







ORIGINAL ARTICLE OPEN ACCESS

Changes in the Use of Hydrochlorothiazide and Other Antihypertensive Drugs in Switzerland in Association With the Swissmedic Safety Alert Regarding Non-melanoma Skin Cancer: An Interrupted Time-Series Analysis Using Swiss Claims Data

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Received: 13 December 2023 | **Revised:** 19 July 2024 | **Accepted:** 16 August 2024

Funding: This study was internally funded by the Basel Pharmacoepidemiology Unit (BPU).

Keywords: direct healthcare professional communication | drug utilisation study | hydrochlorothiazide | non-melanoma skin cancer | Swissmedic

ABSTRACT

Purpose: Long-term use of hydrochlorothiazide increases the risk of non-melanoma skin cancer. We aimed to evaluate potential changes in the use of hydrochlorothiazide in Switzerland after a direct healthcare professional communication (DHPC) in November 2018 by Swissmedic.

Methods: We performed interrupted time-series analyses using a large Swiss healthcare claims database (2015–2021). Within monthly intervals, we quantified the total number of claims and the total dispensed ‘defined daily doses’ (DDD) for preparations containing (1) hydrochlorothiazide, (2) angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II-receptor blockers (ARB), (3) calcium-channel blockers (CCB) and (4) thiazide-like diuretics per 10000 persons. Using segmented linear regression, we quantified the pre-DHPC trend, the immediate change and the post-DHPC change in trend for total claims and DDD for the four drug classes weighted for the demographic distribution of the Swiss population.

Results: ACE inhibitors and ARB were the most frequently claimed antihypertensive drugs with 300–400 claims per 10000 persons, which increased by 5.4% during the study period. The average number of hydrochlorothiazide claims (157/10000 persons in 2015) declined by 35% between 2015 and 2021. The decrease started prior to the DHPC, but the DHPC was associated with an immediate 6.1% decline and an accelerated decline in claims over time after the DHPC (similar results for DDD). This coincided with a 23% increase in claims of CCB (dihydropyridine type) over 7 years, whereas use of other antihypertensives increased less.

Conclusion: Our results suggest that the DHPC by Swissmedic in 2018 accelerated a pre-existing decline in the use of hydrochlorothiazide in Switzerland.

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Summary

- Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer (NMSC). Swissmedic issued a DHPC in November 2018.
- Number of hydrochlorothiazide users in Switzerland decreased by 32% with claims decreasing by 35% between 2015 and 2021.
- Hydrochlorothiazide claims already declined before NMSC was associated, but the DHPC was associated with an immediate 6.1% decline in claims of hydrochlorothiazide and an accelerated decline thereafter.
- Use of calcium-channel blockers (mainly amlodipine) increased proportionally to the decline in use of hydrochlorothiazide.
- Our findings suggest that the DHPC accelerated a pre-existing decline in use of hydrochlorothiazide in Switzerland.

1 | Introduction

Hydrochlorothiazide is a thiazide diuretic, which is indicated as first-line therapy for essential arterial hypertension, as well as for the treatment of heart failure and oedema [1]. In 2017, an observational study conducted in Denmark revealed an association between the use of hydrochlorothiazide (HCTZ) and an increased risk of squamous cell carcinoma (SCC) of the lip, which is a type of non-melanoma skin cancer (NMSC) [2]. Subsequent studies reported an increased risk of SCC of any location of the skin and to a lesser degree of basal cell carcinoma (BCC), another type of NMSC [3] and of certain malignant melanoma subtypes [4] of the skin in association with the use of hydrochlorothiazide. Since then, the association between hydrochlorothiazide and SCC has been consistently confirmed in several observational studies using various data sources from different countries [5–11]. Most studies observed a dose–response or duration effect, suggesting an increasing risk of SCC with increasing cumulative doses of hydrochlorothiazide. To date, it is commonly accepted that the use of hydrochlorothiazide increases the risk of SCC, which seems to be specific for hydrochlorothiazide, whereas other thiazide diuretics, such as bendroflumethiazide, did not show the same association [3, 10, 12]. The association between hydrochlorothiazide and BCC could be seen in some subsequent studies but was always weaker than the one with SCC [5, 8, 9, 11]. However, other studies found no association between hydrochlorothiazide and BCC [7, 10, 12, 13]. Thus, the association with BCC remains less clear, and if present at all, it is weaker than the association with SCC. The association with malignant melanoma was only seen in one subsequent study [6], whereas other studies showed a null result [5, 12]. Hydrochlorothiazide is by far the most commonly used thiazide diuretic in Switzerland and is considered a first-line antihypertensive drug [1]. Contrary to most other European countries, alternative thiazide diuretics such as bendroflumethiazide are not available in Switzerland.

Based on the Danish studies, the European Medicines Agency (EMA) published a ‘dear health care provider’ (DHCP) letter on 17 October 2018, to warn prescribers about this possible

risk. On 18 November 2018, Swissmedic issued a ‘direct health care professional communication’ (DHPC) in Switzerland. The DHPC additionally pointed out that the product information of all products containing hydrochlorothiazide registered in Switzerland has been amended accordingly [14]. The association of hydrochlorothiazide use and SCC and BCC is now mentioned in the sections ‘Warnings and Precautions’ as well as under ‘Adverse Effects’. Patients treated with medicines containing hydrochlorothiazide are advised to regularly check their skin for new lesions and to apply appropriate sun protection. In patients with a history of NMSC, hydrochlorothiazide therapy should be reconsidered.

In Denmark, the use of hydrochlorothiazide declined by 44% between 2016 and 2020 [15]. The possible reduction in hydrochlorothiazide use in Switzerland in response to the DHPC has not previously been studied, and no information on compensatory use of other antihypertensive drugs is available. Thus, we aimed to evaluate whether the Swissmedic DHPC alert regarding NMSC was associated with a change in the use of hydrochlorothiazide and other first-line antihypertensive drugs in clinical practice in Switzerland.

2 | Methods

2.1 | Study Design and Data Source

We conducted interrupted time-series analyses using administrative claims data from the Helsana Group for the study period of 1 January 2015, to 31 December 2021. The Helsana Group is the largest health insurance company in Switzerland, covering about 15% of the Swiss population (approx. 1.2 million individuals in 2021) from all 26 cantons with basic mandatory health insurance [16]. The Helsana claims database provides anonymised information on demographics, insurance model, start and end of insurance coverage, as well as all drug claims, outpatient procedures and consultations, diagnostic tests and bundled information on hospitalisations. Recorded drug claims include information on the dispensed drugs, including the date of dispensation, strength, formulation and pack size.

Ethics approval was not required because data were anonymised and informed consent was not required according to Swiss Human Research Act (Art. 34).

2.2 | Exposure Groups

We identified all claims of four first-line antihypertensive drug classes of interest during the study period. The first-line antihypertensive drugs of interest were (1) hydrochlorothiazide, (2) angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II-receptor blockers (ARB), (3) calcium-channel blockers of the dihydropyridine type (CCB) and (4) thiazide-like diuretics (TZLD, i.e., chlorthalidone and indapamide). We selected first-line antihypertensive drugs based on the guidelines for the management of arterial hypertension published by the European Society of Cardiology (ESC) [1] and identified them according to the Anatomical Therapeutic Chemical (ATC) classification system (Supplement M1 in Data S1) [17]. We did not

analyse beta-blockers because they are not considered first-line antihypertensive drugs for the treatment of arterial hypertension by the ESC [1]. They are prescribed in the presence of other cardiovascular comorbidities or for the treatment of hypertension during pregnancy.

We created four exposure groups based on these four drug classes of interest, each also including combinations with other antihypertensive drugs. We excluded claims of patients who were insured for less than one full calendar year (1 January–31 December) during the study period.

2.3 | Measurement of Exposure Variables

To evaluate the use of hydrochlorothiazide and other first-line antihypertensive drugs in Switzerland, we defined four variables reflecting drug use: (1) Number of claims per 10000 persons per month, (2) number of users per 10000 persons per year, (3) dispensed ‘defined daily doses’ (DDD) per 10000 persons per month, and (4) new users per 10000 persons per month (detailed definitions in Supplement M2 in Data S1).

2.3.1 | Statistical Analyses

We performed three separate interrupted time-series analyses for each exposure group to evaluate whether the DHPC was associated with changes in use (claims, dispensed DDD and new users) of hydrochlorothiazide or of the other first-line antihypertensive drugs. The event date was the date when Swissmedic issued the DHPC (i.e., 18 November 2018). We defined the time-series by two time-segments, that are, the baseline period before the DHPC (January 2015 [2016 for new users] to—but not including—November 2018), and the post-DHPC period (December 2018–December 2021). The units of analysis were time-periods of 30 days, beginning on 1 January 2015, and ending on 24 December 2021. For the analysis of new users, time-periods began on 1 January 2016, and ending on 29 December 2021. Within these time-periods, we quantified the number of exposure units (claims/DDD/new users) per 10000 persons. Patients had to be enrolled in the database for at least 1 day during the respective time-period to be part of the denominator.

We constructed segmented linear regression models allowing for first-order autocorrelation to assess the average number of the defined exposure variables. We applied a lag-time after the release of the DHPC that consisted of four periods. We adjusted for seasonal variation of drug use by including sine and cosine terms of $2 \times \pi \times t/T$ (t is month and T is 12). We quantified the following effect estimates: the trend before the release of the DHPC, the immediate effect right after DHPC release, and the slope change (modelled trend) over the time after release of the DHPC. We further modelled the hypothetical trend over time in the absence of the DHPC (predicted trend).

Additionally, we performed a sensitivity analysis on the number of hydrochlorothiazide claims, where we only included persons between 25 and 50 years of age to see whether effects are different in a younger age group. We also quantified the

monthly number of hydrochlorothiazide and CCB claims per 10000 stratified by mono-preparations and in fixed-dose-combinations (FDC).

Because the average age within the Helsana population slightly decreased during the study period (Supplement M3 in Data S1), we weighted all analyses by the demographic distribution of the overall Swiss population (details in Supplement M4 in Data S1).

3 | Results

3.1 | Number of Claims of Different First-Line Antihypertensive Drugs

Overall, ACE inhibitors/ARB were the most frequently claimed antihypertensive drugs in Switzerland during the study period, with approximately 300–400 claims per 10000 persons per month. The average number of claims for ACE inhibitors/ARB fluctuated at a constant level, with a tendency towards a slight increase over time. Hydrochlorothiazide and CCB were claimed approximately equally frequently in 2015 (HCTZ: 156/10000 persons, CCB: 144/10000 persons), but use of hydrochlorothiazide continuously declined over time between 2015 and 2021 (to 109 claims per 10000), whereas use of CCB increased over time (to 173 claims per 10000 persons in 2021). Use of TZLD increased between 2015 and 2021, although at a low level (of approx. 34 claims per 10000) throughout the study period (Figure 1).

The number of hydrochlorothiazide users dropped by 32% from 608 to 415 users per 10000 persons between 2015 and 2021. The number of CCB users increased by around 15%, starting at 548 users per 10000 persons. The number of TZLD users showed the largest proportional increase of approximately 22%–24%, although at a low level of 100–125 users per 10000 persons. The number of ACE inhibitor/ARB users remained more or less stable over the 7 years at around 1400 users per 10000 persons (Figure 2).

FDC accounted for almost all claims of hydrochlorothiazide (98%) in 2015, which decreased by 30% between 2015 and 2021. Of all CCB claims, about one third (34%) accounted for FDC, which increased by 47% during the study period, whereas CCB mono-preparations increased by 25% (Figure S6).

3.2 | Interrupted Time-Series Analyses

3.2.1 | Hydrochlorothiazide

In the segmented linear regression models, the number of monthly claims for hydrochlorothiazide per 10000 persons (157 in 2015) declined by 35% over the 7-year study period. During the almost 4 years prior to the DHPC, the number of claims steadily declined by 10%. The release of the DHPC was associated with an immediate 6.1% decline in the number of claims (−8.6 claims per 10000, $p < 0.0001$). After the release of the DHPC, the pre-DHPC trend was accelerated (change in trend pre- vs. post-DHPC) by −0.4 claims per 10000 persons per period ($p < 0.0001$) (Table 1, Figure 3A).

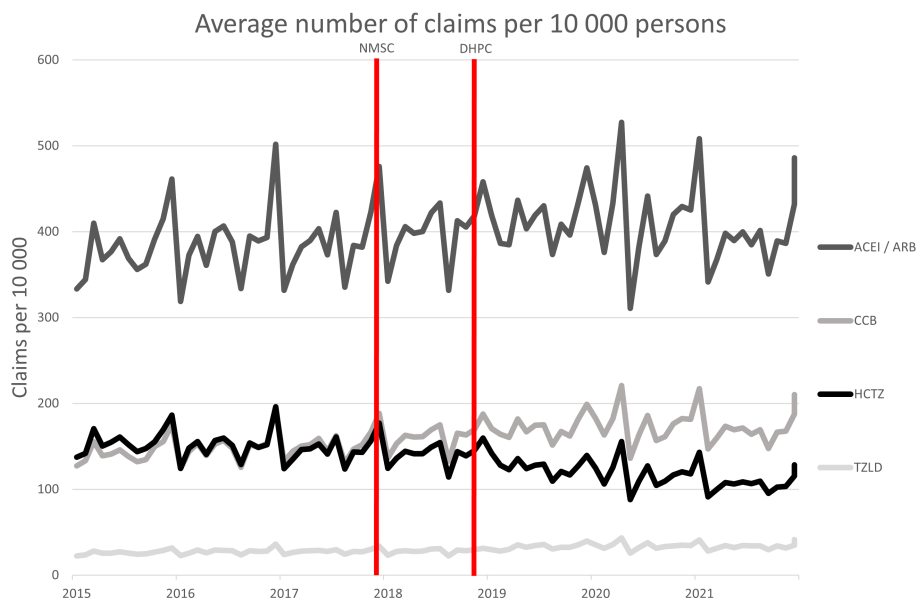


FIGURE 1 | Average number of claims per 10000 persons per month of different first-line antihypertensive drugs between 2015 and 2021 among individuals insured by the Swiss health insurance ‘Helsana’ weighted by the demographic distribution of the Swiss population. (NMSC = Publication revealing association between use of HCTZ and NMSC, 3rd December 2017) [3].

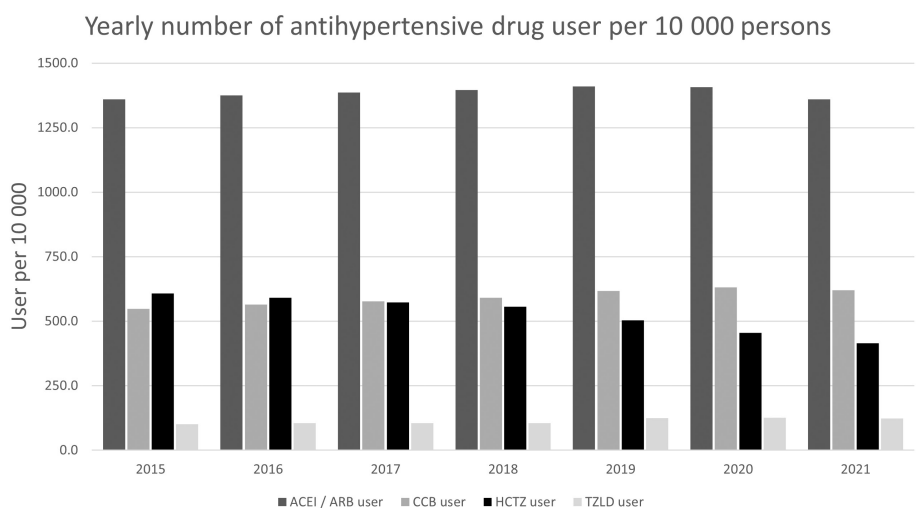


FIGURE 2 | Yearly number of antihypertensive drug users per 10000 persons between 2015 and 2021 among individuals insured by the Swiss health insurance ‘Helsana’ weighted by the demographic distribution of the Swiss population.

Likewise, the number of dispensed DDD declined by 36% during the study period, with a statistically significant declining trend of dispensed DDD prior to the DHPC of -24 dispensed DDD per 10000 persons per month, and an immediate declining effect after the DHPC of -5.7% (Table 1, Figure 3B). The number of new users declined by 27% over time, with an immediate decline after the release of the DHPC of 22%. However, there was no statistically significant trend prior to the DHPC or a change in trend after the DHPC (Table 1, Figure 3C).

The sensitivity analysis in persons aged 25–50 years showed an overall decrease of 49% in the number of claims, beginning with 32 claims per 10000 per month. The DHPC was

associated with an immediate 11% decrease (-3.1 claims per 10000 persons, $p < 0.0001$) after its release (Supplement R1 in Data S1).

3.2.2 | ACE Inhibitors/ARB

The average monthly number of claims of ACE inhibitors/ARB was 374 claims per 10000 persons. Overall, the number of claims and dispensed DDD of ACE inhibitors/ARB slightly increased by 5.4% and 3.3% over time, respectively, with an immediate increase of 17 claims per 10000 persons ($p = 0.0114$, Table 1, Figure 4A,B) in association with the DHPC. No statistically significant increase in the number of new users of ACE

TABLE 1 | Periodic linear regression of average numbers of claims, dispensed DDD and new users of hydrochlorothiazide, thiazide-like diuretics, ACE inhibitors and ARB and calcium-channel blockers per 10 000 persons per 30 days, weighted by the demographic distribution of the Swiss population.

	Hydrochlorothiazide			ACE inhibitors/ARB			CCB			TZLD		
	β Coeff.	SE	p	β Coeff.	SE	p	β Coeff.	SE	p	β Coeff.	SE	p
Baseline average no. of claims per 10 000 persons before DHPC	157.2	1.3		374.3	4.4		139.1	1.9		26.1	0.5	
	Number of claims											
Trend in no. of claims before DHPC	-0.34	0.05	<0.0001	0.64	0.16	0.0002	0.52	0.07	<0.0001	0.06	0.02	0.0011
Immediate effect	-8.57	2.05	<0.0001	17.35	6.68	0.0114	9.42	2.98	0.0023	4.37	0.73	<0.0001
Change in trend post vs. pre-DHPC	-0.45	0.09	<0.0001	-1.37	0.29	<0.0001	-0.55	0.13	<0.0001	-0.04	0.03	0.226
Baseline average no. of dispensed DDD per 10 000 persons before DHPC	9951	85.5		54 029	623.3		16 246	229.3		1 380	24.3	
	Number of dispensed DDD											
Trend in no. of dispensed DDD before DHPC	-24.30	3.15	<0.0001	77.84	22.92	<0.0001	52.48	8.43	<0.0001	5.83	0.89	<0.0001
Immediate effect	-501.37	130.40	0.0003	1 509	952.79	0.1175	860.97	351.59	0.0167	160.47	37.34	<0.0001
Change in trend post vs. pre-DHPC	-29.31	5.63	<0.0001	-169.04	40.89	<0.0001	-48.31	14.97	<0.0001	-1.22	1.58	0.4442
Baseline average no. of new users per 10 000 persons before DHPC	7.2	0.2		15.9	0.5		10.8	0.4		2.1	0.2	
	Number of new users											
Trend in no. of new users before DHPC	-0.02	0.01	0.1088	0.01	0.02	0.7947	0.03	0.02	0.107	-0.004	0.01	0.6758
Immediate effect	-1.47	0.29	<0.0001	-0.13	0.72	0.8611	0.82	0.58	0.1581	1.27	0.29	<0.0001
Change in trend post vs. pre-DHPC	-0.02	0.01	0.1541	-0.002	0.03	0.9619	-0.04	0.03	0.1165	-0.02	0.01	0.1141

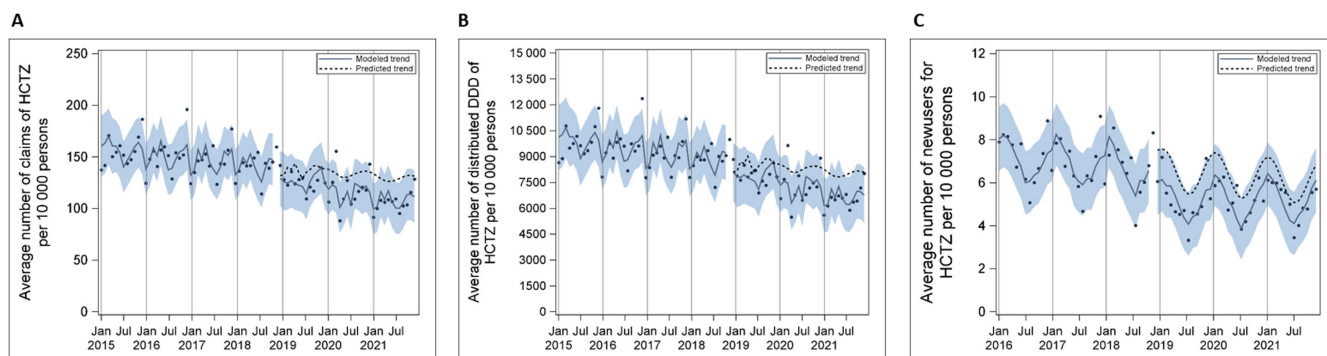


FIGURE 3 | Segmented linear regression of the monthly number of claims/10 000 persons (A), monthly number of dispensed DDD/10 000 persons (B) and monthly number of new users/10 000 persons (C) of hydrochlorothiazide, weighted by the demographic distribution of the Swiss population.

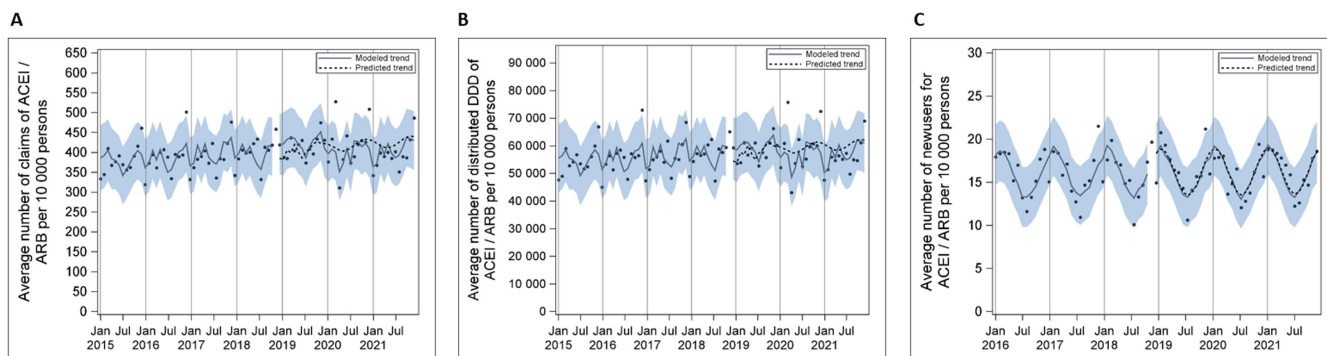


FIGURE 4 | Segmented linear regression of the monthly number of claims/10 000 persons (A), the monthly number of dispensed DDD/10 000 persons (B) and the monthly number of new users/10 000 persons (C) of ACE inhibitors and angiotensin-II-receptor blockers, weighted by the demographic distribution of the Swiss population.

inhibitors/ARB was observed in association with the DHPC (Table 1, Figure 4C).

3.2.3 | Calcium-Channel Blockers

The average monthly number of claims of CCB per 10 000 was similar to hydrochlorothiazide in January 2015 with 139 claims per 10 000 persons and increased by 23% during the study period. The number of claims increased (by 0.5 claims per 10 000 per period, $p < 0.0001$) before the DHPC, which was followed by an immediate increase of 9.4 per 10 000 persons after the DHPC. However, with a change in trend of -0.5 claims per 10 000 persons ($p < 0.0001$), the prior increasing trend stagnated after the DHPC (Table 1, Figure 5A).

The number of dispensed DDD per 10 000 persons increased by 21% over 7 years, which was mainly driven by an increasing trend of $+52$ DDD per 10 000 persons per period ($p < 0.0001$) prior to the DHPC. The DHPC was associated with an immediate change in the number of dispensed DDD of $+861$ DDD per 10 000 ($p = 0.0167$), and the prior increase flattened after the DHPC to $+4.2$ DDD per 10 000 persons per period ($p < 0.0001$, Table 1, Figure 5B). No meaningful or statistically significant changes in the number of new users of CCB could be observed during the study period and in association with the release of the DHPC (Table 1, Figure 5C).

3.2.4 | Thiazide-Like Diuretics

The use of TZLD slightly increased during the study period and in association with the DHPC, but remained at a low level (detailed results in Supplement R2 in Data S1).

Unweighted results for all analyses are provided in the appendix (Supplement R3 in Data S1).

4 | Discussion

Between 2015 and 2021, the number of hydrochlorothiazide users in Switzerland declined by 32%, from 6.1% of all insured persons in 2015 to 4.2% in 2021. The DHPC, issued by Swissmedic in November 2018 to raise awareness of the increased risk of NMSC, was associated with an immediate approximately 6% decline in the number of claims and dispensed DDD of hydrochlorothiazide, with an accelerated steady decline in use thereafter. The number of new users of hydrochlorothiazide also declined by 22% immediately after the release of the DHPC.

These results suggest that the DHPC had a direct effect on prescribing patterns of hydrochlorothiazide in routine care in Switzerland, and that it accelerated a pre-existing decline in the use of hydrochlorothiazide. It remains unknown why

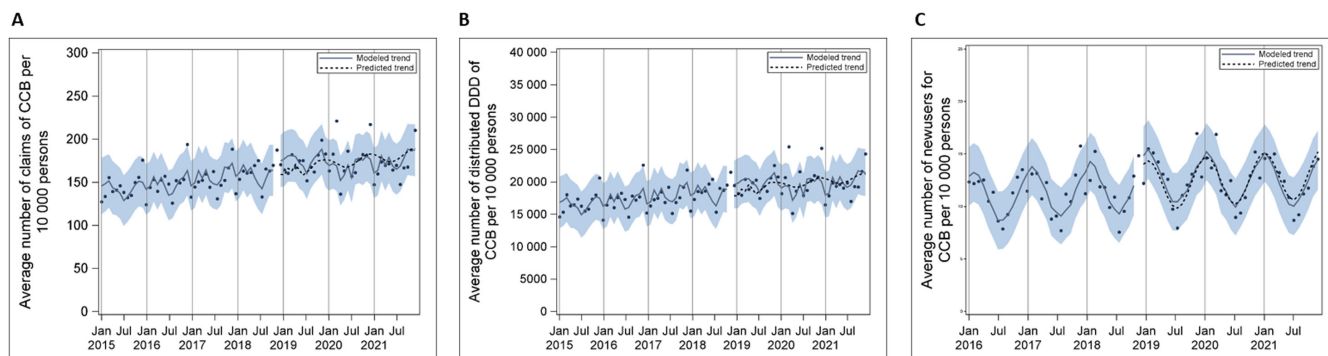


FIGURE 5 | Segmented linear regression of the monthly number of claims/10000 persons (A), the monthly number of dispensed DDD/10000 persons (B) and the monthly number of new users/10000 persons (C) of calcium-channel blockers, weighted by the demographic distribution of the Swiss population.

the number of claims and dispensed DDD of hydrochlorothiazide already slightly decreased prior to the release of the Swissmedic DHPC in 2018 and prior to the first publication on an increased risk of SCC of the lip in association with hydrochlorothiazide in June 2017 [2]. However, prior studies have shown a decline in the use of hydrochlorothiazide over time in other countries [12].

The use of other first-line antihypertensive drugs increased proportionally to the decrease in use of hydrochlorothiazide over the course of the study period. The number of claims and the number of dispensed DDD of all alternative first-line antihypertensive drugs combined (ACE inhibitors/ARB, CCB, TZLD) increased by 11% and 8.2% between 2015 and 2021. This was mainly driven by the increased use of CCB (claims: +23% and DDD: +21%), and among those mostly of amlodipine. In absolute numbers of dispensed DDD, a 21% increase in CCB is proportional to a 96% decline in claimed DDD of hydrochlorothiazide. The immediate decrease of hydrochlorothiazide claims after the DHPC coincided with an immediate increase in CCB (+9.4 claims per 10000, HCTZ: -8.6 claims per 10000). Also, the number of CCB users continuously increased and surpassed the declining number of hydrochlorothiazide users after 2017 (Figure 2). The increase in the number of CCB claims started prior to the DHPC, around the time when publications started to emerge corroborating the association between use of hydrochlorothiazide and NMSC in December 2017, suggesting that changes in routine care may have started before the DHPC in reaction to emerging literature [3] (Figure 1).

The ESC guidelines suggest to treat hypertension with a combination of an ACE inhibitor/ARB with either a CCB or a diuretic, and to follow a single-pill strategy whenever possible [1]. Given that use of ACE inhibitors/ARB did not increase as much as that of CCB, our results suggest that many patients switched from a ACE inhibitors/ARB plus hydrochlorothiazide to ACE inhibitors/ARB plus a CCB. In total, 98% of all claims for hydrochlorothiazide in 2015 were FDC. Among all CCB claims in 2015, 34% were for FDC products, but FDC products increased more strongly (47%) than mono-preparations (25%) during the study period, which suggests that CCB were often selected to replace hydrochlorothiazide in a combination therapy with ACE inhibitors. Besides hydrochlorothiazide, indapamide and

chlorthalidone are two TZLD on the Swiss market, which are equally effective antihypertensive drugs compared with hydrochlorothiazide according to current guidelines [1, 18]. However, TZLD only compensated for approximately 15% for the decline in hydrochlorothiazide. This is likely due to the paucity of FDC of indapamide or chlorthalidone with an ACE inhibitor/ARB.

A German claims-based study, which included data representative of more than 80% of the German population, found that the number of claims of hydrochlorothiazide preparations decreased by around 25% within a year after the warning in October 2018 in Germany. Contrarily to our study, there was a stronger increase in ACE inhibitors/ARB (12%) than in CCB claims (7.1%), but TZLD also remained at a low level. Thus, similarly to the results of our study, the decline in use of hydrochlorothiazide in Germany seems to have been compensated by other non-diuretic first-line antihypertensives [19].

In Denmark, the overall number of claims of hydrochlorothiazide declined more extensively than in our study, by 44% between 2016 and 2020 [15]. The monthly number of new users of hydrochlorothiazide even dropped by 70% between 2017 and 2020. Contrarily to Switzerland and Germany, the number of new users of mainly bendroflumethiazide, and to a lesser degree also of ACE inhibitors and CCB increased proportionally to the decline in the number of new users of hydrochlorothiazide. Bendroflumethiazide is an alternative thiazide diuretic, which has not been associated with NMSC [3, 10, 12]. In Denmark, bendroflumethiazide is available as single-drug preparation with added on potassium chloride, but combination products with ACE inhibitors or CCB do not exist. The lacking or limited availability of bendroflumethiazide in Switzerland (not on the market) and Germany (only available in combination with amiloride, another diuretic) may explain why the use of hydrochlorothiazide declined less strongly in these countries compared to Denmark. Thus, when triple-therapy is required for the treatment of refractory hypertension, hydrochlorothiazide is often the only thiazide available, especially when aiming at a single-pill strategy where combination products with ACE inhibitors or CCB are preferred. However, the increasing use of bendroflumethiazide in Denmark may reflect a trade-off against the recommended single-pill strategy whenever combination therapy is required.

The Swiss Society of Hypertension (SSH) published a statement, highlighting that sufficient blood pressure control to reduce the risk of fatal or non-fatal thromboembolic cardiovascular events outweighs the risk of developing NMSC in patients with ongoing hydrochlorothiazide therapy [20]. Thus, current guidelines in Switzerland do not generally discourage treatment with hydrochlorothiazide in patients with essential hypertension except for certain subgroups. Guidelines specifically advise to use alternative antihypertensives in young patients, because the risk of skin cancer increases with duration of hydrochlorothiazide use, as well as patients with a (family) history of NMSC and patients under treatment with immunosuppressants [20, 21]. Our sensitivity analysis showed a stronger relative decrease in the number of claims of hydrochlorothiazide in patients aged 25–50 years than in the entire population (49% vs. 35%), and also the immediate decrease after the DHPC was slightly stronger (11% vs. 6.1%).

Despite comprehensive analyses using a representative and large Swiss-based claims database, some limitations need to be considered. First, the Helsana claims database does not capture outpatient diagnoses, and we could therefore not identify whether patients had a prior diagnosis of hypertension or whether patients were treated for an indication other than hypertension (i.e., heart failure, coronary heart disease, history of myocardial infarction). Second, we performed analyses of aggregated claims data and did not analyse individual switching patterns in routine care on a patient-level. Finally, the Helsana claims database only captures information on 15% of the Swiss population. Because these may not be entirely representative of the overall Swiss population, we extrapolated them to the entire Swiss population based on demographic factors. However, we cannot rule out certain discrepancies in unmeasured factors, such as socioeconomic status, income or occupation between our study population and the overall Swiss population.

5 | Conclusion

Between 2015 and 2021, the number of hydrochlorothiazide users in Switzerland declined by 32%. The decrease in use started before hydrochlorothiazide was associated with an increased risk of NMSC but accelerated after the release of the DHPC by Swissmedic alerting healthcare professionals on this issue. Thus, our results suggest, that the DHPC by Swissmedic in 2018 accelerated a pre-existing decline in the use of hydrochlorothiazide in Switzerland, which was mostly compensated by an increase in use of CCB, mainly amlodipine.

5.1 | Plain Language Summary

Hydrochlorothiazide, a commonly used drug to treat high blood pressure, leads to an increased risk of NMSC. Swissmedic, the Swiss regulatory authority responsible for the authorisation and supervision of therapeutic products, warned healthcare professionals on this issue in a DHPC in November 2018. In our study, we evaluated potential changes in the use of hydrochlorothiazide and other drugs to treat high blood pressure (i.e., ACE inhibitors and ARB, CCB and thiazide-like diuretics) between 2015 and 2021 in Switzerland using electronic data from a large

Swiss health insurance. The number of hydrochlorothiazide claims decreased by 35% between 2015 and 2021. This decrease already started before Swissmedic warned healthcare professionals but was accelerated thereafter. The number of claims of other analysed blood pressure drugs increased by 11% overall, which was mainly driven by an increase in claims of CCB and among those mainly of amlodipine. Thus, our study suggests that DHPC accelerated a pre-existing decline in the use of hydrochlorothiazide, which may have been compensated by an increase in the use of CCB, mainly amlodipine.

Acknowledgment

Open access funding provided by Universitat Basel.

Disclosure

Early results of this study were presented in a poster session at the International Conference on Pharmacoepidemiology (ICPE) 2022 in Copenhagen.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.