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ORIGINAL ARTICLE

Between-country variation in the utilization of antihypertensive agents: guidelines and clinical practice

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Variation in antihypertensive drug utilization and guideline preferences between six European countries (Denmark, Finland, Germany, Norway, Sweden, the Netherlands) was investigated. Our objectives were to compare between-country variability in utilization per class of antihypertensive agents and to assess guideline preferences in relation to actual use. Antihypertensive consumption data (2003) was retrieved. We classified antihypertensive agents using ATC-codes: C02CA – alpha-blockers (AB), C03A – thiazide diuretics (TD), C07AB – beta-blockers (BB), C08CA – dihydropyridine calcium antagonists (CA), C09A/C09BA/C09BB – ACE-inhibitors + combinations (AI) and C09C/C09D – angiotensin II receptor blockers + combinations (AT2). For each class, DDDs/1000 persons/day and share (%) of total antihypertensive utilization was calculated. Per class, relative standard deviations (RSD) across countries were computed. Current hypertension guidelines were requested from national medical associations. Total antihypertensive utilization varied considerably, ranging from 152.4 (Netherlands) to 246.9 (Germany) DDDs/1000 persons/day. RSD was highest for TD (106.2%) and AB (93.6%). Where guidelines advocated TDs (Norway and Netherlands), TD utilization was below (Norway) or just above (Netherlands) median TD use. Guidelines recommended TD (Norway and Netherlands), TD/BB/AI (Finland, German Physicians Association) or TD/BB/CA/AI/AT2 (Denmark, German Hypertension Society), Sweden had no recent national guideline. In conclusion, antihypertensive utilization patterns varied largely across these six countries, in absolute and relative terms. Furthermore, guidelines seem disconnected from clinical practice in some countries, and none of the guidelines discuss current utilization. Whether this reflects a need for change in prescribing or re-evaluation of guidelines warrants further research.
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Introduction

Hypertension is one of the most important risk factors for cardiovascular disease. In recent decades, the management of hypertension has improved markedly, contributing to a strong decrease in death rates in North America and Western Europe.[1,2] Improvements in reducing this risk factor can be attributed to lifestyle modifications and better detection, but an increase in the use of effective pharmacological therapies has also played an important role.

The widespread use of antihypertensive agents, the public health relevance of hypertension as a risk factor, and the costs involved have made this drug class a topic in drug utilization research and 'evidence-based medicine' from early on.[3,4] Moreover, many national medical associations and international organizations aim to promote certain prescribing behaviour by publishing and implementing 'evidence based' guidelines.

Although international differences in the prevalence of hypertension have been the subject of several studies,[5,6] between country differences in drug utilization and guideline preferences are less well-documented. Therefore, our objective in this study was to evaluate, within the class of antihypertensive agents, the variation of drug utilization between six Northern European countries by using a relative standard deviation (RSD) measure and to assess guideline preferences in relation to current use.

Materials and methods

We defined six classes of antihypertensive agents based on Anatomical Therapeutic Chemical (ATC)

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codes, as determined by the World Health Organization Collaborating Centre for Drug Statistics Methodology,[7] namely: alpha-blockers (C02CA), thiazide diuretics (C03A), selective beta-blockers (C07AB), dihydropyridine calcium antagonists (C08CA), ACE-inhibitors + combinations (C09A/C09BA/C09BB) and angiotensin II receptor blockers + combinations (C09C/C09D). We only included these drug classes in this study, since we considered them to be the most important classes for the treatment of (uncomplicated) hypertension, and classes for which hypertension will be the main indication within the class. For example, centrally acting compounds are considered obsolete or used for specific types of hypertension (e.g. hypertension during pregnancy). For non-selective beta-blockers, and non-dihydropyridine calcium antagonists we assumed, based on current evidence and guidelines, that these are primarily prescribed for other indications, such as angina pectoris or cardiac arrhythmias.

Six Northern European countries were selected for this analysis: Denmark, Finland, Germany, Norway, Sweden and the Netherlands. These countries are comparable in terms of a variety of factors, including demographic characteristics and GDP per capita (see Table 1).[8,9]

We collected drug utilization data for the six included countries for the year 2003 from public sources, an overview of these sources is given in Table 2. Drug utilization was captured using either reimbursement data (2), wholesaler figures (2), or dispensing information (2). All sources report drug use as Defined Daily Doses (DDD), a dosage measure developed by the World Health Organization. For all countries except Germany the reported data were estimates for the whole population. The German data reported drug consumption of patients insured through the sick fund (Gestzliche Krankenversicherung), consisting of 70.42 million people, or about 85.3% of the total German population in 2003.

Utilization rates were calculated as DDDs per 1000 persons per day, a measure widely used in drug utilization research. We computed these rates on the basis of the average population in a year as reported

Table 1 Characteristics of countries. All data for 2003

	Denmark	*Finland*	*Germany*	*Norway*	*Sweden*	*The Netherlands*
Population (millions)	5.4	5.2	82.5	4.6	9.0	16.2
Population aged 65 and over (%)	15	16	18	15	17	14
GDP per capita (US Dollar)	30 733	28 455	27 094	37 017	28 881	30 315
Health expenditure as a share of GDP (%)	9.0	7.4	11.1	10.3	9.4	9.8
Pharmaceutical spending (% of all health spending)	9.8	16.0	14.6	9.4	12.6	11.4
Pharmaceutical spending per capita (US Dollar PPP)	272	339	436	341	340	340
Ischemic heart disease (standardized death rates per 10 000 persons)						
Males	148.0	223.9	163.0	148.0	162.6	105.5
Females	74.5	108.9	84.6	67.6	77.6	48.7
Cerebrovascular disease (standardized death rates per 10 000 persons)						
Males	63.2	64.4	61.3	58.5	59.0	57.9
Females	51.9	53.6	47.9	46.8	48.1	47.5

Source: OECD Health Data 2005[8]

Table 2 Sources of utilization data and guideline preferences for first choice antihypertensive agents in uncomplicated hypertension (shaded boxes)

	Utilization data source	*Data type*	*Guideline source*	*Year*	*TD*	*BB*	*AI*	*CA*	*AT2*
Denmark	Danish Medicines Agency	Dispensing	Danish Hypertension Society	2004					
Finland	National Agency for Medicines	Wholesaler	Finnish Medical Society	2002					
Germany	Sick Fund (Arzneiverordnungsreport 2004)	Reimbursement	(1) German Physicians Association	2004					
			(2) Hypertension Union	2003					
Norway	Institute of Public Health	Wholesaler	College of General Practitioners	2000					
Sweden	Apoteket	Dispensing	— (Last national guideline: 1993)	—					
Netherlands	Health Care Insurance Board	Reimbursement	College of General Practitioners	2003					
Europe	NA	—	European Society for Hypertension	2003					
United States	NA	—	JNC-7	2003					
Worldwide	NA	—	WHO/ISH	1999					

Abbreviations: AI = ACE-inhibitors, AT2 = angiotensin II receptor blockers; BB = beta-blockers, CA = calcium antagonists, ISH = International Society for Hypertension, JNC-7 = seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, TD = thiazide diuretics, WHO = World Health Organization.

by the national statistics agency of a country, or, in the German case, based on the number of persons insured through the sick fund.

The level of between-country variation in drug utilization was calculated for each class of antihypertensive agents across the countries with a relative standard deviation (RSD) measure, defined as:

$$100 * \frac{\text{Standard deviation of class utilization as \% of total antihypertensive use}}{\text{International average of class utilization as \% of total antihypertensive use}}$$

A large RSD value indicates a large variation in relative usage share between countries. A similar measure was also used elsewhere to assess variation in drug utilization between countries.[10]

We retrieved general practice hypertension guidelines from national (medical) associations. We screened each guideline for the recommended first choice drug(s) in patients with uncomplicated hypertension (i.e. in adults with no co-morbidities or other special circumstances), and it was determined whether or not the guideline discussed current utilization of antihypertensive agents in the respective country. For comparison, we also retrieved the WHO/International Society for Hypertension (ISH) guideline, the guideline of the European Society of Hypertension and the US guideline from the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7).

Results

The calculated utilization rates of antihypertensive drugs are shown in Table 3. The absolute utilization rates of antihypertensive agents ranged from 152.4 to 246.9 DDDs/1000 persons/day for the Netherlands and Germany respectively, a difference of 62% (Figure 1). The relative consumption of antihypertensive classes as a percentage of total antihypertensive consumption, based on DDDs, is shown in Figure 2. The Figure shows that in all countries ACE inhibitors & combinations are the primary drug class used. Relative use of thiazide diuretics use shows large variation, ranging from 25.0% of all antihypertensives in Denmark to 2.4% in Finland. The Finnish data also show a relatively low use of beta-blockers. Furthermore, Norway has a higher utilization of alpha-blockers and angiotensin II receptor blockers compared to the other countries.

When relative standard deviations were calculated, RSDs varied from 14.1% for dihydropyridine calcium channel blockers to 106.2% for thiazide diuretics (Figure 3).

Thiazide diuretics and alpha-blockers remain the classes with the highest variation even when the two extreme values with regards to thiazide or alpha-blocker use, Denmark and Norway, were excluded from the analysis.

Guideline preferences for first choice antihypertensive agents in uncomplicated hypertension in the six countries are depicted in Table 2. With respect to the preferences of the guidelines we discerned three groups. First, in the Dutch (2003)[11] and Norwegian (2000)[12] general practice guidelines for the treatment of uncomplicated hypertension there is a stated preference for thiazides as monotherapy. This is comparable to JNC-7, which recommends thiazide diuretics as the first treatment of choice as well.[13] Where guidelines advocated TDs, TD usage was

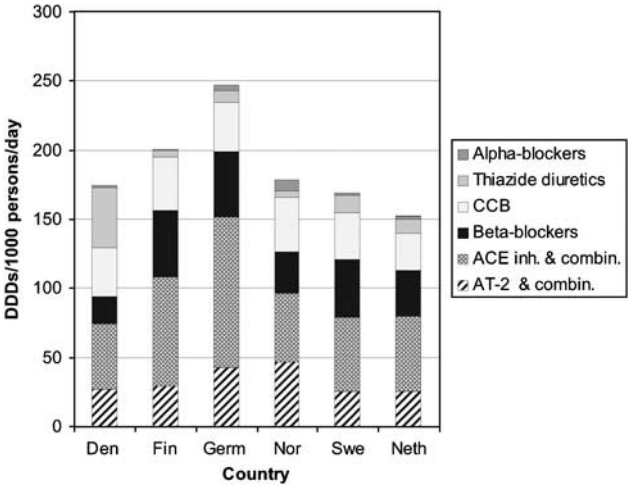

Figure 1 Total utilization of antihypertensive agents per country (AT2 & combin. = angiotensin II receptor blockers and combinations, ACE inh. & combin. = ACE-inhibitors and combinations, CCB = dihydropyridine calcium antagonists).

Table 3 Utilization of antihypertensives in DDDs/1000 persons/day. % of total utilization is shown between parenthesis

Drug class	*Denmark*		*Finland*		*Germany*		*Norway*		*Sweden*		*Netherlands*	
Alpha-blockers	1.60	(0.9)	0.47	(0.2)	3.59	(1.5)	7.80	(4.4)	1.50	(0.9)	2.20	(1.4)
Thiazide diuretics	43.70	(25.0)	4.84	(2.4)	9.24	(3.7)	4.95	(2.8)	13.12	(7.8)	10.32	(6.8)
Selective beta-blockers	19.70	(11.3)	48.39	(24.1)	47.34	(19.2)	30.20	(16.9)	42.00	(24.8)	32.56	(21.4)
Dihydropyridine calcium antagonists	35.50	(20.3)	39.04	(19.5)	35.52	(14.4)	39.70	(22.2)	33.84	(20.0)	27.25	(17.9)
ACE-inhibitors+combinations	47.10	(27.0)	78.83	(39.3)	108.68	(44.0)	49.60	(27.8)	53.18	(31.4)	55.02	(36.1)
Angiotensin II receptor blockers+combinations	27.00	(15.5)	28.99	(14.5)	42.56	(17.2)	46.40	(26.0)	25.50	(15.1)	25.01	(16.4)
Total	174.60	(100.0)	200.56	(100.0)	246.93	(100.0)	178.65	(100.0)	169.15	(100.0)	152.37	(100.0)

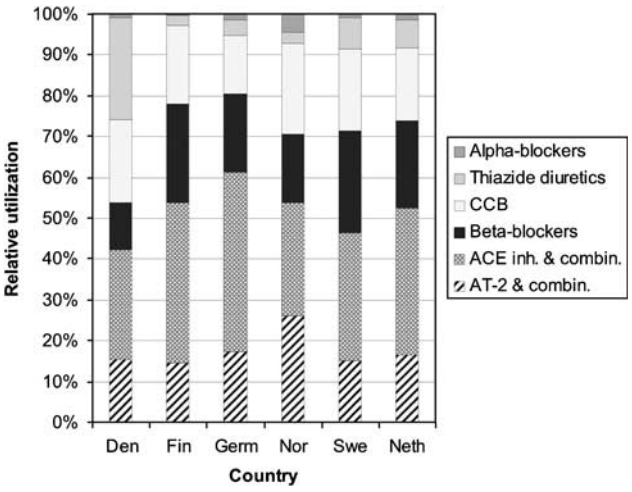

Figure 2 Relative utilization of antihypertensive drug classes (AT2 & combin. = angiotensin II receptor blockers and combinations, ACE inh. & combin. = ACE-inhibitors and combinations, CCB = dihydropyridine calcium antagonists).

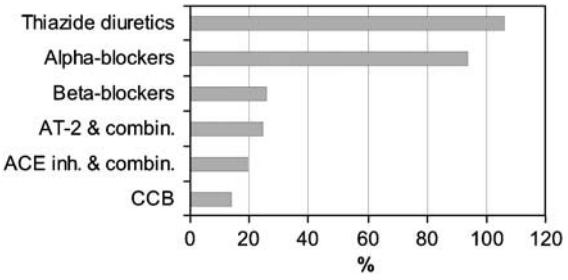

Figure 3 RSD across countries per drug class (AT2 & combin. = angiotensin II receptor blockers and combinations, ACE inh. & combin. = ACE-inhibitors and combinations, CCB = dihydropyridine calcium antagonists).

below (Norway) or just above (Netherlands) median use.

The second group consists of guidelines stating a preference for thiazides, ACE-inhibitors or beta-blockers as a first choice. A previous Danish guideline (1999),[14] the Finnish general practice guideline (2002)[15] and the guideline published by the Drug Committee of the German Medical Association (2004)[16] are examples of this group.

A third group of guidelines is in line with the WHO/ISH guideline (1999)[17] and the guideline published by the European Society for Hypertension (2003).[18] In these guidelines either thiazide diuretics, β-blockers, calcium antagonists, ACE inhibitors or angiotensin II receptor blockers, are suitable first choice drugs in the treatment of uncomplicated hypertension. The 2004 guidelines by Danish Heart Association/Danish Hypertension Society,[19] and the German Hypertension Society[20] belong to this group.

In Sweden, the most recent national guideline was published in 1993 and seems to be outdated in the light of the recent evidence. A few years ago, county level formulary committees were made responsible for drug lists and clinical practice guidelines in Sweden.[21] We did not evaluate these local guidelines. Recently, the Swedish Council on Technology Assessment in Health Care published a systematic review in which all drug classes were regarded as equally effective.[22]

In none of the guidelines the current utilization of antihypertensive agents in the respective country was discussed.

Discussion

This study shows large differences in both the relative and absolute utilization of antihypertensive agents. Furthermore, the RSD, as depicted in Figure 3, shows that the between-country variation of classes such as thiazide diuretics and alpha-blockers is particularly pronounced. Especially for thiazide diuretics the difference between the six countries is remarkable. Thiazide diuretics are recommended in all included guidelines as a valid first choice, they have a long track record, are cost-effective and are supported by solid evidence.[23] However, they also show the largest variation in use, indicating strong variability in acceptance in clinical practice across the six studied countries. The variation in utilization for this class remains large even when the use of thiazide diuretics in combination preparations, that is, together with an angiotensin II receptor blocker or an ACE-inhibitor, is taken into consideration. The high use of alpha-blockers for the treatment of hypertension in Norway has also been described elsewhere.[24]

From a cost perspective special interest goes out to one of the newest drug classes for the treatment of hypertension: the angiotensin II receptor blockers and their combinations. In this analysis, this class did not show a variation in use distinct from ACE-inhibitors, beta-blockers or calcium antagonists. This suggests comparable market penetration in all six countries.

Part of the absolute differences in utilization may be explained by dissimilarity in the prevalence of hypertension. A recent survey in people between the ages of 35 and 64 has shown a relatively high prevalence of hypertension in Germany (55.3%) and Finland (48.7%) when compared to Sweden (38.4%), this study used the same measurement method in each country.[5] When adjusted for these figures, nearly all variation in absolute utilization rates can be explained by differences in hypertension prevalence. For the other countries no data on hypertension was available, to our knowledge, that compared the prevalence using the same methodology. However, we assume that a major part of absolute variation in these countries can be explained in this way as well. Furthermore, international differences in dosing and varying undertreatment of hypertension may also be an

explanation.[25] Differences in population age and gender composition of the respective countries were relatively small.[8] For both absolute and relative differences, the various approaches to cope with the challenges of the pharmaceutical marketplace when it comes to price setting, reimbursement restrictions and insurance schemes surely also play a role. For example, the general absence of co-payments in the Netherlands creates little economic disincentives for prescribing more expensive antihypertensive drugs. However, the effects of more graduated reimbursement systems (e.g. depending on total drug use of a patient), as used in Denmark and Sweden in 2003, make the effects hard to ascertain.

In these Northern European countries, we did not find guideline preferences to be related to the established prescribing practices. International studies on guideline adherence in other fields of cardiovascular disease, such as coronary heart disease[26] and heart failure[27] show that the discrepancy between guidelines and clinical practice is a common phenomenon. Furthermore, the lack of convergence between international guidelines has also been suggested to play a role.[28,29] Of course, it is not realistic to assume that preferences in hypertension guidelines are always reflected in drug utilization, given the nature of the disease, the fact that the majority of patients may not be 'uncomplicated' (although a recent study in an American population estimated this to be about 69% of patients[30]), the various indications of the drugs, and the lag time between guideline publication and clinical uptake. However, guidelines are an important tool to translate research into clinical practice, and guidelines such as the Norwegian, which emphasize mono-therapy with a drug hardly popular in day-to-day practice, may find the obstacles posed by established prescribing patterns especially large. Furthermore, none of the guidelines addresses the current utilization pattern of antihypertensive agents in its target country. The evaluation of existing prescribing habits in guidelines can be an important aid for setting goals and for connecting to current clinical practice.

A limitation of this analysis is the assumption that the major indication for prescribing the studied drugs in all these countries was hypertension. We believe this is true for the Netherlands and Sweden (where a survey of the prescribing of antihypertensives for the indication hypertension corresponds well with our aggregate utilization data[22]). However, this is an assumption for all other studied countries. Alpha-blockers are especially susceptible to misclassification in this study, since their use in the treatment of benign prostatic hyperplasia is sometimes clustered under the same ATC-code. Furthermore, since the indication of prescribing is unknown, it is impossible to judge guideline adherence at the patient level with these findings. We were also not able to study the influences of comorbidities.

The data were extracted from various sources (wholesaler/dispensing/reimbursement). However, in this study, our main focus was on the relative use of antihypertensive agents of the different drug classes. We have no reason to believe that selective misclassification of antihypertensive utilization in a country with regards to drug class plays a significant role. For both countries where reimbursement data was used (Netherlands and Germany), insurance coverage was extensive. Therefore, we believe that in these countries all data sources give a reasonably complete and comparable estimate of drug consumption in the population, making bias introduced by the different sources of the data small.

Finally, the RSD measure used here may have a tendency to overemphasize the variation when relative utilization as a percentage of total utilization is small. However, large differences remain when these limitations are taken into account. The between-country variation in this study is substantial, and should form the basis for further discussion.

In conclusion, utilization patterns of antihypertensive agents vary largely across the six countries studied, both in absolute and relative terms. In this study, the RSD proved to be a practically feasible and useful tool to study variation in drug utilization between countries. Although thiazide diuretics are included in all guidelines and have a proven record, the absolute level of use was low and the between-country variability in utilization high. Thiazide diuretics share this high variability with alpha-blockers, of which the effectiveness is disputed. Furthermore, none of the guidelines discussed current utilization, and in some studied countries guidelines seem disconnected from drug use in clinical practice. Whether this reflects a need for a change in prescribing or a re-evaluation of guidelines warrants further research.

What is known about this topic

- As a result of its public health relevance, many countries employ practice guidelines to promote the evidence based prescribing of antihypertensive agents
- At this moment, international differences in the use of antihypertensive agents and in the main recommendations of general practice guidelines remain largely unevaluated

What this study adds

- Both absolute and relative use of antihypertensive agents varied strongly between the six studied countries. This is especially the case for thiazide diuretics, which have a solid evidence base
- When aggregate utilization data is studied, primary recommendations in guidelines sometimes seem disconnected from clinical practice

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