

# Diuretics for Hypertension—Reasons for a Contradiction in Primary Care Prescribing Behavior: A Qualitative Study

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There has been a long international discussion on diuretics as first-line therapy for hypertension. In Germany, thiazide diuretics are very rarely prescribed in monotherapy and concurrently highly prescribed in fixed-combinations. The aim of this study was to approach the reasons for this inconsistency in primary care prescribing behavior. A qualitative study design consisting of single interviews with general practitioners (GPs) was chosen. Most GPs perceived diuretics as too weak to treat arterial hypertension effectively in monotherapy. In combination therapy,

GPs expected to spare the dose and to offset certain side effects of other drugs. The convenient availability of diuretics in most fixed-dose combinations on the German drug market was seen as an important reason for their frequent prescription in combination therapy. Thus, the reasons given by the GPs differed from the main arguments of the academic debate. Dissemination strategies for guidelines should take the perceptions and opinions of practicing GPs into account. *J Clin Hypertens (Greenwich)*. 2012; 14:680–685. ©2012 Wiley Periodicals, Inc.

Cardiovascular disease (CVD) is the leading cause of death in industrial nations. Its prevention by taking care of the risk factors is of high significance. A major risk factor of CVD includes high blood pressure (BP).<sup>1</sup>

There are different BP-lowering treatments available, including thiazide diuretics,  $\beta$ -blockers (BB), calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). In Germany, there are two major guidelines for hypertension. According to one, diuretics, BB, and ACE inhibitors are the drugs of first choice to treat hypertension.<sup>2</sup> The other guideline takes the view that all available drug classes are equally appropriate as first-line drugs for hypertension.<sup>3</sup> Worldwide, many guidelines, eg, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure in the United States, recommend that diuretics should be prescribed as first-line therapy for most hypertensive patients<sup>4</sup>; however, internationally, there has been an ongoing debate about the use of diuretics as first-line medication before all others. In the 1990s, vigorous marketing of newer drugs led to a decline in their prescribing.<sup>5</sup> In response to this trend, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), financed by public money, was conducted. The conclusion was that newer antihypertensive agents are not superior to thiazide-based treatment.<sup>6</sup>

Based on a systematic literature search, the German Institute for Quality and Efficiency in Health Care (IQWiG) published a preliminary report in November 2009. The IQWiG recommended that diuretics should be prescribed as first-line therapy for most patients.<sup>7</sup> This recommendation initiated an intense national discussion in Germany. Arguments against diuretics as first-line therapy were mainly based on pathophysiologic reasoning, eg, their influence on glucose and electrolyte metabolism. Other arguments referred to their low persistence rates.<sup>8–10</sup> However, there is no scientific evidence that poor tolerance in patients or side effects are responsible for this. The international discussion about the role of diuretics as first-line therapy may be considered predominantly academic, because most patients need diuretics in combination with other antihypertensive agents in order to achieve BP targets.<sup>11</sup> A descriptive cross-sectional study by Kuehlein and colleagues<sup>12</sup> found that in monotherapy, thiazide diuretics such as hydrochlorothiazide (HCTZ 1.5%) were very rarely prescribed in Germany. On the other hand, 79% of patients receiving combination therapy had a diuretic, mostly HTCZ (80.8%), of which 76.2% were fixed combinations.<sup>12</sup> In view of the arguments for and against diuretics quoted in the debate, we perceived this nonprescribing of diuretics in monotherapy and their almost constant prescribing in combination therapy as a contradiction. Therefore, the aim of our study was to approach the reasons for this inconsistency in primary care prescribing behavior.

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## METHODS

### Design of the Study

A qualitative study design consisting of semistructured interviews was chosen to allow an intensive analysis of

subjective motives, attitudes, and ideas of participating general practitioners (GPs).

### Sample

The cross-sectional study by Kuehlein and colleagues that showed the contradiction in prescribing was based on data from the Continuous Morbidity Registration Epidemiologic Network (CONTENT), a scientific network of 22 primary care practices in Germany. CONTENT is a project of the Department of General Practice and Health Services Research at the University Hospital Heidelberg. It aims to establish a system for adequate record-keeping and analysis in primary care based on the International Classification of Primary Care (ICPC-2). The project is described in detail elsewhere.<sup>13</sup> In the present study, all GPs contributing their data to the CONTENT database were included.<sup>12</sup> In February 2011, letters of invitation were sent to all 22 of the participating primary care practices. Ten GPs agreed to be interviewed. Of the remaining primary care practices, two GPs gave time constraints as the reason not to participate. The rest did not respond to this first invitation. Table I shows characteristics of the participating practices and physicians.

### Data Collection

The interviews, performed by the first author (HL), lasted between 30 and 60 minutes each and took place in the physicians' offices between March and April 2011. All GPs gave their consent to participate by signing a form. The interviews were semi-structured by open ended questions. Data were treated on a numbered pseudonym basis so that they could not be traced back to any named person. A list of questions was developed by an interdisciplinary team of researchers on the basis of intensive literature work, including the following key topics:

- Personal opinion of single therapeutic agents as:
  - first-line therapy
  - second-line therapy
- Personal opinion of diuretics
- Personal explanation for the inconsistency of concurrent nonprescribing of diuretics in monotherapy and prescribing in combination therapy
  - Reasons for personal therapeutic decisions and role of combination therapy

Data collection was continued until clear saturation of new information was achieved.

### Ethics Approval

The study was approved by the ethics committee of the University of Heidelberg (approval number S-338/2010).

### Data Analysis

The 10 interviews were conducted, audiovisually recorded, and transcribed consecutively. Key issues were identified, summarized, coded, and sorted into

**TABLE I.** Characteristics of the Participating Practices and Physicians

	Number
Participating general practitioners	10
Participating primary care practices	
Solo practices	5
Group practices	4
Localization	
Urban	3
Suburban	3
Rural	4
Mean age in y (SD)	55.9 (6.54)
Mean time in private practice in y (SD)	18.6 (8.48)
Abbreviation: SD, standard deviation.	

themes and categories based on the principles of qualitative content analysis by Mayring.<sup>14</sup> Qualitative content analysis means an inductive development of categories followed by a deductive application of these categories. Analysis was done separately by the first (HL) and the last author (TK) using ATLAS.ti-Software (Berlin, Germany).<sup>15</sup> According to the rules of qualitative content analysis, the categories were developed near to the original material. A quotation was used to illustrate each of the categories.<sup>16</sup> To control for empirical saturation of the case material, interviews and analyses were conducted consecutively.<sup>17</sup> Empirical saturation was reached after the seventh interview. The analysis of the last 3 interviews did not show any new aspects or arguments. The categorizing system was consequently modified and disagreements during this process were discussed until consensus was achieved.

## RESULTS

Through the analytical process, four main themes could be identified:

- (1) attitudes towards diuretics,
- (2) prescribing strategies,
- (3) influences on prescribing behavior, and
- (4) interpretation of the observed inconsistency in primary care prescribing behavior.

The themes and the corresponding categories are also displayed in Table II.

### Attitudes Towards Diuretics

As positive aspects of diuretics, the GPs mentioned the possibility of dose saving of other drugs when using diuretics in combination therapy. This also led, in their opinion, to a reduction of side effects by prescribing lower doses for each drug. Furthermore, it was important for the doctors to even offset certain side effects when using an appropriate combination of the single substances. An example given was the combination of an ACE inhibitor and diuretic:

“Well, in combination, ACE inhibitors/HCTZ they partly counterbalance each other. The

**TABLE II.** Results Classified by Themes and Categories

Theme	Category
Attitudes towards diuretics	Positive aspects Negative aspects
Prescribing strategies	Considerations of first-line therapy Considerations of second-line therapy Considerations of combination therapy
Influences on prescribing behavior	Basis for decision-making Influence of pharmaceutical industry Attitudes to guidelines and evidence-based medicine
Interpretation of the observed inconsistency in primary care prescribing behavior	Effectiveness of diuretics Availability of drug combinations

potassium-sparing part of the ACE inhibitor will be compensated a little bit by the potassiuretic part” (GP 6).

Furthermore, some doctors assumed a synergistic effect of diuretics in combination therapy, especially in combination with an ACE inhibitor.

“In principle, HCTZ amplifies the BP-lowering effect of the ACE inhibitor. For me it is synergism” (GP 3).

Despite some positive aspects when using diuretics in combination therapy, the majority of GPs had a negative attitude towards them. Concerns about side effects of diuretics, ie, their influence on glucose, lipid, and electrolyte metabolism, were mentioned by many as reasons for not prescribing diuretics in monotherapy.

“Yes, in my eyes, HCTZ has no satisfying BP-lowering effect. It is something, if you want a little bit more, on the top. [...] In diabetic patients it appears to be rather poor. Because of all these exclusions, there are not many patients for whom it is good to prescribe” (GP 10).

The doctors explained that the occurrence of these side effects depends on the dose. At a dose of 12.5 mg HCTZ, most of the GPs reported seeing no significant side effects. They agreed that the side effects of diuretics perceivable by the patients, if present in monotherapy, should also play a role in combination therapy. However, this could not be observed in clinical practice. The GPs stated that they saw side effects caused by diuretics at a dosage of 12.5 mg only as a theoretical problem.

“No, there are no other side effects at a dosage of 12.5 mg HCTZ. [...] They do not play a role at this low dosage of 12.5 mg HCTZ” (GP 5).

**Prescribing Strategies**

Most GPs stated a preference for ACE inhibitors as first-line agents to treat hypertension.

“In my opinion the best drugs are ACE inhibitors, I also start with them [...] Regarding to diastolic hypertension an ACE inhibitor is superior to other antihypertensive drugs. The second point is, that ACE inhibitors are better analyzed related to cardiovascular endpoints and that is the reason why I always use an ACE inhibitor as first-line therapy” (GP 5).

The minority who use diuretics as first-line agents stated their reluctance to increase the dose. In cases of insufficient effectiveness, they would prefer to switch to combination therapy at an early stage instead. For second-line therapy, GPs favored diuretics, mostly as a fixed combination.

“Then I add on HCTZ, but I do not start with HCTZ. Well, then I use a combination of an ACE inhibitor plus HCTZ. They are readily available, 5 mg/12.5 mg. There is also a combination of ARB and HCTZ, but this is my second choice, if the ACE inhibitor can’t be given” (GP 8).

**Influences on Prescribing Behavior**

GPs held many different factors responsible for their decision for or against a drug. Above all, they gave the differential therapy according to comorbidities of individual patients and long clinical experience with certain drugs as the main basis for decision-making.

“The choice for or against a drug depends on the comorbidity of the patient, especially coronary heart disease or heart failure” (GP 2).

The routine and reflex-like mechanism in making therapeutic decisions was a recurring theme. Modifications of these routines were said to be rare and to require an active cognitive process and discussion. The GPs described the change of prescribing behavior from one to another drug class as a long and difficult process.

“You know, you do it for 10 years, it works, you are happy with it. Then these people come, do this study, and tell you to do it in a different way. You can try to consider that, but I do not know if you have habits, habits for more than 20 years? Until you change them, it takes another 20 years [...] It is like a tankship. If you want to change the direction of a big tankship, it takes a while. And if you got it in the new lane, the newest study says, you are wrong, turn around” (GP 4).

Guidelines were formally accepted as important but perceived as unaccommodating advices. The GPs insisted on a nonbinding nature of guidelines because of the individuality of patients.

“The guideline collapses because of the variety of the case histories in daily practice, because of the patients. You cannot force them to use it. Every single patient is too individual for a guideline” (GP 10).

Most GPs perceived guidelines as academically afflicted and incompatible with their clinical practice. From their point of view, to read them in their full extent takes too long in everyday practice.

### Interpretation of the Observed Inconsistency in Primary Care Prescribing Behavior

The GPs explained the contradiction of the nonuse of diuretics in monotherapy mainly as a result of their ineffectiveness in treating hypertension. Diuretics seemed to them to be too weak in monotherapy to reach a sufficient decrease of BP.

“Well, it just depends on the fact that it is too weak. That it works ineffectively in monotherapy, but much better in combination” (GP 8).

Their convenient availability in fixed combinations on the German drug market was seen as the main explanation for their frequent prescription in combination therapy.

“It is because of the convenient availability of fixed combinations [...] and because they are offered this way by the pharmaceutical industry” (GP 10).

The willingness of patients to take diuretics was perceived to be higher in a fixed-dose combination than in monotherapy.

## DISCUSSION

Most GPs saw diuretics as too weak to treat arterial hypertension effectively in monotherapy. For combination therapy, GPs not only expected to spare the dose of other drugs, but also to offset certain side effects of the single substances. At a dosage of 12.5 mg, doctors perceived side effects caused by diuretics mainly as a theoretical problem. Habits, but also differential therapy according to comorbidity and long clinical experience, were given as the basis for decision-making. Guidelines were seen as nonbinding advice and as often incompatible with clinical practice. GPs perceived the willingness of their patients to take diuretics to be higher in fixed-dose combinations than in monotherapy. The convenient availability of diuretics in most fixed combinations on the German drug market was seen as an important reason for their frequent prescription in combination therapy.

The GPs in our study named an insufficient BP-lowering effect as the main reason for their rejection of diuretics in first-line therapy. However, diuretics were expected to act as a supplement if the BP goal is not reached. Evidence suggests that diuretics can, in fact, reduce resistance to antihypertensive therapy

when given in combination with other antihypertensive agents.<sup>11,18,19</sup> A large number of hypertension studies come to the conclusion that adequate dosing of all essential hypertension drugs leads to a comparable efficiency in lowering BP.<sup>20</sup> Others have shown that at least in the commonly used low-dose range, HCTZ seems to be less effective.<sup>21,22</sup> The BP-lowering effect of HCTZ might be less pronounced for 24 hours compared with ARBs, ACE inhibitors, CCBs, and BBs.<sup>22</sup> Going beyond mere BP, however, another study concluded that there are no significant differences in total major cardiovascular events between regimens based on ACE inhibitors, CCBs, diuretics, or BBs.<sup>23</sup>

Differential therapy according to comorbidity was frequently named as the basis for decision-making. Despite an intensive literature search, little could be found on the practical process of decision-making of GPs when treating hypertension. In a Norwegian study on guideline implementation in primary care, the reasons given by physicians for not prescribing diuretics as first-line therapy were also fear of side effects, an insufficient BP-lowering effect, the influence of the pharmaceutical industry, and old habits and tradition.<sup>24</sup> A Canadian study of prescribing practices for antihypertensives in the elderly showed that age, sex, and comorbidities influenced the use of thiazides.<sup>25</sup> Men and diabetic patients were less likely to be prescribed thiazide diuretics.<sup>25</sup> From the perspective of pathophysiologic reasoning, it makes sense to prescribe diuretics together with other drugs, eg, ACE inhibitor or ARB, as these drugs have antipotassiuretic effects. Negative effects of diuretics on electrolyte and glucose metabolism might indeed be counterbalanced by combination with an ACE inhibitor or ARB.<sup>26</sup> Research has shown that a daily thiazide dose of 25 mg to 50 mg (low-dose) is similarly effective as higher dosages, for example, 5 mg/d to 100 mg/d.<sup>27</sup> Furthermore, low doses are usually well tolerated and improve quality-of-life measures.<sup>28</sup>

The recommendation of the IQWiG has no guideline character.<sup>7</sup> However, the two most important guidelines in Germany recommend at least the use of diuretics in treating hypertension as first-line therapy equally among others.<sup>2,3</sup> Actual prescribing behavior contrasts also with these recommendations. In a German cross-sectional study on the management of hypertension and diabetes, it was shown that less than half of the physicians generally followed current guidelines.<sup>29</sup> The question arises why guidelines receive so little attention. Similar to our results, a recent qualitative study in Germany observed that many GPs do not accept them.<sup>30</sup> They perceive the personal character of the individual patient care and working with guidelines as a contradiction. However, this does not explain that on the one hand, the patient's individuality is important and difficult to treat in monotherapy, while on the other hand, almost every patient gets a diuretic when it comes to combination therapy.

According to the participants, the patients' willingness to take diuretics was higher in fixed combinations than in monotherapy. Studies about persistence have shown that persistence was shortest for diuretics in monotherapy and longest for diuretic-ARB combinations, followed by an ARB alone.<sup>8,24,31</sup> In addition, it has been shown that initiating therapy with an HCTZ fixed-dose combination with an ACE inhibitor, ARB, or BB was associated with greater persistence and adherence as compared with HCTZ monotherapy.<sup>10,32</sup> There might be two explanations for this phenomenon. Either ARBs indeed counterbalance the negative effects of diuretics perceivable by the patients, or it is the positive nimbus of the modern and expensive ARB that covers the negative attitude towards diuretics for patients and physicians alike. Not only for diuretics, however, but also for other antihypertensive drugs, fixed-dose combinations of antihypertensive agents are associated with a significant improvement in adherence.<sup>33</sup> It is highly improbable that only patient-associated factors account for the fact that persistence for diuretics is longest in fixed combinations and shortest in monotherapy.

The majority of GPs in our study supposed that the convenient availability of diuretics in fixed-dose combinations on the German drug market might lead to the fact that diuretics are highly prescribed in combination therapy. There are 4 agents that belong to the group of thiazide diuretics on the German market: HCTZ, chlorthalidone, xipamide, and indapamide.<sup>34</sup> The amount of their benefit concerning prevention of cardiovascular outcomes is not interchangeable. However, as HCTZ is the thiazide diuretic most frequently used in Germany by far, the observed inconsistency in primary care prescribing behavior relates predominantly to prescribing patterns of HCTZ. According to our findings, the reason for this preference of HCTZ might simply be its predominance in fixed-dose combinations on the German market.

One of the main sources of German prescribing epidemiology reported an increased use of thiazide diuretics in the past 10 years.<sup>34</sup> The prescription volume of thiazide diuretics has doubled since 2000. However, this analysis also includes all fixed-dose combinations of thiazide diuretics with other antihypertensive drugs. In 2009, 84% of the prescriptions of diuretics accounted for fixed combinations.<sup>34</sup>

The inconsistency in primary care prescribing behavior concerning diuretics seems not to be only a German phenomenon. A Turkish study found that almost half of the patients on dual-combination therapy were treated with mostly diuretic-based, fixed-dose combinations.<sup>35</sup> In a study on prescribing patterns of antihypertensive drugs in Finland, Wallenius and colleagues<sup>36</sup> found that of 3638 patients taking antihypertensives, 48% received monotherapy and 52% combination therapy. A diuretic was the second choice in monotherapy for women, whereas men were

often prescribed BBs, ACE inhibitors, or CCBs before using a diuretic. Of patients receiving combination therapy, 75% received two different agents, most often a diuretic with a BB.<sup>36</sup>

Poluzzi and colleagues<sup>31</sup> evaluated the prescribing pattern of the initial treatment of hypertension in general practices in Italy. Monotherapies with an ACE inhibitor or a CCB were the most frequently prescribed regimens (79%). About 75% of the 2-drug combinations included a diuretic.<sup>31</sup>

## STRENGTHS AND LIMITATIONS OF THE STUDY

A limitation of the study might be seen in the small number of interviews (only 10). However, compared with other interview studies and due to the fact that topic saturation occurred after the seventh interview, 10 interviews seem to be sufficient to answer our research question. According to the qualitative design, the results presented here can only generate hypotheses and give an idea of possible reasons for an observed behavior. They can provide a basis for further research.

Since participation in the project is voluntary, it is not precisely known how representative the members of the research network were. Evidence suggests that research-active practices are likely to be comparable to the wider primary care community,<sup>37</sup> but also that there are deviations.<sup>38</sup> An interview tries to transform tacit knowledge into explicit knowledge.<sup>39</sup> The answers of the interviewed physicians must be seen as a first interpretation of their own acting. Nevertheless, the GPs are closest to their own reasons for therapy decisions. The authenticity of a collegial discussion during the interview might result in a good approximation to the real reasons for the prescribing behavior observed.

## CONCLUSIONS

Diuretics are rarely prescribed in monotherapy and highly prescribed in fixed combinations in Germany. This contradiction was explained by the participants for the following reasons: insufficient BP-lowering capacity and concerns about side effects associated with monotherapy on the one hand and convenient availability of diuretics in fixed combinations on the other. National and international guidelines for the treatment of hypertension are insufficiently accepted and thus do not translate into clinical practice. Independent of scientific correctness of the reasons given by the GPs, these are the opinions that translate into prescribing practice. Therefore, dissemination strategies for guidelines should take these ideas and perceptions of practicing physicians into account.

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