHD, adult congenital heart disease; ADE, adverse drug event; CDR, Cause of Death Register; DDR, Dispensed Drug Register; HDR, Hospital Discharge Register; MPRD, Municipal Personal Records Database.

Supplementary table 2: Categorization of main congenital heart defect by severity.

Severity	Primary CHD lesion	Definition of EPCC code	EPCC code
Severe CHD			
	Functionally univentricular heart	Tricuspid atresia	06.01.01
		Functionally univentricular heart	01.01.22
		Double inlet LV	01.04.04
		Double inlet RV	01.04.03
	Transposition complex	Complete transposition of great arteries (IVS)	01.01.02
		Discordant VA connections (TGA)	01.05.01
		Congenitally corrected transposition of great arteries	01.01.03
	Double outlet right ventricle	Double outlet RV	01.01.04
		Double outlet RV - transposition type	01.01.18
		Double outlet RV - Fallot type	01.01.17
		Double outlet RV - with non-committed VSD	01.01.19
	Pulmonary atresia	Pulmonary atresia + VSD (including Fallot type)	01.01.06
		Pulmonary atresia + intact ventricular septum	01.01.07
		Pulmonary atresia + VSD + 'MAPCA'(s)	01.01.25
		Pulmonary atresia	09.05.11
	Other severe CHD	Common arterial trunk	09.01.01
		Total mirror imagery (atrial situs inversus)	03.01.03
Moderate CHD			
	AVSD	AVSD: isolated atrial component (primum ASD)	06.06.01
		AVSD: atrial & ventricular components (complete)	06.06.09
		Atrioventricular septal defect	06.06.00
		AVSD: isolated ventricular component	06.06.08
	Aortic valve/ LVOT lesion	Marfan syndrome	14.02.17
		Subaortic stenosis due to fibromuscular shelf	07.09.03
		Supravalvar aortic stenosis	09.16.00
		LV outflow tract obstruction	07.09.01
		Subaortic stenosis	07.09.00
		Ascending aorta abnormality	09.16.10
	Aortic coarctation	Aortic coarctation	09.29.01
		Interrupted aortic arch	09.29.31
		Aortic arch hypoplasia (tubular)	09.29.11
		Aortic arch abnormality	09.28.00
	Mitral lesion	True cleft of mitral valve	06.02.36
	Other left-sided CHD	Cor triatriatum (divided left atrium)	05.02.01
	ASD (non-secundum type)	Sinus venosus ASD	05.05.00
		Common atrium (virtual absence of atrial septum)	05.06.01
		Interatrial communication (ASD) through coronary sinus orifice	05.05.03
	VSD (multiple)	Multiple VSDs	07.15.04
	Aorto-pulmonary window	Aortopulmonary window	09.04.01
	Tetralogy of Fallot	Tetralogy of Fallot	01.01.01
		Absent pulmonary valve syndrome – Fallot type	09.05.25
		RV outflow tract obstruction	07.05.01
	Pulmonary valve/ RVOT lesion (non-ToF)	Supravalvar pulmonary trunk stenosis	09.07.13
		Pulmonary valvar abnormality	09.05.00
		Subpulmonary stenosis	07.05.30
	Ebstein's anomaly	Ebstein's malformation of tricuspid valve	06.01.34
	Other CHD	Double chambered RV	07.03.01
		Partially anomalous pulmonary venous connection(s)	04.07.01
		Totally anomalous pulmonary venous connection	04.08.05
		Coronary fistula	09.45.01
		Anomalous origin of coronary artery from pulmonary artery	09.41.01
		Partially anomalous pulmonary venous connections: Scimitar syndrome	01.01.16

Severity	Primary CHD lesion	Definition of EPCC code	EPCC code
		Coronary artery: anomalous aortic origin/course	09.42.00
		Coronary arterial abnormality	09.46.00
		Arteriovenous fistula	09.19.01
		Coronary sinus abnormality	04.04.00
		Pulmonary arteriovenous fistula	09.19.05
Mild CHD			
	Aortic valve/ LVOT lesion	Bicuspid aortic valve	09.15.22
		Aortic valvar stenosis - congenital	09.15.01
		Aortic regurgitation - congenital	09.15.07
		Aortic valvar abnormality	09.15.00
		Ascending aorta dilation	09.16.09
		Aortic valvar stenosis	09.15.13
	Mitral defect	Mitral valvar prolapse	06.02.35
		Mitral valvar stenosis - congenital	06.02.07
		Mitral regurgitation - congenital	06.02.25
		Mitral valvar abnormality	06.02.00
		Supravalvar mitral ring	05.02.02
	Other left-sided CHD	Double aortic arch	09.28.09
		Right aortic arch	09.28.15
		LA abnormality	05.02.00
	VSD	VSD	07.10.00
		Perimembranous VSD	07.10.01
		Muscular VSD	07.11.01
		Subarterial VSD	07.12.00
		Doubly committed subarterial VSD	07.12.01
		Inlet VSD	07.14.05
	ASD	ASD within oval fossa (secundum)	05.04.02
		ASD	05.04.01
	PDA	Patent arterial duct (PDA)	09.27.21
	Pulmonary valve/ RVOT lesion (non-ToF)	Pulmonary valvar stenosis - congenital	09.05.04
		Pulmonary stenosis	09.05.92
		Peripheral pulmonary arterial stenoses - at/beyond hilar bifurcation	09.10.06
		Pulmonary trunk (MPA) abnormality	09.07.00
		Pulmonary regurgitation - congenital	09.05.22
	Other right-sided CHD	Tricuspid valvar abnormality	06.01.00
		RA abnormality	05.01.00
		Tricuspid regurgitation - congenital	06.01.25
	Other mild CHD	Congenital complete heart block	11.06.16
		Dextrocardia: heart predominantly in right hemithorax	02.01.02
		Aneurysm of membranous septum	07.20.01
		Left SVC persisting to coronary sinus	04.01.01
		Superior caval vein abnormality	04.01.00

In CONCOR, diagnoses are coded using the EPCC[1]. In patients with multiple CHDs, the most severe defect is coded as the main CHD, according to a consensus-based classification[2].

Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; EPCC, European Paediatric Cardiac Code; IVS, intact ventricular septum; LA, left atrial; LV, left ventricle; LVOT, left-ventricular outflow tract; MAPCA, major aortopulmonary collateral artery; MPA, main pulmonary artery; PDA, patent ductus arteriosus; RA, right atrial; RV, right ventricle; RVOT, right-ventricular outflow tract; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; VA, ventriculoarterial; VSD, ventricular septal defect

Supplementary table 3: ATC codes of non-chronic drugs, excluded for sensitivity analysis.

ATC code		Description	Includes the following (3rd or 4th level of ATC classification)
1st	2nd		
B	05	Blood substitutes and perfusion solutions	
D	02	Emollients and protectives	
D	08	Antiseptics and disinfectants	
D	09	Medicated dressings	
J	01	Antibacterials for systemic use	
J	07	Vaccines	
P	01	Antiprotozoals	
P	02	Anthelmintics	
P	03	Ectoparasiticides, incl. scabicides, insecticides and repellents	
V	01	Allergens	
V	03	All other therapeutic products	I.a. drugs for treatment of hyperkalemia, hypoglycaemia, antidotes
V	04	Diagnostic agents	
V	06	General nutrients	
V	07	All other non-therapeutic products	I.a. plasters, diluting agents
V	08	Contrast media	
V	09	Diagnostic radiopharmaceuticals	
V	10	Therapeutic radiopharmaceuticals	
V	20	Surgical dressings	

For sensitivity analysis to test the influence of non-chronic drugs on the cumulative definition of polypharmacy, these drug types were excluded.
Abbreviations: ATC, anatomical therapeutic chemical; i.a., among others.

Supplementary table 4: Baseline characteristics.

	All patients N=14,138	Mild CHD N=8,126	Moderate CHD N=4,757	Severe CHD N=1,255
Age at inclusion, years	35 (24-48)	38 (27-51)	34 (23-46)	25 (21-33)
Male	6969 (49)	3748 (46)	24930 (52)	7280 (58)
Congenital heart defects				
Ventricular septal defect	2329 (16)	2306 (28)	23 (0.5)	
Atrial septal defect	2284 (16)	2077 (26)	207 (4)	
Bicuspid aortic valve	1435 (10)	1535 (18)		
Left ventricular outflow tract obstruction	945 (7)	582 (7)	363 (8)	
Right ventricular outflow tract obstruction	1076 (8)	1022 (13)	54 (1)	
Patent ductus arteriosus	337 (2)	337 (4)		
Coarctation of the aorta	1402 (10)		1402 (30)	
Tetralogy of Fallot	1103 (8)		1103 (23)	
Marfan syndrome	530 (4)		530 (11)	
pAVSD	429 (3)		429 (9)	
cAVSD	214 (2)		214 (5)	
Ebstein's anomaly	211 (1)		211 (4)	
Functionally univentricular heart	202 (1)			202 (16)
Transposition of the great arteries	563 (4)			563 (45)
ccTGA	136 (1)			136 (11)
Double outlet right ventricle	119 (1)			119 (10)
Pulmonary atresia	201 (1)			201 (16)
Other	622 (4)	367 (5)	221 (5)	34 (3)

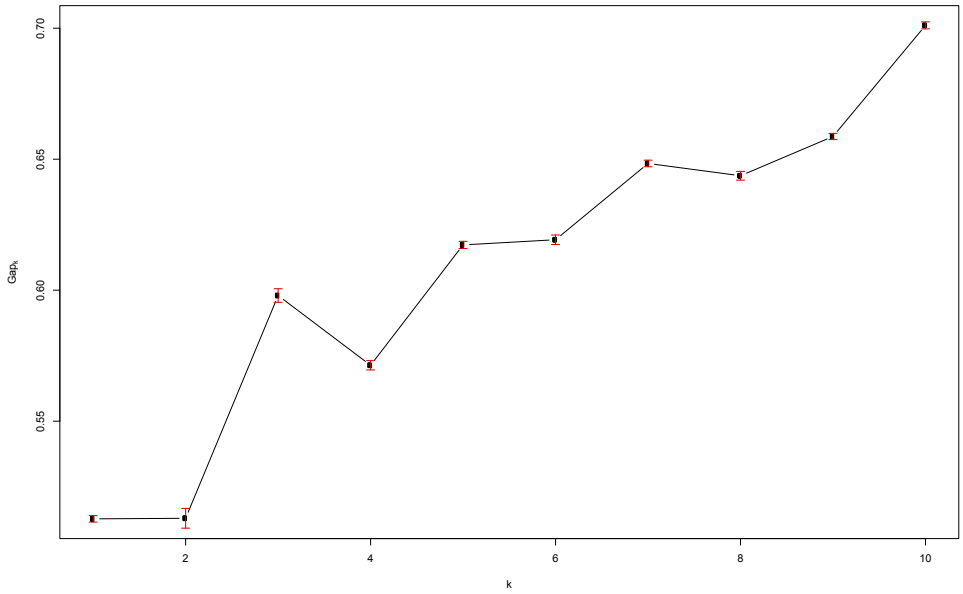
Data are presented as n (%) and median (interquartile range). Abbreviatons: ACHD, adult congenital heart disease; cAVSD, complete atrioventricular septal defect; ccTGA, congenitally corrected transposition of the great arteries; CHD, congenital heart defect; IQR, interquartile range; pAVSD, partially atrioventricular septal defect.

Supplementary table 5: Most common drugs in patients and referents with polypharmacy.

ACHD patients with polypharmacy at inclusion n=4,037		Matched referents with polypharmacy at inclusion n=18,878	
Age at inclusion, years	46 (33-59)		49 (35-62)
Male sex	40%		43%
Top 5 most dispensed drugs			
1. Systemic antibiotics	64%	1. Systemic antibiotics	55%
2. Antithrombotics	54%	2. Anti-inflammatory and antirheumatic products	47%
3. β-blockers	46%	3. Drugs for acid related disorders	39%
4. RAAS inhibitors	41%	4. Dermatological corticosteroids	33%
5. Drugs for acid related disorders	37%	5. Lipid modifiers	27%

Most common drug classes at year of inclusion of subjects with polypharmacy during year of inclusion. Abbreviations: ACHD, adult congenital heart disease; RAAS, renin-angiotensin-aldosterone-system.

Supplementary figure 2: Gap statistic analysis for the identification of the optimal number of clusters.



Supplementary table 6: Comparison of medication and clinical characteristics between clusters.

	Cluster 1 *"cardio-vascular"* n = 8,317, %	Cluster 2 *"low medication use"* n = 3,501, %	Cluster 3 *"comorbid-ity"* n = 2,320, %	p-value
Medication use				
Medication group[a]				
Alimentary tract	26.7	13.3	23.6	<0.001
Blood & blood forming organs	38.9	10.1	8.6	<0.001
Cardiovascular	50.6	5.6	36.3	<0.001
Dermatologicals	15.5	21.6	49.1	<0.001
Genito-urinary system & sex hormones	10.3	52.6	8.0	<0.001
Systemic hormonal preparations	7.4	4.7	11.7	<0.001
Antiinfectives for systemic use	29.9	58.9	45.6	<0.001
Antineoplastic & immunomodulating agents	1.4	1.4	0.4	<0.001
Musculo-skeletal system	12.0	26.8	38.3	<0.001
Neurological	18.1	15.1	45.3	<0.001
Nervous system	0.7	3.6	0.3	<0.001
Respiratory system	22.3	20.9	31.5	<0.001
Sensory system	12.7	11.3	15.3	<0.001
Amount of medication types				<0.001
0	29.0	0.0	0.0	
1 - 4	40.0	82.3	63.8	
Polypharmacy (≥ 5)	31.0	17.7	36.2	
Patient characteristics				
Age, years (IQR)	38 (26-52)	28 (22-39)	37 (25-48)	<0.001
Male	57.1	29.8	50.6	<0.001
CHD severity				
Mild	55.8	60.7	58.5	<0.001
Moderate	34.6	30.9	34.5	<0.001
Severe	9.6	8.5	7.0	<0.001
Main diagnosis (most common)				
Ventricular septal defect	14.5	20.4	17.6	<0.001
Atrial septal defect	17.2	14.1	15.6	<0.001
Bicuspid aortic valve	11.2	7.9	9.9	<0.001
Coarctation of the aorta	10.4	8.8	10.1	0.030
Tetralogy of Fallot	7.5	7.8	8.8	0.15
Right ventricular outflow tract obstruction	6.0	10.8	8.5	<0.001
Left ventricular outflow tract obstruction	6.7	7.2	5.9	0.14
Transposition of the great arteries	4.1	4.1	3.5	0.42
Marfan syndrome	4.7	1.3	4.0	<0.001
Partial atrioventricular septal defect	3.0	3.4	2.6	0.23
Patent ductus arteriosus	2.1	2.6	3.0	0.031
Complete atrioventricular septal defect	1.3	2.0	1.4	0.025
Ebstein's anomaly	1.6	1.3	1.5	0.40
Functionally univentricular heart	1.8	1.0	0.9	<0.001
Genetic syndrome with cardiac involvement[b]	5.1	6.3	6.6	0.003
Down's syndrome	2.8	2.7	4.1	0.003

[a]: Medication groups are stated per cluster at the anatomical level of the Anatomical Therapeutic Chemical classification (Supplementary table 1). [b]: excluding Marfan syndrome.

Supplementary references

1. Franklin RC, Anderson RH, Daniels O, et al. Report of the Coding Committee of the Association for European Paediatric Cardiology. *Cardiology in the young*. 2002;12(6):611-618.
2. Warnes CA, Liberthson R, Danielson GK, et al. Task force 1: the changing profile of congenital heart disease in adult life. *Journal of the American College of Cardiology*. 2001;37(5):1170-1175.