ORIGINAL RESEARCH

Twenty-Three-Year Trends in the Use of Potentially Nephrotoxic Drugs in Denmark

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Background: The occurrence of acute and chronic kidney diseases has been rising in the last decades. Although drug use is a common risk factor for impaired kidney function, changes in utilization of potential nephrotoxic drugs have received little attention. **Purpose:** To describe temporal trends in the utilization of potentially nephrotoxic drugs in Denmark between 1999 and 2021.

Methods: Specific drugs known or suspected to be nephrotoxic were identified in the literature. Data on the sold defined daily doses (DDDs) of potentially nephrotoxic drugs between 1999 and 2021 were retrieved using the Danish Register of Medical Product Statistics. Trends in sales of DDDs per 1000 inhabitants per day were tabulated and illustrated graphically.

Results: From 1999 to 2021, the total sale of all selected drugs increased from 286 to 457 DDDs per 1000 inhabitants per day. The overall sale reached a preliminary peak in 2012 with 449 DDDs per 1000 inhabitants per day and remained relatively stable thereafter until reaching an all-time high in 2021 with 457 DDDs per 1000 inhabitants per day. Contributing with the majority in volume, sales of drugs inhibiting the renin-angiotensin-aldosterone system (RAAS) increased dramatically throughout the period. The same was observed for acetaminophen, methotrexate, tacrolimus, and iodinated contrast dye. In contrast, the sales of diuretics, acetylsalicylic acid, and ciclosporin decreased during the last decade of the study period.

Conclusion: From 1999–2021 considerable changes in sales of potentially nephrotoxic drugs were observed. In general, the sales increased, in volume predominated by RAAS inhibiting drugs. This increase in sales of potential nephrotoxins could contribute to an increasing occurrence of kidney diseases.

Keywords: adverse events, nephrotoxins, drug utilization, acute kidney injury, kidney disease

Introduction

Drug use is a common risk factor for kidney disease, including acute kidney injury (AKI) and chronic kidney disease (CKD).^{1,2} These diseases are associated with an increased risk of short- and long-term mortality, prolonged hospital admission, and dependence on dialysis.³ The occurrence of kidney diseases has been rising during the last 20 years.^{4–7} The pathogenic mechanisms of drugs causing nephrotoxicity are diverse, and several drugs can cause nephrotoxicity by more than one pathogenic mechanism. These include, but are not limited to, altered intraglomerular hemodynamics, crystal nephropathy, inflammation, rhabdomyolysis, direct tubular cell toxicity, crystal nephropathy, chronic interstitial nephropathy, and interference with renal hemodynamics (Figure 1).^{1,8–19}

Recently, several Danish studies have examined changes in the utilization of different groups of drugs, generally demonstrating increasing use and sales. These include antithrombotic drugs,²⁰ antihypertensive drugs,²¹ statins,²² antidiabetic drugs,²³ antiarrhythmic drugs,²⁴ and opioids.²⁵ However, only a few population-based studies have examined changes in utilization of potentially nephrotoxic drugs.^{20,26–28} In the Nordic countries, the total sales of acetaminophen (paracetamol) increased from 2000 to 2015.²⁶ Between 1999 and 2014, the use of low-dose acetylsalicylic acid in Denmark increased before a slight decline after 2010.²⁰ Moreover, recent cohort studies have investigated the use among critically ill and in patients with chronic kidney disease, demonstrating widespread use of potential nephrotoxic drugs.^{27,28} To our knowledge, no previous studies have specifically examined trends in

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Figure I Mechanisms of drug-induced acute kidney injury. Inspired by Schetz et al.⁸ Abbreviations: ACE-I, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug.

the use of potentially nephrotoxic drugs in a nationwide, population-based setting. Such information would contribute to our understanding of changes in risk factors for kidney disease in the general population. Therefore, we examined temporal changes in the sales of selected potentially nephrotoxic drugs from 1999 to 2021 in Denmark.

Methods

Setting

We conducted this study in Denmark between 1 January 1999 and 31 December 2021. In 2021 Denmark had a population of approximately 5.8 million inhabitants.²⁹ All Danish inhabitants have equal access to universal tax-supported health-care including hospitals, general practitioners, and partial reimbursement for prescribed drugs.

Data Source

Information on the sale of potentially nephrotoxic drugs according to the Anatomical Therapeutic Chemical (ATC) classification system is available from the publicly accessible Danish database Medical Statistics (MEDSTAT).³⁰ Based on the Register of Medical Product Statistics,³¹ the database has provided aggregated statistics on annual drug sales from the Danish primary and hospital sectors since 1996 and 1997, respectively.³² Registration includes both prescription and non-prescription drug sales in defined daily doses (DDD), a statistical measure of drug consumption defined by WHO. DDD represents the assumed average maintenance dose for the main indication in adults, thus facilitating comparison of trends in drug use, independent of prices or pack sizes. Reporting of drug sales to the Register of Medical Product Statistics is mandatory and data from Medical Statistics are considered valid and complete from 1999 onwards.³² However, certain formulations containing ATC groups J01 (antibacterials for systemic use) and L01 (antineoplastic drugs) were incompletely recorded until 2011. Therefore, trends in the sales of these drugs before 2012 should be interpreted with caution.³³

Drugs Altering Intraglomerular Hemodynamics	Drugs Associated with Chronic Interstitial Nephropathy	Drugs Associated with Crystal Nephropathy	Drugs Associated with Tubular Cell Toxicity	Diuretics
ACE-I	Acetylsalicylic acid	Sulfonamides	Amphotericin	Thiazides
C09A	B01AC06	JOIEB	A01AB04	C03A
С09В	Acetaminophen	JOIEC	J02AA01	Low ceiling
ARB	N02BE01	JOIEE	Aminoglycosides	(except thiazides)
С09С	N02BE51	Aciclovir	JOIG	С03В
C09D	Lithium	J05AB01	Ciclosporin	Loop diuretics
NSAIDs	N05AN01	Methotrexate	L04AD01	C03C
M01A (except M01AX05)		LOIBAOIª	Tacrolimus	Potassium sparing
		L04AX03	L04AD02	diuretics
		Cisplatin ^b	Contrast dye	C03D
		LOIXAOI	V08A	C03E

Table I Selected Potentially Nephrotoxic Drugs with ATC Codes

Notes: ^aL01BA01 was reported in grams, which were converted to DDD assuming a methotrexate DDD of 2.5 mg (which is the value for L04AX03); ^bThe amount of cisplatin sold (grams per 1000 inhabitants per day) was incompletely recorded until 2011.

Abbreviations: ACE-I, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; NSAID, non-steroidal anti-inflammatory drug.

Statistical Analysis

Trend in sales (DDDs) of different groups of potentially nephrotoxic drugs were illustrated graphically. The selection and grouping of drugs altering hemodynamics, drugs associated with chronic interstitial nephropathy, crystal nephropathy, tubular cell toxicity, and diuretics, was adapted from Naughton et al¹ (Table 1). Glucosamine (ATC: M01AX05) was excluded from the main group of non-steroidal anti-inflammatory drugs (NSAID) (ATC: M01A), because it does not share pharmacodynamic properties with other NSAIDs.³⁴ DDDs were not available for cisplatin (ATC: L01XA01) and radio-contrast. As the sold amount of cisplatin was too small to assess from MEDSTAT, total sales were obtained through correspondence with the Danish Health Data Authority and grams sold per 1000 inhabitants per day were calculated using census statics from Statistics Denmark.^{29,30} Radiocontrast was limited to contrast dyes containing iodine (ATC: V08A).

Results

During 1999–2021, the aggregated annual sales of all selected drugs increased from 286 to 457 DDDs per 1000 inhabitants per day (Figure 2 and Table 2). The overall use reached a preliminary peak in 2012 with 449 DDDs per 1000 inhabitants per day and remained relatively stable hereafter until reaching an all-time high in 2021.

Drugs Altering Intraglomerular Hemodynamics

Drugs altering intraglomerular hemodynamics comprised the largest subgroup from 2004 and onwards and included angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and NSAIDs (Figure 2). Predominated by ACE-Is and ARBs, the sales of drugs with effect on intraglomerular hemodynamics increased from 70.8 to 246.8 DDDs per 1000 inhabitants per day (Figure 3A). From 1999 to 2021 the sale of ARBs rose steadily from 11.6 to 116 DDDs per 1000 inhabitants per day. The sale of ACE-Is increased from 28.7 DDDs per 1000 inhabitants per day in 2012 and remained relatively stable thereafter. NSAIDs did not share the same trend, as a rise from 30.5 DDDs per 1000 inhabitants per day in 1999 to 59.1 DDDs per 1000 inhabitants per day decrease to 27 DDDs per 1000 inhabitants per day in 2021.

Drugs Associated with Chronic Interstitial Nephropathy

The group of drugs associated with chronic interstitial nephropathy consisted of lithium, acetaminophen and acetylsalicylic acid (NSAIDs were included in 3A). In total, the sales peaked in 2010 at 139.5 DDDs per 1000 inhabitants per day, preceded by a rise from 108.4 DDDs per 1000 inhabitants per day in 1999 (Figure 3B). From 2010 to 2014, the sales decreased to 122.7 DDDs per 1000 inhabitants per day and remained stable thereafter.



Total sales of potential nephrotoxic drugs

Figure 2 Sales of selected drugs between 1999 and 2021 in DDDs per 1000 inhabitants per day. Abbreviation: DDD, Defined Daily Dose.

The sales of acetaminophen steadily increased from 48.4 to 77.3 DDDs per 1000 inhabitants per day during the 23year period. Following an increase from 58.9 to 74.1 DDDs per 1000 inhabitants per day from 1999 to 2009, acetylsalicylic acid sales decreased to 43.5 DDDs per 1000 inhabitants per day between 2009 and 2021. Sales of lithium remained stable between 1.1 and 1.2 DDDs per 1000 inhabitants per day during the study period.

Drugs Associated with Crystal Nephropathy

Drugs associated with crystal nephropathy included methotrexate (MTX), sulfonamide antibiotics, and aciclovir. Being overshadowed by MTX, sales of sulfonamides decreased from 0.5 to 0.2 DDDs per 1000 inhabitants per day, while sales of aciclovir increased from 0.1 to 0.5 DDD per 1000 inhabitants per day. Sales of MTX increased fivefold during the study period, from 1.3 to 6.88 DDDs per 1000 inhabitants per day (Figure 3C).

Drugs Associated with Tubular Cell Toxicity

Trends in sales of drugs associated with tubular cell toxicity varied between the selected subgroups of drugs (Figure 3D). The sales of tacrolimus had the most pronounced annual rise increasing from 0.0 to 0.6 DDD per 1000 inhabitants per day during the study period. The opposite was seen for ciclosporin, decreasing from 0.4 to 0.1 per 1000 inhabitants per day. The sales of aminoglycosides and amphotericin B were stable during the period ranging from 0.0 to 0.1 DDD per 1000 inhabitants per day. Overall, a clear trend in the sales of these drugs was not present. In total, the sales remained between 0.5 and 0.8 DDD per 1000 inhabitants per day. During the study period a steady increase in the sales iodinated contrast dye was observed, growing from 2.0 grams per 1000 inhabitants per day in 1999 to 9.8 grams per 1000 inhabitants per day in 2021 (Figure 4A). Between 2012 and 2021 the sales of cisplatin remained relatively stable around micrograms per 1000 inhabitants per day.

Diuretics

The group of diuretics included loop diuretics, potassium sparing diuretics, thiazides, and sulfonamide diuretics. Overall, the number of sold DDDs decreased during the study period. After an increase from 104.1 DDDs per 1000 inhabitants per day in 1999 to 112.9 DDDs per 1000 inhabitants per day in 2007, the sales decreased to 80.2 DDDs per 1000 inhabitants per day in 2021 (Figure 3E). The decreasing trend was observed for most subgroups.

АТС	Unit	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Drugs altering hemodynamics																								
C09A ACE-I, plain	DDD	27.1	29.7	33.6	38.6	43.9	49.4	55.5	62.3	67.8	74.7	84	90.9	91.3	92.1	91.3	89.4	87.8	86	85	87.4	91.8	96.3	94.7
C09B ACE-I, combinations	DDDª	1.6	1.8	2.1	2.5	3.5	5.2	6.7	8.5	10.7	13.2	16.8	19.2	19.6	19.5	19	18.3	17.6	16.9	16	13.9	10.6	9.6	9.1
C09C ARB, plain	DDD	8.9	10.6	12.1	15	18	20	22.1	24.6	27.7	31	30.1	32.1	34.7	39	41.9	45	48.7	52.3	54.9	65.6	81.5	90.6	99.8
C09D ARB, combinations	DDDª	2.7	3.7	4.9	6.9	9	10.9	12.5	14.2	16.2	18.5	17.2	17.3	18.7	20.7	21.8	22.7	23.2	23.9	24.1	21.5	17	15.9	16.2
MOTA ^d NSAIDs	DDD⁵	30.5	31.3	34.8	38.4	39.4	39.5	37.8	37.9	38	38.3	36.9	37.2	37.6	36.8	34.9	33.1	33.2	32	29.8	28.1	27.8	26.6	27
Total	DDD	70.8	77.1	87.5	101.4	113.8	125	134.6	147.5	160.4	175.7	185	196.7	201.9	208.1	208.9	208.5	210.5	211.1	209.8	216.5	228.7	239	246.8
Drugs associate	ed with chr	onic inte	erstitial	nephrop	athy																			
B01AC06 Acetylsalicylic acid	DDD	58.9	59.5	60	62.1	63.9	65.7	66.6	68.8	70.6	73.6	74.1	73.6	72.1	69.5	65.2	61.1	57.4	53.4	50	47.7	45.5	44.7	43.5
N02BE01 Acetaminophen, plain	DDD	48.4	50	51	52.4	54.1	55.6	57.7	59.4	61.4	62.6	63.6	64.8	65.7	65.9	65	60.5	65.1	67	67.8	69.6	71.8	73.5	76.7
N02BE5 I Acetaminophen, combinations	DDDª	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0	0.1	0.5	0.6	0.6
N05AN01 Lithium	DDD	1.1	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Total	DDD	108.4	110.7	112.2	115.7	9.	122.4	125.4	129.3	133.1	137.3	138.8	139.5	138.9	136.5	131.3	122.7	123.6	121.5	118.9	118.5	118.9	119.9	121.9
Drugs associate	ed with cry	stal nepł	nropathy	/																				
JOIEB Short-acting sulfonamides	DDD	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1
J01EC Intermediate- acting sulfonamides	DDD⁵	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0

Table 2 Sold Amount (Units) per 1000 Inhabitants per Day

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Table 2 (Continued).

АТС	Unit	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
JOIEE Sulfonamides, combinations	DDD ^{a,b}	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
J05AB01 Aciclovir	DDD	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5
L01BA01 Methotrexate	mg ^c	I	0.6	0.7	0.7	0.9	0.9	I	0.9	I	1.2	I	I	2.7	3.1	3.1	3	3.4	3.7	3.2	3.8	5.1	4.2	3.7
L04AX03 Methotrexate	DDD	0.9	1.1	1.3	1.5	1.7	2	2.3	2.6	2.9	3.1	3.4	3.6	3.9	4.1	4.3	4.5	4.7	4.9	4.9	5.1	5.1	5.3	5.4
L01XA01 Cisplatin	μg ^c	131,0	107,9	58,9	60,2	62,6	61,4	59,7	68,7	75,4	88, I	121,3	104,4	280,8	321,1	358,0	378,8	373,2	385,5	361,2	335,5	336,4	321,8	326,5
Total	DDD	1.9	1.94	2.18	2.38	2.76	3.06	3.4	3.66	4	4.28	4.5	4.6	5.68	6.04	6.24	6.4	6.76	7.18	6.98	7.32	7.84	7.68	7.58
Drugs associate	d with tub	ular cell	toxicity																					
A01AB04 Amphotericin B	DDD	0.1	0.1	0.1	0.1	0	0	0	0	0	-	0	0	-	-	-	-	-	-	-	-	-	-	-
J02AA01 Amphotericin B	DDD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
J01G Aminoglycosides	DDD	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0	0	0.1	0.1	0.1	0	0	0.1	0.1	0.1	0.1	0.1	0.1
L04AD01 Ciclosporin	DDD	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1
L04AD02 Tacrolimus	DDD	0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6
V08A Contrast media, iodinated	g	2	2.3	2.5	2.8	3	3.3	3.6	3.9	4.2	4.5	4.9	5.3	5.7	6.1	6.5	7	7.8	7.9	7.9	8.1	9.2	8.9	9.8
Total	DDD	0.6	0.7	0.7	0.7	0.6	0.6	0.5	0.5	0.6	0.6	0.5	0.5	0.7	0.6	0.6	0.6	0.6	0.8	0.8	0.8	0.8	0.8	0.8
Diuretics																								
C03A Low-ceiling diuretics, thiazides	DDD	37.9	38.9	40.1	41.5	43.9	47.4	49.1	50.7	50.4	50.9	49.9	49.2	44.5	41.5	41.1	38.3	35.9	33.8	31.4	31.1	33.4	32	28.5
C03B Low-ceiling diuretics, excl. thiazides	DDD	1.4	1.3	1.2	1.1	1.1	1.1	1.1	0.7	0.7	0.6	0.6	0.5	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.2	0.3	0.4

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C03C High-ceiling diuretics	DDD	54	53.6	53.9	53.6	53.3	53.4	53.5	53.3	53.1	52.6	51.7	50.9	50.1	49.3	48.3	48.5	47.2	46.5	45.1	44.4	44.2	45	45.1
C03D Potassium- sparing diuretics	DDD	2.6	3.2	3.5	3.6	3.6	3.7	3.7	3.8	3.8	3.8	3.7	3.7	3.7	3.8	3.8	3.9	3.9	4	4.1	4.2	4.5	4.9	5.5
C03E Diuretics and potassium- sparing agents, combinations	DDD	8.2	7.8	7.4	7.1	6.8	6.5	5.5	5.1	4.9	4.7	4.3	4.1	3.8	3.6	3.3	3	2.8	2.7	2.4	1.8	1.3	1.2	0.7
Total	DDD	104.1	104.8	106.1	106.9	108.7	112.1	112.9	113.6	112.9	112.6	110.2	108.4	102.5	98.6	96.9	94.1	90.1	87.3	83.3	81.8	83.6	83.4	80.2
Total																								
Total	DDD	285.8	295.2	308.7	327.1	345	363.2	376.8	394.6	411	430.5	439	449.7	449.7	449.8	443.9	432.3	431.6	427.9	419.8	424.9	439.8	450.78	457.28

Notes: ^aContains combination drugs affecting DDD; ^bBased on national DDD values; ^cSale of the drug groups J01 and L01 was incompletely recorded before 2012; ^dExcept M01AX05 (glucosamine). Abbreviations: ACE-I, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; DDD, Defined Daily Dose; NSAID, non-steroidal anti-inflammatory drug.



Figure 3 Sales of selected drug subgroups between 1999 and 2021 in DDDs per 1000 inhabitants per day.

Notes: (A) Drugs altering intraglomerular hemodynamics, (B) Drugs associated with chronic interstitial nephropathy, (C) Drugs associated with crystal nephropathy, (D) Drugs associated with tubular cell toxicity, (E) Diuretics.

Abbreviations: ACE-I, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; DDD, Defined Daily Dose; NSAID, non-steroidal anti-inflammatory drug.



Figure 4 Danish sales of iodinated contrast dye and cisplatin between 1999 and 2021 in grams/micrograms per 1000 inhabitants per day. Notes: (A) Contrast dye, (B) Cisplatin. Sale of cisplatin was incompletely recorded until 2011.

Discussion

This is the first nationwide, population-based study on long-term trends in utilization of potential nephrotoxic drugs. We found considerable changes in the sales of potentially nephrotoxic drugs during the 23-year period from 1999 to 2021. Sales of drugs inhibiting the renin-angiotensin-aldosterone system (RAAS) contributed with the majority in volume and increased dramatically throughout the period. Increases in sales were also observed for acetaminophen, methotrexate, tacrolimus, and contrast dye. In contrast, the use of diuretics, acetylsalicylic acid, and ciclosporin decreased during the last decade of the study period.

Limitations

Our study has a number of strengths, including a long study period, utilization of prospectively collected nationwide data, and accurate population figures. Despite these strengths, several limitations must be considered when interpreting the results: First, it should be noted that the data used for the study are on drug sales and not drug use, why drug adherence merit mentioning here. The prevalence of non-adherence has been reported between 20 and 54%, but small changes over time cannot be ruled out.^{35–38} While sales may vary from the actual use, it is unlikely that the overall observed trends in sales are not accompanied by similar changes in use. Second, a potential confounder to the observed trends in drug sales is the overall increase in patients' comorbidity burden.^{39,40} We did not stratify by demographic variables such as age or sex as this was not possible for the aggregated statistics on total sales in MEDSTAT. Therefore, we are not able to provide data on the potential impact of the rising proportion of older individuals with more comorbidities as well as exposure to more diagnostic and therapeutic procedures. Third, while the use of DDDs allows comparison of sales of a drug over time, caution must be taken when evaluating the overall change in nephrotoxic burden as adverse event profiles and the degree of nephrotoxicity vary widely between drug groups. Although rating systems for the nephrotoxic potential of drugs exist, comparisons of direct nephrotoxicity of different drugs are rarely available. For instance, if a drug is five times more toxic and prescribed twice as much as another, the former would have an overall nephrotoxic impact ten times larger than the latter of the two. A recent study aimed to assign a nephrotoxic potential for 167 drugs, rating these on a scale from 0 to 3, with 3 corresponding to a definite nephrotoxic potential.⁴¹ However, the overall changes in nephrotoxic potential arising from changes in the sales of numerous drugs are difficult to assess. In addition, the aggregated data used in this study does not disclose patients receiving multiple potentially nephrotoxic drugs, which could in theory have synergistic (or antagonistic) effects on kidney function. Keeping this in mind, monitoring of kidney function in high-risk patients through blood or urine samples is pivotal. Lastly, even though changes to the DDD are generally avoided, they sometimes undergo revision.⁴² Such alterations could potentially complicate the interpretation.

Interpretation ACE-is and ARBs

Between 1999 and 2012 an almost fourfold rise in the use of ACE-Is was observed, whereafter the use remained stable. Likewise, the use of ARBs increased dramatically during the study period, being ten times higher in 2021 than in 1999. Due to effectiveness and a favorable safety profile ACE-Is and ARBs are currently first-line drugs in the treatment of high blood pressure.^{43–45} The rising trend in use correlates with a gradual development of a more aggressive approach to blood pressure control, especially among a growing population of elderly. Though the renal benefits of RAAS inhibitors have been well established, the treatment is also known to inhibit regional hemodynamic autoregulation, which may lower the threshold for developing or worsening AKI in certain circumstances.⁴⁶ Importantly, it is not unusual that ACE-Is and ARBs are taken together with diuretics and NSAIDs, a combination known as "the triple whammy", which is associated with an increased risk of AKI.⁴⁷ The changes in use of RAAS inhibitors are substantial, and it cannot be ruled out that the drugs could contribute to the development of AKI in some cases, although the widespread use might conversely lower the overall incidence of AKI and CKD due to their nephroprotective properties.

NSAIDs

Since 2004 the sales of NSAIDs have been declining. This can be explained by multiple factors, including withdrawal of selective COX-2 inhibitors due to the risk of cardiovascular events⁴⁸ and a bigger awareness of other serious side effects, such as gastrointestinal bleeding.⁴⁹ In 2008 and 2009 respectively, the Danish Medicines Agency and Danish Society for Cardiology recommended that diclofenac should be used with caution due to the risk of cardiovascular toxicity.⁵⁰ However, NSAIDs known to increase the risk of AKI through alterations of intraglomerular hemodynamics are still widely used and easily accessible.⁵¹

Acetaminophen

During the study period the use of acetaminophen increased 1.5-fold. A minor, abrupt fall in 2013 can be attributed to Danish legislators restricting sales of large packs of painkillers to prescriptions only, which was done to prevent suicidal poisonings.²⁶ Similarly, an 18-year-old minimum age for purchase was implemented in 2011.⁵² Both legislative initiatives were followed by a significant decrease in the number of non-opioid analgesic poisonings.⁵²

Acetylsalicylic Acid

Acetylsalicylic acid was commonly used between 1999 and 2021, but the sales decreased from 2009 and onward. This could be due to Danish and European guidelines no longer recommended low-dose acetylsalicylic acid as routine thromboprophylaxis in patients >65 years without cardiovascular disease.⁵³

Contrast Dye

The use of iodinated radiocontrast increased almost fivefold between 1999 and 2021. As diagnostic procedures using iodinated radiocontrast are becoming more routine, the use of the agents is growing. Additionally, parts of the dramatic increase might be due to an increasing number of invasive procedures in a growing population of elderly.^{39,40} Importantly, the group of iodinated contrast agents (V08A) comprises several different kinds of solutions, which are not necessarily comparable regarding level of toxicity. However, generally the use of all subgroups increased during the study period.

Conclusion

This study is the first to provide nationwide, population-based data on long-term trends in the use of potentially nephrotoxic drugs. During the past 23 years, considerable changes in the use of potentially nephrotoxic drugs have occurred. Notably, sales of drugs inhibiting RAAS, methotrexate, tacrolimus, and acetaminophen increased steadily. Additionally, the use of iodinated radiocontrast increased almost fivefold. In contrast, sales of other drugs of interest, including diuretics, acetylsalicylic acid, and ciclosporin, decreased. The reported increases in total use of potential nephrotoxins aligns with reported increases in occurrence of kidney diseases globally. However, whether the temporal

changes in use of potential nephrotoxins is causally related to a possible increase in the incidence of AKI and CKD requires further examination.

Abbreviations

ACE-I, Angiotensin converting enzyme inhibitor; AKI, Acute kidney injury; ARB, Angiotensin receptor blocker; ATC, Anatomical therapeutical chemical classification; CKD, Chronic kidney disease; COX-2, Cyclooxygenase-2; DDD, Defined daily dose; MTX, Methotrexate; NSAID, Non-steroid anti-inflammatory drug; RAAS, Renin-angiotensin-aldosterone system.

Data Sharing Statement

The data reported in this article are publicly available through the online database Medical Statistics.³⁰

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The study was funded by the Independent Research Fund Denmark (grant number: 0134-00407B).

Disclosure

The authors have no conflicts of interest to disclose in this work.

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