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ORIGINAL ARTICLE

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Use of hydrochlorothiazide in Denmark following publication of skin cancer risk findings

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Abstract

Purpose: The antihypertensive agent hydrochlorothiazide has recently been linked to increased risk of skin cancer. We sought to describe the impact of the dissemination of these findings on the use of hydrochlorothiazide and health care utilization among antihypertensive users in Denmark.

Methods: In this nationwide observational study, we performed descriptive analyses of a cohort comprising all Danish antihypertensive treatment users January 2016 through September 2020 ($n = 1\,316\,476$) with special focus on hydrochlorothiazide users ($n = 309\,743$). Data were retrieved from the Danish nationwide health registries, including the Danish National Prescription Registry.

Results: The use of hydrochlorothiazide dropped by 44% from January 2016 to September 2020, with the proportion of all antihypertensive fills constituted by hydrochlorothiazide dropping from 12.7% to 7.2%. This decline was more pronounced among younger patients and patients with a history of skin cancer. Simultaneously, the monthly rate of new hydrochlorothiazide users in Denmark dropped from ≈2350 throughout 2017 to 652 during 2020. The publication of an increased risk of non-melanoma skin cancer led to an estimated excess of up to 11 510 physical and 22 870 e-mail/phone consultations to general practitioners. No evidence for increased risk of adverse outcomes was found.

Conclusions: The publication of increased risk of skin cancer with hydrochlorothiazide use has led to a marked decline in the use of hydrochlorothiazide in Denmark. A temporary increase in rate of GP contacts was also observed. This highlights the potential impact from disseminating research findings to patients and clinicians.

KEYWORDS
drug utilization, hydrochlorothiazide, pharmacoepidemiology, risk communication, skin cancer

Key Points

- The publication of an association between hydrochlorothiazide and skin cancer has led to a substantial drop in use of hydrochlorothiazide in Denmark.
- The decrease in use of hydrochlorothiazide was most pronounced among younger patients and those with a history of skin cancer, suggesting that the new knowledge on skin cancer risk has been implemented clinically.

- A considerable decrease in use of hydrochlorothiazide occurred already at the time of the original publications, thus preceding the regulatory evaluation, emphasizing the need for caution when disseminating new research findings.

1 | INTRODUCTION

The antihypertensive agent hydrochlorothiazide is known to possess photosensitizing properties[1] and have, mainly based on one previous study associating hydrochlorothiazide to an increased risk of lip cancer,[2] been classified by the International Agency for Research on Cancer (IARC) as "possibly carcinogenic to humans" (Group 2B).[3,4] In a recent series of papers based on Danish nationwide health registries, this putative association has been investigated further, associating hydrochlorothiazide use to an increased risk of squamous cell carcinoma (SCC) of the lip,[5] SCC and basal cell carcinoma of the skin,[6] and potentially certain melanoma subtypes.[7] This was seemingly specific to hydrochlorothiazide, as a similar association was not seen for bendroflumethiazide, another thiazide commonly used in Denmark. The three papers were published in rapid succession on June 6, 2017, December 4, 2017, and May 29, 2018, respectively, and the findings, including a replication study performed on the initiative of the regulators,[8] were subsequently evaluated by the Pharmacovigilance Risk Assessment Committee (PRAC) under the European Medicines Agency (EMA), who concluded that the reported associations between hydrochlorothiazide use and nonmelanoma skin cancer (NMSC) likely represent causality.[9] On this basis, Summary of Product Characteristics (SmPC) were updated and "dear health care provider" (DHCP) letters were distributed to prescribers across Europe October 17, 2018. The finding of an increased skin cancer risk has later been replicated in other data sources,[8,10-13]

The link between hydrochlorothiazide and skin cancer risk have received considerable attention both from the scientific and clinical communities as well as in lay media. In Denmark in particular, the presentation of the study findings via lay media spurred a debate on the effects of such dissemination on both patient worries, potentially leading to noncompliance, and the strain this poses on the health care system, when patients seek out their prescriber for clarification. While there is little doubt that Danish general practitioners were contacted by worried patients, the extent of this increased workload has not been quantified. Further, it is unknown to what extent the dissemination of the skin cancer association, through publications as well as the subsequent recommendations from the authorities, have impacted the use of hydrochlorothiazide. In this study, we therefore aimed to describe the use of hydrochlorothiazide in Denmark as well as health care contacts among antihypertensive users from January 2016 through September 2020.

2 | METHODS

2.1 | Cohort identification and data sources

We identified a cohort of all Danish residents filling at least one prescription for an antihypertensive agent between January 1, 2016 and September 31, 2020, as registered in the Danish National Prescription Registry.[14] Within this cohort, an individual was considered a user of a given antihypertensive drug or drug class from the date of filling a prescription for that drug and 120 days onwards. This interval was selected as most antihypertensives in Denmark are dispensed in packages of 100 tablets, thus covering 3–4 months of treatment. For members of the cohort, we obtained data from four nationwide registries: the Danish National Prescription Registry,[14] the Danish National Patient Register,[15] National Health Insurance Service Register,[16,17] and the Civil Registration System.[18] The data sources are described in detail in Supporting Information S1, and codes defining drugs and drug classes, as well as other covariates, are provided in Supporting Information S2. In Denmark, antihypertensives are only available via prescription, and as virtually all medical care in Denmark is furnished by the national health authorities, these data sources allow complete capture of all Danish antihypertensive users. In Denmark, hydrochlorothiazide and bendroflumethiazide are the two dominant thiazides and are used equally, while the use of indapamide is very limited and chlorthalidone is almost never used. Data were linked by the personal identification number, a unique identifier assigned to all Danish residents since 1968.[19]

2.2 | Analyses

First, the distribution between individual antihypertensive drug classes (of the total number of prescriptions filled while handling combination products as two distinct substances), was assessed in 1-month intervals throughout January 2016 to September 2020.

Second, the monthly number of new users of hydrochlorothiazide, and for comparison bendroflumethiazide, ACE inhibitors, and vascular CCBs, was assessed per month. New users were defined as a person filling a prescription for that drug or drug class with no previous prescription for the same drug or drug class within the last 5 years.

Third, the use of hydrochlorothiazide was assessed monthly throughout January 2016 to September 2020, relative to the use (number of prescriptions filled) during January 2016. This analysis was performed among all hydrochlorothiazide users, as well as stratifying by age (<50, 50–69, and ≥70 years) and by skin cancer history (any diagnosis in the Danish National Patient Registry prior to December 31, 2017).

Fourth, temporal changes in health care service utilization were assessed in data from the National Health Insurance Service Register by calculating the weekly rate of physical consultations and phone or e-mail consultations, respectively, to general practitioners. This was done specifically for hydrochlorothiazide users as well in the full cohort of all antihypertensive users.

Finally, to assess potential changes in rate of adverse outcomes, the monthly rate of hospital admissions due to myocardial infarction, stroke, and heart failure recorded in the Danish National Patient Registry among hydrochlorothiazide users was assessed.

2.3 | Other

Analyses were performed using Stata Release 16.1 (StataCorp, College Station, TX). According to Danish law, studies based solely on register data do not require approval from an ethics review board.[20] The data that support the findings of this study are available from the Danish Health Data Authority. Restrictions apply to the availability of these data, which were used under license for this study.

3 | RESULTS

We identified 1 316 476 unique users of antihypertensives during January 2016 to September 2020, of which 309 743 (24%) had filled at least one prescription for a hydrochlorothiazide-containing drug within the period (total 3 658 039 prescriptions; mean 12; median 11; interquartile range [IQR] 6–16). In January 2016, 12.7% of all filled prescriptions were for hydrochlorothiazide (Figure S1). By September 2020, this proportion had dropped to 7.2% (Figure S1).

The rate of new users of hydrochlorothiazide was initially stable around 2350 new users per month throughout most of 2017 but dropped at the time of the publication of the NMSC findings to 1133 new users in December 2017 month, afterwards declining slightly to 779 new users per month in December 2019 (Figure 1) and with a mean of 652 during January to September 2020. This decline was accompanied by a slight increase in the rate of new users of bendroflumethiazide, ACE inhibitors and vascular CCBs (Figure 1).

Compared to January 2016, the monthly total number of fills of hydrochlorothiazide was stable until the time of the publication of the NMSC finding (December 2017), after which it dropped by 44% by September 2020 (Figure S2). This drop was more pronounced among patients with a history of NMSC as well as among younger patients (Figure 2).

The publication of the NMSC findings were associated with a slight increase over 3 weeks in the number of physical consultations (Figure 3A) and a larger increase in the rate of e-mail/phone consultations (Figure 3B). The publication of the lip cancer and the melanoma findings as well as DHCP letters was not accompanied by any

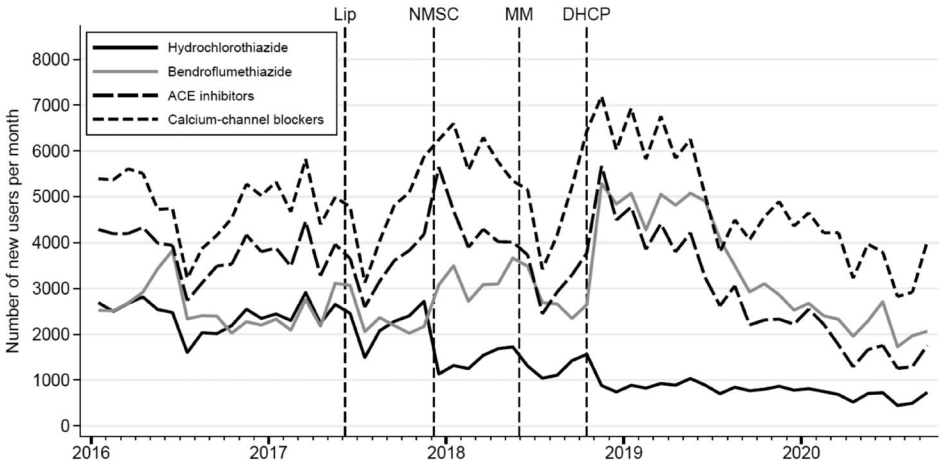

FIGURE 1 The rate of new users of selected antihypertensive drugs in Denmark January 2016 to September 2020. New use was defined as the first fill of a given drug or drug class, with no previous fill for that drug or drug class in the last 5 years. The vertical lines denote the time of publication of the increased risk of lip cancer (Lip), nonmelanoma skin cancer (NMSC), and melanoma (MM) associated with use of hydrochlorothiazide, as well as the distribution of "dear health care provider" (DHCP) letters

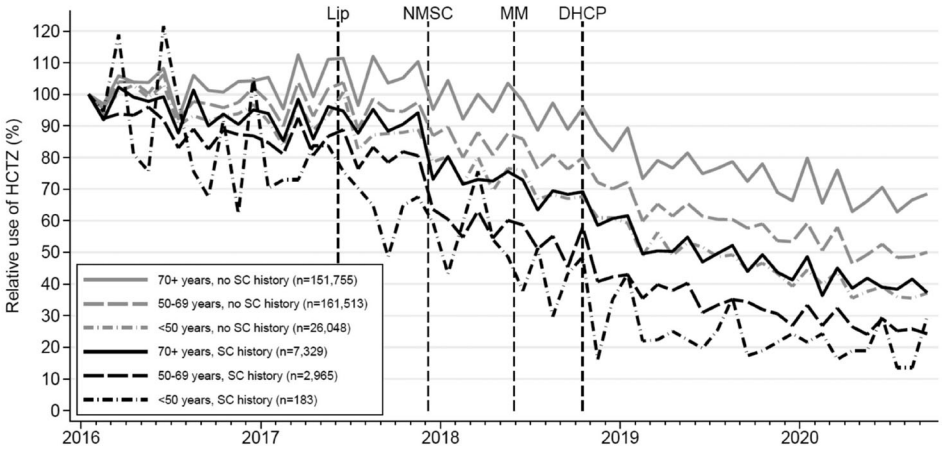

FIGURE 2 The relative use of hydrochlorothiazide (number of fills per month) January 2016 to September 2020 compared to January 2016, stratifying users by age and history of skin cancer (SC). The dashed lines denote the publication of findings of an increased risk of lip cancer (Lip), nonmelanoma skin cancer (NMSC), and melanoma (MM) as well as the distribution of "dear health care provider" (DHCP) letters

discernible increase in health care utilization. The datasets underlying these figures are provided in full in Supporting Information S3 and S4. The excess number of contacts at the time of the NMSC findings was quantified as follows: The average number of contacts in the 3 weeks where an increased rate of contacts was apparent was assessed and so was the average number of contacts in the 6 weeks immediately prior to this, as an estimate of baseline contacts. Among hydrochlorothiazide users, the difference in the averages, multiplied by the 3 weeks, yielded an excess of 8090 physical consultations and 17 300 e-mail/phone consultations. However, a similar trend was seen at the same time the previous year, as this was the 3 weeks leading up to the Christmas holiday. When subtracting the excess number of contacts seen in the previous year (calculated in the same way), the estimated number of excess contacts among hydrochlorothiazide users was 4630 physical consultations and 11 730 e-mail/phone consultations. When instead using the full cohort of all antihypertensive users (Figure S3) we estimated an excess of 11 510 physical consultations and 22 870 e-mail/phone consultations. The datasets provided in Supporting Information S3 and S4 allow others to perform their own assessments, in acknowledgement of the post hoc nature of these estimations. We performed two sensitivity analysis. First, we expanded the window of interest from 3 to 4 weeks, thereby also taking into account contacts during the week of the Christmas holiday. This led to an estimated excess of 2380 physical consultations and 9820 e-mail/phone consultations among hydrochlorothiazide users and 1420 physical consultations and 11 760 e-mail/phone consultations in the overall cohort of antihypertensive users. Second, we compared the three last weeks of 2018 directly to those in 2017, that is, without adjusting for the baseline level during the preceding 6 weeks. This led to an estimated excess of 1700 physical consultations and 4220 e-mail/phone consultations specifically among hydrochlorothiazide users and 5230 physical consultations and 10 770 e-mail/phone consultations among all antihypertensive users.

No increase in the rate of adverse outcomes, specifically admissions related to myocardial infarction, stroke, and heart failure, was seen with the publication of the three studies (Figure S4).

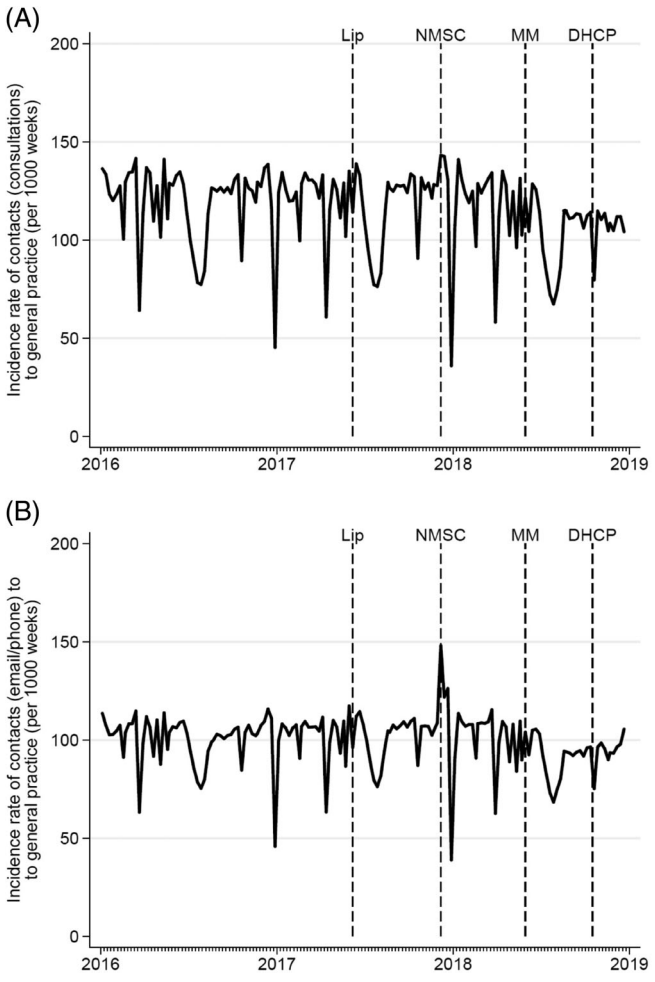

FIGURE 3 The rate of contacts to (A) physical and (B) e-mail/phone contacts to general practitioners among users of hydrochlorothiazide during 2016–2018. The dashed lines denote the publication of findings of an increased risk of lip cancer (Lip), nonmelanoma skin cancer (NMSC), and melanoma (MM) as well as the distribution of "dear health care provider" (DHCP) letters

4 | DISCUSSION

In this nationwide study of the use of hydrochlorothiazide, we found that the publication of studies linking hydrochlorothiazide use to an increased risk of skin cancer has led to a marked overall drop in the use of hydrochlorothiazide, most pronounced among younger patients and patients with a history of skin cancer. Further, the dissemination of the study linking hydrochlorothiazide to NMSC led to a moderate temporary increase in the rate of contacts to general practitioners among users of antihypertensives.

The primary strength of the present analysis is the use of nationwide data on prescription fills, allowing full and unselected capture of all Danish antihypertensive users and eliminating the risk of recall bias. However, several limitations need to be acknowledged. First, we do not have data on the specific reason for GP contacts. As such, we have assumed that the temporary increase in number of contacts can be attributed solely to the publication of the association between hydrochlorothiazide and NMSC. Further, the estimation of excess contacts should be considered a crude approximation, as illustrated by the fact that the two sensitivity analyses returned estimates that were approximately half of what was estimated in the main analyses. Another weakness is the crude marker used to identify patients with a history of skin cancer, that is, a hospital diagnosis. First, this diagnosis might be underrecorded, and, further, it does not capture patients with other skin disorders. Another limitation is the lack of data on other relevant risk factors for NMSC, such as a history of high UV exposure, which might make patients or physicians prefer other antihypertensives over hydrochlorothiazide. Lastly, the analysis of safety outcomes might be too crude to detect minor increases in risk. While a detailed individual-level analysis of risk is outside the

scope of the present paper, this is a potential topic for future research.

The 44% overall reduction in the use of hydrochlorothiazide highlights the impact that dissemination of new findings can have on prescribing patterns. This is in accordance with previous report of similar, yet more subtle, effects of news coverage of, for example, statins.[21] This, on one hand, shows the rapid uptake of new safety information among patients and prescribers, which is seemingly implemented quickly and in a differentiated manner regarding patient characteristics (in this case age and skin cancer history). On the other hand, however, a decline in hydrochlorothiazide use is also seen prior to the EMA recommendation in October 2018 and the distribution of DHCP letters, that is, before the official recommendations from the authorities were available. This, in combination with the excess number of health care contacts triggered by the dissemination of the NMSC findings, underscores the caution that researchers should apply when dissemination new findings via lay media. For this particular safety signal, the signal was judged to represent causality by the authorities and regulatory action was taken, however, in the event that the authorities had reached a different conclusion, or if subsequent studies had found different results or had uncovered unrecognized biases or design flaws, the situation would have been very different.

5 | CONCLUSION

The publication of an increased risk of skin cancer with use of hydrochlorothiazide has made a significant impact on the use of hydrochlorothiazide, alongside a temporary increase in the rate of GP contacts. This highlights the impact that new findings can have on drug utilization patterns as well as the health care systems, which needs to be considered when deciding if and how findings of new studies should be disseminated to patients and clinicians ahead of regulatory decisions.

CONFLICT OF INTEREST

Anton Pottegård declares that he has received funding from LEO Pharma (the Danish manufacturer of bendroflumethiazide) for unrelated projects, all paid to the institution where he is employed. The remaining authors report no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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