Cardiology in the Young

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Trends in prescription of cardiovascular drugs to children in relation to prevalence of CHD from 1999 to 2016

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Abstract

Introduction: Owing to massive improvements in the diagnostics and surgery of children with CHD, fatality has decreased substantially. As more children with CHD survive from infancy into later childhood, more will need medication for chronic heart failure. However, surprisingly little is actually known about which drugs are being used to treat children with CHD, and whether prescription rates and CHD prevalence have changed over time. *Objective:* The objective of this study was to assess the total prescription of cardiovascular drugs to children during an 18-year period and to assess concomitant CHD prevalence. *Methods:* All prescription data of cardiovascular drugs to children aged 0–19 years were extracted from publicly available databases in Norway and Denmark from 1999 to 2016. This was coupled with data on CHD prevalence and birth rates. *Results:* The number of defined daily doses of cardiovascular drugs prescribed to children doubled in the study period. This was because of an increased use of beta blockers, angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, and anti-arrhythmic agents. The use of some classes of drugs was significantly reduced over time. The prevalence of CHD remained constant in both countries – 80 per 10,000 births. *Conclusion:* We show that there is an increase in the overall prescription of cardiovascular drugs to children. Beta blockers, angiotensin-converting enzyme/angiotensin receptor blockers, and anti-arrhythmics account for the largest increase. Birth rates decreased or remained constant together with CHD prevalence, suggesting that the increased use of cardiovascular drugs reflected increased prescription per patient, rather than more patients receiving a constant amount of drugs.

CHD represent a broad spectrum of disease, which spans from minor subclinical anomalies to severe defects that are incompatible with life. The incidence of CHD is known to vary across geographical regions and over time. From the 1930s through to the 1990s, a substantial increase in CHD prevalence was observed. Interestingly, the increase over time was not constant (per unit time) but rather S-shaped; that is it increased from 1930 to 1960 (0.6 to 5.3 per 10,000), followed by a plateau phase, and a new sharp increase from the late 1970s until the mid 1990s where it stabilised around 9.1 per 10,000.[1] Routine use of echocardiography has been shown to increase the detection of minor anomalies,[2] and it is generally agreed upon that some of the increased CHD prevalence may well reflect advances in diagnostics rather than true changes in prevalence.[1,3] Concurrently, surgical and pharmacological therapies have substantially reduced fatality among children with CHD.[4,5] Furthermore, deaths from CHD have shifted away from infants and towards adults, with an increasing age at death.[6] The reduced fatality rate from CHD has been brought along by more specialised care for both surgical and non-surgical admissions,[5] but the hospitalisation rate for paediatric chronic heart failure has remained stable.[7] Although massive improvements in management of chronic heart failure in adults have been achieved,[8] data on optimal management of paediatric chronic heart failure are lagging. This has prompted some authors to suggest that there is a state of "nihilism" regarding paediatric chronic heart failure therapy such that treatment known to be effective in adults is withheld to children.[9] To our knowledge, no study has addressed prescription of cardiovascular drugs to children, except in children admitted with acute decompensated heart failure.[10] Owing to a paucity of data on prescription of cardiovascular drugs to children, it is, in our opinion, difficult to argue a case of either under- or over-treatment.

We sought to examine trends in prescription of cardiovascular drugs to children in two Nordic countries and correlate this with the prevalence of CHD over an 18-year period.

Methods

Data were included in Norway from 1 January, 2004 to 31 December, 2016 and in Denmark from 1 January, 1999 to 31 December, 2016. We retrieved data on the use of cardiovascular

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drugs according to the Anatomical Therapeutic Chemical classification system from a publicly accessible database in Norway[11] and Denmark.[12] The registers include drug sale from pharmacies in defined daily doses. Defined daily dose is a World Health Organization-defined statistical measure of drug consumption. It represents the assumed average maintenance dose required by an adult taking the drug for its primary medical indication. We compiled data on the sale and use of the cardiovascular drug (Anatomical Therapeutic Chemical code: C03–C09) in defined daily doses. Data on cardiovascular drugs were divided into the following categories: C01A, cardiac glycosides (Digoxin); C01B, anti-arrhythmic drugs (Class I, III, IV); C03C and C03DA, diuretics; C07, beta blockers; C08D, selective calcium-channel blockers; C09, drugs affecting the renin–angiotensin system. Total sale of cardiovascular drugs was defined as follows: the total amount of defined daily doses sold by Norwegian and Danish pharmacies in the period. The sale therefore reflects prescription from both outpatient clinics at hospitals and from general practitioners. It does not include data on drugs used while the patients were admitted to hospital.[13] When extracting data from the Norwegian and Danish databases, we noted a slight discrepancy between the total defined daily doses prescribed of a given Anatomical Therapeutic Chemical code Fourth-level class of drugs (e.g. beta blockers) and the number we found by adding all Anatomical Therapeutic Chemical code Fifth-level drugs (e.g. metoprolol, atenolol etc.) in that class together. In all these instances, we have used the summed value for the Fifth level to account for the total Fourth-level prescriptions. All original data extracts are provided in the supplement along with detailed data analysis (Supplementary material S1).

All CHD prevalence data from Norway and Odense (Denmark) were accessed through the European Surveillance of Congenital Anomalies website[14] Both the Norway and Odense registry covers geographical defined areas and are thus not hospital based. Total annual number of births were accessed from Statistics Norway[15] and Statistics Denmark.[16]

CHD: all ICD-10 diagnosis Q20–Q26

Patent arterial duct (Q250) and patent foramen ovale (DQ211) were excluded if gestational age was < 37 weeks.

Severe CHD

Severe CHD was defined as all cases of common arterial truncus (Q200), transposition of great vessels (Q203), single ventricle (Q204), atrioventricular septal defect (Q212), Tetralogy of Fallot (Q213), pulmonary valve atresia (Q220), tricuspid atresia or stenosis (Q224), Ebstein's anomaly (Q225), hypoplastic right heart (Q226), aortic valve atresia or stenosis (Q230), hypoplastic left heart (Q234), coarctation of aorta (Q251), and total anomalous pulmonary vein return (Q262).

Calculation of prevalence rates

The total prevalence rate (TPR) was calculated as:

$$\text{TPR} = \text{No. cases (LB + FD + IA)} \,/\, \text{No. Births (live and still)}$$

where cases are the cases of congenital anomaly in population; LB the live born; FD the fetal deaths from 20 weeks gestation; IA the induced abortion or termination of pregnancy after prenatal diagnosis, at any gestational age; Birth (live and still) the all live and stillbirths in the population as declared on official birth registrations. Please note that, for Norway, data are available in the time period from 1 January, 1999 to 31 December, 2012 and in Denmark from 1 January, 1999 to 31 December, 2014.

Statistical analysis

Change in prevalence over time was analysed with a chi-square test for heterogeneity, divided into the trend component – "χ^2 test for trend" and the non-linear component – "χ^2 test for non-linear change". Changes in defined daily doses over time were analysed using linear regression. For all statistical tests, differences were considered significant at $p < 0.05$, but in order to correct for multiple testing a post-hoc Bonferroni was performed, which gave a new critical α of 0.04; i.e. only p-values below this α were considered significant. Calculations were performed using GraphPad Prism (GraphPad Software, San Diego, California, United States of America).

Results

Prescription of cardiovascular drugs

During the period, in both Norway and Denmark, the prescription of cardiovascular drugs to children and adolescents increased significantly – by 67% in Norway, that is 275–458 defined daily doses, $p < 0.0001$, and by 110% in Denmark, that is 235–493 defined daily doses, $p < 0.0001$, Fig 1. In both nations the trends in prescribed medication were similar. The specified prescription of drugs in both Denmark and Norway is shown in Table 1. Angiotensin-converting enzyme inhibitor therapy increased by

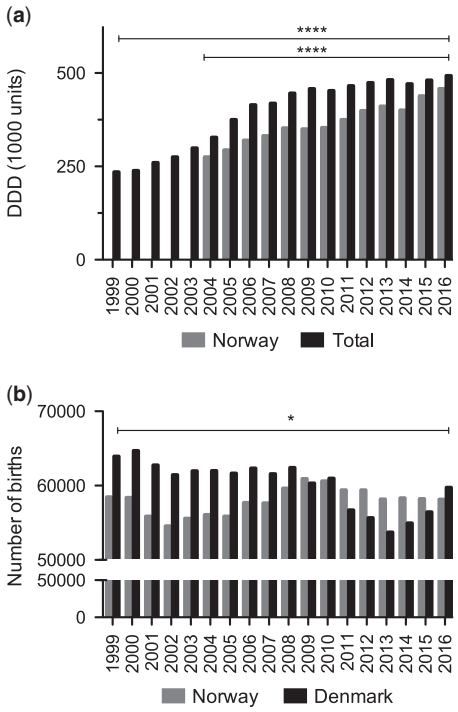

Figure 1. (*a*) Yearly prescription of all cardiovascular drugs to children (ages 0–19) in daily defined doses (DDD) for both Norway and Denmark. The observed increase in total prescription is statistically significant in both countries (****$p < 0.0001$). (*b*) Total annual number of births that occurred from 1999 to 2016. No significant change occurred in Norway, while the number of births decline by 6% in Denmark during the study period (*$p < 0.0001$).

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Table 1. Shown is the yearly total prescription of cardiovascular drugs to children (ages 0–19) from 1999 to 2016 in defined daily doses.

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Norwegian data																		
Glycosides						17	16	15	12	12	10	9	8	7	8	7	4	3****
Anti-arrhythmics						9	9	9	11	11	9	9	9	12	14	16	17	17***
Diuretics						46	42	47	45	49	45	48	46	50	53	45	46	49
Beta blocker						63	70	75	82	84	88	89	96	100	105	99	108	116****
Calcium blocker						3	5	4	3	4	3	3	4	4	3	4	3	2
ACE inhibitors						54	59	72	80	91	104	106	121	119	110	103	107	104****
ARB						16	26	35	38	45	50	47	57	60	53	66	87	87****
Total						275	294	320	332	353	350	354	375	399	411	401	439	458****
Danish data																		
Glycosides	11	11	11	10	10	8	9	6	5	4	3	3	3	4	3	2	2	1****
Anti-arrhythmics	1	3	2	3	2	1	1	3	3	4	3	3	2	2	4	5	5	4*
Diuretics	113	112	117	113	95	111	126	139	128	127	136	112	102	106	109	96	98	106
Beta blocker	65	58	65	71	79	85	97	100	101	106	110	108	126	125	118	113	120	121****
Calcium blocker	4	3	2	1	2	3	2	2	5	6	5	5	6	4	6	8	6	3*
ACE inhibitors	37	50	57	68	96	105	118	134	146	157	167	190	199	203	204	203	202	205****
ARB	4	2	6	9	15	15	22	31	31	42	34	32	28	30	38	44	48	53****
Total	235	239	260	275	299	328	375	415	419	446	458	453	466	474	482	471	481	493****

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers
Norwegian prescription data before 2004 are not available
Statistically significant changes during the study period: *$p < 0.05$, **$p < 0.005$, **$p < 0.0005$, ****$p < 0.0001$

52% in Norway ($p < 0.0001$) and by 454% ($p < 0.0001$) in Denmark. Enalapril was predominantly favoured in Norway, whereas in Denmark it was ramipril (Fig 2a and b). Angiotensin II receptor blocker prescription increased by 444% ($p < 0.0001$) in Norway and 1225% ($p < 0.0001$) in Denmark. In Norway, candesartan accounted for more than 85% of prescriptions, whereas in Denmark prescriptions were approximately equally divided among candesartan and losartan: 44 and 53%, respectively, Fig 2c and d. Beta-blocker therapy increased by 86% (both, $p < 0.0001$) in both countries. More than 70% of beta blockers used were either metoprolol or propranolol (Fig 2e–f). Prescription of anti-arrhythmic drugs increased by 100% ($p < 0.0005$) in Norway and 300% ($p < 0.0001$) in Denmark, whereas calcium-channel blockers remained constant in Norway and decreased by 33% ($p = 0.004$) in Denmark. The only class of drugs to be reduced in both countries were cardiac glycosides – that is by 399% in Norway ($p < 0.0001$) and by 1000% in Denmark ($p < 0.0001$). There were no statistically significant changes in prescription of diuretics in either Norway or Denmark. In both countries, furosemide and, to a less extent, spironolactone were most often prescribed (Fig 2g–h).

Live births

In Norway, the total number of live births remained stable around 58,000 in the study period. In Denmark, a slight decline occurred, from 63,943 in 1999 to 59,739 in 2016 ($p < 0.0001$), corresponding to a 6% reduction in birth rate (Fig 1).

Prevalence of CHD

In Norway, the total prevalence of CHD was 96 per 10,000 births (95% confidence interval: 104–88) in 1999 and 62 per 10,000 births (95% confidence interval: 68–56) in 2012; these change were not statistically significant. The total prevalence in Denmark in 1999 was 120 per 10,000 births (95% confidence interval: 120–68) and 71 per 10,000 births (95% confidence interval: 101–49) in 2014. The live-birth prevalence of CHD was not notably different from the total CHD prevalence in the study period for both Norway and Denmark (Fig 3).

Prevalence of severe CHD

In Norway, the prevalence was 20 per 10,000 births (95% confidence interval: 24–17) in 1999 and did not change significantly until 2012 – 22 per. 10,000 births (95% confidence interval: 26–19). In Denmark, the total prevalence in 1999 was 32 per 10,000 births (95% confidence interval: 50–19) and 9 per. 10,000 births (95% confidence interval: 23–3) in 2014; this change was not significant (Fig 3).

Discussion

From 1999 to 2016, the prescription of cardiovascular drugs to children roughly doubled, predominantly owing to increased prescription of beta blockers and angiotensin-converting-enzyme

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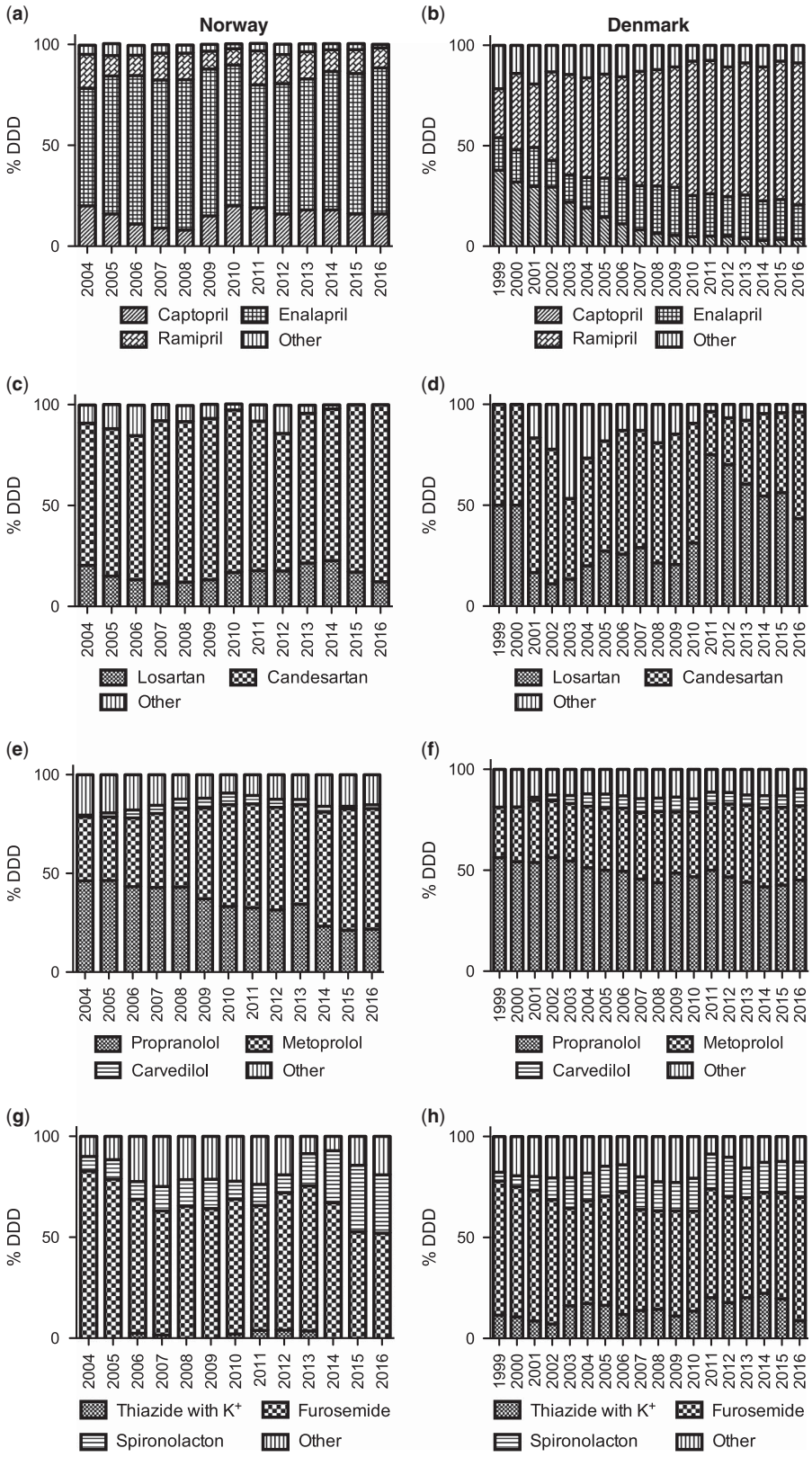

Figure 2. Overview of which ATC fifth level drugs were used for each pharmacological fourth level class of drugs in the study period for both Norway and Denmark. All values are in defined daily dosages (DDD). (*a* and *b*) Prescription of angiotensin-converting-enzyme inhibitors in both countries, note how enalapril was the most favoured. For Norway the category "Other" includes: lisinopril, perindopril, fosinopril, trandolapril, etc. For the Danish data the category "Other" includes: lisinopril, perindopril, quinapril, benazepin, etc. (*c* and *d*) Prescription data of angiotensin II receptor blockers, in Norway candesartan was almost exclusively prescribed whereas in Denmark both losartan and candesartan was used. For Norway the category "Other" includes: eprosartan, valsartan, irbesartan, telmisartan, etc. (*e* and *f*) Prescription of beta-blockers; propranolol (non-cardioselective β1- and β2-adrenergic blocker) and metoprolol (β1 selective blockers) were almost exclusively prescribed. For Norway the category "Other" includes: alprenolol, oxprenolol, pindolol, timolol, etc. For the Danish data the category "Other" includes: alprenolol, oxprenolol, pindolol, timolol, etc. (*g* and *h*) Diuretics prescribed in both countries. Furosemide was the most widely prescribed diuretic. Thiazide with K+ refers to bendroflumethiazide with potassium. For Norway the category "Other" includes: bendroflumethiazide, hydrochlorothiazide, trichlormethiazide, chlortalidone, etc. For the Danish data the category "Other" includes: bendroflumethiazide, hydroflumethiazide, hydrochlorothiazide, chlorothiazide, etc. For further details please see supplementary material S1.

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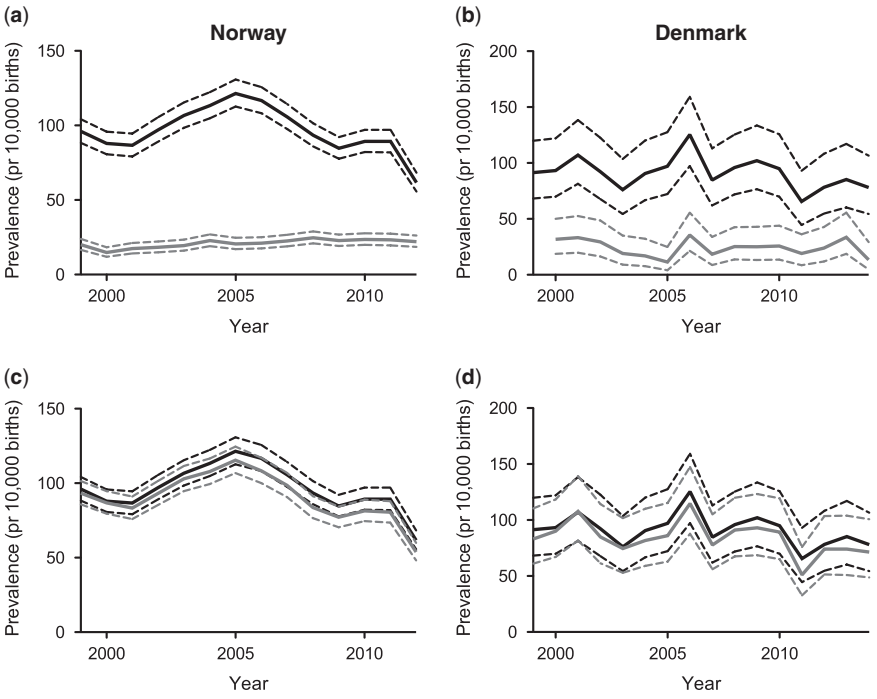

Figure 3. Total and live birth prevalence of CHD and severe CHD in both Norway (from 1 January 1999 to 31 December 2012) and Denmark (from 1 January 1999 to 31 December 2014). (*a*) The total prevalence (black) and prevalence of severe CHD (grey) in Norway. Although the prevalence of total CHD fluctuates, none of the observed changes over time are significant. (*b*) The total prevalence (black) and prevalence of severe CHD (grey) in Denmark. Due to the smaller number of births registered in the Danish registry the confidential intervals are notably wider than those from the Norwegian registry. (*c*) The total (black) and live birth prevalence (grey) of all CHD in Norway. Note that although the live birth prevalence is lower than the total prevalence throughout the study period there is only a marginal difference, which is not significant. (*d*) The total (black) and live birth prevalence (grey) of CHD in Denmark. As for Norway there is only a marginal not significant difference between these two. Dotted lines represent 95% confidence intervals.

inhibitors/angiotensin II receptor blockers, whereas CHD prevalence and birth rates remained constant or declined in both countries.

Currently, there are well-established guidelines for the treatment of heart failure in adults, but no equivalent consensus for children exists.[17] The most striking changes in prescription pattern in the two countries were the increased use of beta blockers and angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers. The prescription of beta blockers increased throughout the study period despite the fact that one of the few available randomized controlled trials (RCTs) on paediatric chronic heart failure (CHF) patients found that the beta-blocker carvedilol "did not significantly improve clinical heart failure outcomes in children and adolescents with symptomatic systolic heart failure".[18] This is in contrast to the COMET trial, which suggested a survival benefit of carvedilol as compared with metoprolol in adults with chronic heart failure.[19] However, there are a few caveats with regard to the study by Shaddy et al. that are worth mentioning. First, as pointed out by the authors, owing to low event rates of the composite end point, the trial may have been underpowered. Second, down-regulation of β_2-receptors in children with heart failure[20] might favour β_1-selective blockers, such as metoprolol and bisoprolol, compared with carvedilol, which blocks both β_1- and β_2-adrenergic receptors, and α_1-adrenergic receptors.[21] We show that the β_1-selective blocker metoprolol is one of the two most frequently prescribed beta blockers, the other being the non-cardioselective β_1- and β_2-adrenergic propranolol. It should be emphasised that the prescription databases do not contain information regarding drug indication; it is therefore possible that propranolol was prescribed for other conditions – i.e. infantile haemangioma and so on. Although no conclusive studies have been performed, beta blockers continue to be recommended as standard therapy in children.[21] The studies supporting the current guideline recommendation[17] of angiontension-converting-enzyme inhibitors are either observational[22] or based on RCTs performed in children with Duchenne muscle dystrophi – a condition known to cause heart failure over time owing to the absence of dystrophin.[23] Thus, the standard use of angiotensin-converting enzyme inhibitors is mainly based on experience from clinical trials in adults, which are not necessarily representative for the paediatric population. In both countries, the use of glycosides decreased significantly, a decline that began before the publication of a randomised controlled trial showing no benefit of digoxin to children with chronic heart failure owing to intracardiac left-to-right shunts.[24] The use of diuretics remained constant in both nations, although this has been recommended by some authors for the management of paediatric CHF.[25] A classic axiom of paediatrics is that *children are not small adults*,[26] but from the above discussion it would appear that we are treating them as such with regard to chronic heart failure. The paucity of valid paediatric chronic heart failure trials essentially forces clinicians to choose between pathways: either withhold drugs for children with chronic heart failure – drugs documented beyond reasonable doubt for adults – or extrapolate data from adult chronic heart failure trials to children and treat according to these, thus violating that old axiom. Our data would seem to suggest that more clinicians are opting for the latter option.

It is interesting to note that there was no significant difference in the total and live-birth prevalence of CHD in the study, suggesting that foetal diagnosis of CHD seldom leads to termination

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of pregnancy in these populations. A change in CHD prevalence could therefore not in itself account for the observed changes in prescription rates likely reflecting an increased prescription per patient, rather than more patients receiving a constant amount of drugs. In both Norway and Denmark, there was a tendency towards a decline in CHD prevalence in the last year for which data are available; missing data probably cause this – that is all cases for the final year have not been reported to the database yet.

An important limitation of this study is that the databases do not allow identification of prescription on the level of the individual patient. It is therefore not possible to asses exactly which diagnosis is driving the increased use of cardiovascular drugs.

In conclusion, the prescription of cardiovascular drugs to children has doubled, particularly beta blockers and angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers, whereas CHD prevalence has remained constant, suggesting that the increased use of cardiovascular drugs reflected increased prescription per patient, rather than more patients receiving a constant amount of drugs. Further studies are needed to determine whether this affects patient morbidity and mortality.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951118000951

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Conflicts of Interest. None.

Ethical standards. The study was conducted in full compliance with the Declaration of Helsinki (https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2008.pdf).

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