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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Choice of initial antihypertensive drugs and persistence of drug use—a 4-year follow-up of 78,453 incident users

Randi Selmer · Hege Salvesen Blix · Knud Landmark · Åsmund Reikvam

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Abstract
Purpose To investigate patterns of initial drug therapy for the treatment of hypertension and to evaluate treatment persistence and change of treatment during a 4-year period in patients receiving thiazides (TZs) and/or angiotensin II-receptor blockers (ARBs) as first-line treatment.
Methods All initial users of antihypertensive drugs in 2005 and 2009 registered in the Norwegian Prescription Database were included. Treatment on five index dates at 1-year intervals was recorded. A patient was considered to be under treatment on an index date if a drug had been dispensed within the previous 180 days and to have maintained treatment persistence if he/she was on any antihypertensive treatment on the index date and all previous index dates.
Results Among 78,453 new users of antihypertensives in 2005, women started more often with TZs than men (30 vs. 25 %) and less often with ARBs (22 vs. 25 %). In men, the hazard of non-persistence with antihypertensive treatment was significantly lower among initial ARB users than among TZ users (hazard ratio 0.87, 95 % confidence interval 0.81–0.94); in women no significant difference was found. After 4 years, 49 % of the men and 51 % of the women who had started with plain TZs were still using TZs, whereas 65 % of the male ARB users and 60 % of the female ARB users were still using ARBs.
Conclusion TZs and ARBs were the most widely used first-line antihypertensives. Among the men enrolled in the study, ARB users had a somewhat better persistence with antihypertensive treatment than TZ users. Among both genders, continuation on ARBs was more common than continuation on TZs.

Keywords Hypertension · Antihypertensives · Persistence · Thiazides · Angiotensin II-receptor blockers

R. Selmer (✉) · H. S. Blix
Department of Pharmacoepidemiology,
Norwegian Institute of Public Health,
PO Box 4404, 0403 Nydalen, Oslo, Norway
e-mail: Randi.Selmer@fhi.no

K. Landmark · Å. Reikvam
Department of Pharmacology, Institute of Clinical Medicine,
University of Oslo,
Oslo, Norway

Introduction

Hypertension is a major health problem. Norwegian population health surveys carried out in 2000–2003 showed that 45 % of men and women aged 60 years had moderately high or high blood pressure levels, increasing to 70 % in the age group 75 years [1] . The use of antihypertensives was reported in 39 % of men and women aged 75 years. Treatment of hypertension has been shown to prevent cardiovascular diseases and to prolong life. A meta-analysis has shown that all classes of blood pressure-lowering drugs have a similar effect in reducing coronary heart disease events and stroke for a given reduction in blood pressure [2]. Discontinuation of antihypertensive drug treatment in primary prevention increases the risk of acute myocardial infarction (AMI) and stroke [3]. For many years, and in particular after publication of the ALLHAT study, thiazides (TZs) were commonly recommended as the drug of choice in uncomplicated hypertension cases [4] .

The first aim of the study reported here was to determine which types of antihypertensives—that is, TZs, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II-receptor blockers (ARBs)—were used as first-line treatment in 2005 and 2009.

TZs and ARBs are primarily used for treating hypertension, whereas the other drug groups are also widely used for other indications [5]. Some studies have shown that patient persistence with antihypertensive treatment depends largely on the choice of the initial drug therapy [6–19]. Thus, the second aim of this study was to follow patients receiving TZs and ARBs, drugs with quite different properties, as first-line treatment in 2005 and to evaluate persistence and change of treatment for each individual during a 4-year follow-up.

Materials and methods

The Norwegian prescription database (NorPD) includes prescription data from the total population (4.9 million) in Norway since 2004 [20]. It contains information on all prescription drugs, reimbursed or not, dispensed at pharmacies to individual patients living outside institutions. The identity of individuals has been encrypted, but each record contains a unique person identifier, which makes it possible to identify all prescriptions for specific individuals. The drugs are classified according to the Anatomical Therapeutic Chemical Classification System (ATC) [21]. Data included in this study were each patient's unique identifying number (encrypted), gender, age, the date of dispensing, ATC-code and, for patients who had died, the month of death.

The inclusion of reimbursement codes (ICD10 and ICPC-2) in the NorPD was initiated in March 2008 and fully implemented from 2009 onwards. Many of the antihypertensive drugs are used for indications other than hypertension. We analysed the distribution of reimbursement codes for the different antihypertensives prescribed to new users in 2009, including ICD10 codes I10, I11, I12, I13, I15 and ICPC-2 codes K86 and K87 as proxies for hypertension.

All individuals registered in NorPD who received a drug belonging to one of the drug classes used for hypertension in 2005 were included in the study. This means that incident users were defined as not having any antihypertensive drug in 2004 and having their first prescription dispensed in 2005. Incident users in 2009 were defined similarly.

The following drug groups were analysed:

- centrally acting antiadrenergics (ATC code C02A),
- TZs (ATC code C03A),
- TZs and potassium-sparing agents (ATC code C03E),
- beta-blockers (ATC code C07A),
- beta-blockers and TZs in combination (ATC code C07B),
- calcium channel blockers (ATC code C08C),
- ACE inhibitors (ATC code C09A),
- ACE inhibitors and TZs in combination (ATC code C09B),
- ARBs (ATC code C09C),
- ARBs and TZs in combination (ATC code C09D).

Incident users, whose first dispensed drug was plain TZs, plain ARBs or combinations of these agents, were followed for 4 years after treatment initiation for use and change of drugs. We defined five index dates for each user: the first date of dispensing, and the same date 1, 2, 3 and 4 years after the first dispensing date. In Norway, most prescriptions are dispensed for 90 days. We defined a patient to be under treatment with a given drug on an index date if she/he had a drug dispensed within the previous 180 days. A patient was regarded to be a persistent user on an index date if he/she was under any antihypertensive treatment on the index date and all previous index dates. The cumulative proportion of persistent patients was calculated by life-table analyses. If patients died when they still were receiving treatment, they were censored at the last index date before death; patients still being treated at the last index date were censored at the end of follow-up, which was 4 years after treatment initiation. Hazard ratios for non-persistence with antihypertensive treatment overall and change of actual treatment were estimated using the Cox's proportional hazards regression model. Gender and age at first prescribing were included as covariates in the main analyses. The use of antidiabetics (ATC code A10) and antithrombotic agents (ATC code B01) in 2004 were included in additional analyses as proxies for diabetes and cardiovascular diseases. The Cox model was also used to test whether mortality differed between the treatment groups.

The users of antihypertensives on each index date were classified according to kind of drugs and combinations of drugs used. The main groups studied were TZs, beta-blockers, calcium channel blockers, ACE inhibitors and ARBs. We did not differentiate between drugs within the same class. Thus, patients who had their drugs switched to other drugs of the same class were regarded as belonging to the groups continuing on the same medication. For each patient we totaled the number of main groups dispensed during the 180 days before the last index date (4 years after first dispensed drug).

Results

There were 78,453 incident users of any antihypertensive drug in 2005 (Table 1). The most commonly prescribed drug class was beta-blockers followed by TZs and ARBs. Table 1 shows that women started more often with TZs compared to men (30 vs. 25 %), whereas the opposite was true for ARBs (22 vs. 25 %). A similar pattern was seen in 2009 (Table 2). However, the number of patients starting treatment with TZs in 2009 had increased and the number of patients starting with ARBs or beta-blockers had decreased slightly compared to the 2005 figures. Reimbursement codes in 2009 included hypertension in more than 90 % of the patients

Table 1 Distribution of the drug initially dispensed among 78,453 incident users of any antihypertensive in 2005

Initial drug or combination of drugs[a]	Men (*n*=38,360)		Women (*n*=40,093)		Total (*n*=78,453)	
	n	%	*n*	%	*n*	%
TZs total[b]	9,627	25	12,078	30	21,705	28
Of these:						
TZs only	4,291	11	6,124	15	10,415	13
TZs+amiloride only	1,764	5	2,938	7	4,702	6
ARBs total[b]	9,653	25	8,719	22	18,372	23
Of these:						
ARBs only	6,986	18	6,664	17	13,650	17
TZs+ARBs combined total[b]	2,244	6	1,811	5	4,055	5
Of these:						
TZs+ARBs only	1,867	5	1,560	4	3,427	4
ACE inhibitors total[b]	5,828	15	4,044	10	9,872	13
Beta-blockers total[b]	16,420	43	16,618	41	33,038	42
Calcium channel blockers total[b]	3,764	10	3,269	8	7,033	9
Centrally acting antiadrenergics total[b]	79	0	174	0	253	0

TZs, thiazides; ARBs, angiotensin II-receptor blockers; ACE, angiotensin-converting enzyme

[a] The categories are not exclusive as combinations of drugs are included in more than one category

[b] Total: alone or in combination with other antihypertensives

starting on ARBs or TZs (Table 3). Among individuals receiving a first prescription for a drug with a code for hypertension in 2009, TZs and ARBs were by far the most commonly used, followed by beta-blockers, ACE inhibitors and calcium channel blockers.

We followed the 4,291 men and 6,124 women whose initial drug in 2005 was TZs only, the 6,986 men and 6,664 women starting with ARBs only and the 1,867 men and 1,560 women starting with the combination of TZs and ARBs, for 4 years after the first dispension of the drug

Table 2 Distribution of drug initially dispersed among 77,757 incident users of any antihypertensive in 2009

Initial drug or combination of drugs[a]	Men (*n*=38,576)		Women (*n*=39,181)		Total (*n*=77,757)	
	n	%	*n*	%	n	%
TZs total[b]	11,700	30	13,218	34	24,918	32
Of these:						
TZs only	6,665	17	8,369	21	15,034	19
TZs+amiloride only	1,714	4	2,374	6	4,088	5
ARBs total[b]	9,207	24	7,700	20	16,907	22
Of these:						
ARBs only	6,440	17	5,736	15	12,176	16
TZs+ARBs combined total[b]	2,452	6	1,728	4	4,180	5
Of these:						
TZs+ARBs only	2,182	6	1,526	4	3,708	5
ACE inhibitors total[b]	6,092	16	3,968	10	10,060	13
Beta-blockers total[b]	14,005	36	14,897	38	28,902	37
Calcium channel blockers total[b]	3,683	10	3,397	9	7,080	9
Centrally acting antiadrenergics total[b]	34	0	62	0	96	0

[a] The categories are not exclusive as combinations of drugs are included in more than one category

[b] Total: alone or in combination with other antihypertensives

Table 3 Reimbursement codes from first prescription of any antihypertensive drug in 2009 among 77,757 patients with no prescription for any antihypertensive drug in 2008

Initial drug alone or in combinations[a]	Reimbursement codes						
	Hypertension[b]		Other		No code[c]		Total *n*
	n	%	*n*	%	*n*	%	
TZs	23,131	93	1,034	4	753	3	24,918
ARBs	15,215	90	306	2	13,86	8	16,907
ACE inhibitors	6,284	62	3,394	34	382	4	10,060
Beta-blockers	8,651	30	15,624	54	4,627	16	28,902
Calcium channel blockers	5,865	83	565	8	650	9	7,080
Any antihypertensive drug	50,924	65	19,169	25	7,664	10	77,757

[a] The categories are not exclusive as combinations of drugs are included in more than one category

[b] ICD-10 codes: I10, I11, I12, I13, I15. ICPC-2 codes: K86, K87

[c] No code: mostly prescriptions without reimbursement

(Table 1). The mean ages of the initial users (men vs. women) of different antihypertensives were: TZs, 60 and 63 years; ARBs, 57 and 58 years; TZs/ARBs combination, 58 and 62 years. A total of 1,377 patients (5 %) died during the follow-up. The proportions of patients who died in the different treatment groups (men vs. women) were: TZs, 6.2 and 4.8 %; ARBs, 4.9 and 4.2 %; TZs/ARBs combination, 5.7 and 5.4 %; the *p* (equality of treatment groups) was 0.50 in men and 0.08 in women after adjustment for age by the Cox model.

Among patients starting with TZs and still alive after 1 year, 82 % of men and 82 % of women were still on treatment with an antihypertensive drug (Fig. 1); corresponding figures in men and women starting with plain ARBs were 85 and 81 %, respectively, and in men and women starting with a combination of ARBs and TZs, 85 and 82 %, respectively. The cumulative proportion of patients still persistent after 4 years dropped to 68 % in men and 67 % in women who started with plain TZs, to 71 % in men and 65 % in women starting with ARBs and to 69 % and 67 % in men and women who started on a combination of ARBs and TZs (Fig. 1). In men, the hazard for non-persistence of any antihypertensive treatment was significantly lower for initial ARBs users than for initial TZs users (Table 4); no significant difference was found among the women. Adjusting for use of antidiabetics and antithrombotic agents in 2004 did not change the estimates (data not shown). The risk of non-persistence decreased with increasing age in both genders and was significantly higher in women than in men (Table 4). Non-persistence was most pronounced during the first year, whereas the persistence was high thereafter. Of patients persistent 1 year after treatment initiation, 91 % were still on treatment at 2 years, and of the patients persistent at 3 years, 96 % were still persistent at 4 years after treatment initiation. The mean and median numbers of redeemed prescriptions during the 4-year period were 18.7 and 17 among persistent users, respectively; 88 % of the persistent users had redeemed ≥14 prescriptions during the 4 years of the study.

Among those starting on TZs, a higher percentage of women compared to men (20 vs. 14 %, respectively) were still receiving treatment with TZs alone after 4 years of therapy (Fig. 1). By comparison, of the men and women starting on plain ARBs, 29 and 30 % were still being treated with ARBs only at 4 years of follow-up. The probability of persisting with the first treatment during follow-up was significantly lower for users of plain TZs than for users of plain ARBs ($p<0.001$). Of those starting with plain TZs, 49 % of the men and 51 % of the women still used TZs alone or TZs combined with other drugs 4 years after treatment initiation; in comparison, of the men and women starting on ARBs, 65 and 60 %, respectively, still used ARBs or ARBs combined with other drugs after 4 years.

Among patients still treated after 4 years, the percentage using only one type of drug was generally higher in women than in men and slightly higher in patients starting with ARBs compared to those starting on TZs (Table 5). The percentage using two types of antihypertensives was correspondingly higher in initial users of TZs than in initial users of ARBs. The second medicine in users of ARBs was most often TZs, and the second medicine in initial users of TZs was most often ARBs (Fig. 1). The following proportions of patients needed at least three drugs after starting with ARBs and TZs, respectively: men, 16 and 16 %; women, 12 and 13 %. Among those starting with a combination of TZs and ARBs, 29 % of men and 23 % of women were being prescribed three or more types of antihypertensive drugs after 4 years (Table 5).

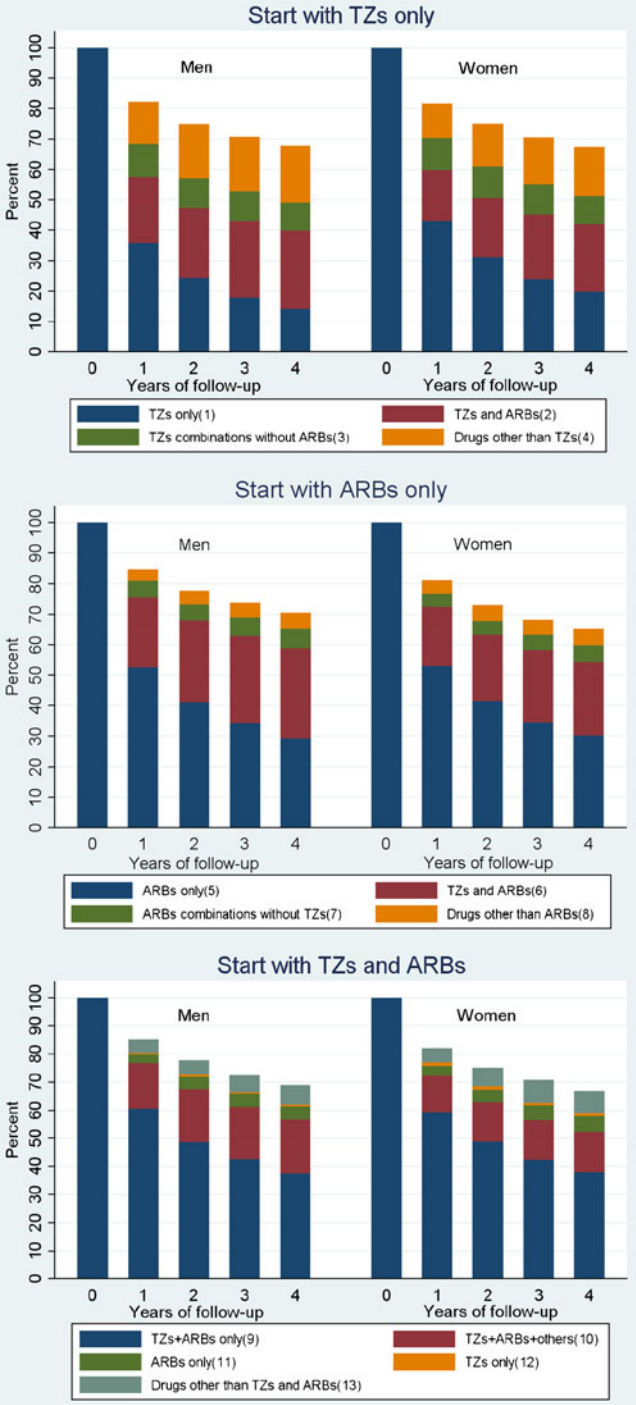

Fig. 1 Persistence and classification of drug use among persistent users starting antihypertensive treatment in 2005 in relation to initial choice of drug and time of follow-up. Classification of antihypertensive treatment: *(1)* plain thiazides (*TZs*), *(2)* use of at least two drugs, including TZs and antiotensin II-receptor blockers (*ARBs*), *(3)* TZs combined with antihypertensives other than ARBs, *(4)* antihypertensives other than TZs, *(5)* plain ARBs, *(6)* use of at least two drugs, including TZs and ARBs, *(7)* ARBs combined with antihypertensives other than TZs, *(8)* antihypertensives other than ARBs, *(9)* use of two drugs: TZs and ARBs, *(10)* use of at least three drugs, including TZs and ARBs, *(11)* plain ARBs, *(12)* plain TZs, *(13)* antihypertensive treatment without TZs or ARBs

Discussion

Thiazides and ARBs were the most commonly used drugs as the first choice for antihypertensive treatment in incident users in both 2005 and 2009. Reimbursement codes in 2009 suggest that >90% of incident users of these drugs had hypertension.

In men, the hazard of non-persistence with antihypertensive treatment was significantly lower for initial users of ARBs than for initial users of TZs. A better persistence on ARBs has also been reported in a number of other studies [8–14, 16–19] . However, in our study the difference was small and not observed in women. Also of note, the probability of staying on the initial drug, alone or on this drug in combination with other antihypertensive drugs, was higher for ARBs users than for TZs users. Accordingly, although our results indicate that TZs are well tolerated, they indicate an even better tolerability for ARBs.

The risk of stopping all antihypertensive therapy was most pronounced during the first year, which is consistent with other study findings [16–18, 22, 23]. Possible reasons might have been uncertainty about whether or not real hypertension existed and the appearance of adverse drug effects. However, it is a matter of concern if many patients needing antihypertensive therapy stop their treatment during the first months after treatment initiation. More research on this topic is needed.

In our study, persistence was favourable compared with other studies [16, 17]. In a general practice study in the UK, one in two patients had discontinued all antihypertensive therapy by 3 years post-treatment initiation [16], and in a German study persistence after 3 years was only 15 % [17]. By comparison, in our study, two-thirds of the initial users of TZs and ARBs were persistent users after 4 years.

The definition of persistence may vary from study to study. We allowed for a time window of 180 days to describe current users. As prescriptions in Norway normally last 90 days, this could imply an adherence rate of only 50 %. This is, however, an unlikely adherence rate, which is a view supported by the finding of a high number of redeemed prescriptions among persistent users in our study. As persistence dissimilarities between countries are pronounced, it is unlikely that they are due to different definitions alone. In our study, both the good persistence with antihypertensive drug treatment and the small differences between the treatment groups are indications of a well-functioning health care system.

A striking finding in our study is the extensive use of ARBs as the first dispensed drug—predominating over ACE inhibitors—despite the fact that in Norway ARBs were more expensive than ACE inhibitors during the study period. Clinical guidelines can not explain the extensive use of ARBs. The use of ARBs was also higher than that in

Table 4 Hazard ratios for non-persistence of antihypertensive treatment by initial drug choice and age estimated by the Cox proportional hazards model

Covariate	Men (n=13,144)		Women (n=14,348)		Men+women	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Initial drug						
Plain TZs	1.00	Reference	1.00	Reference	1.00	Reference
Plain ARBs	0.87	0.81–0.94	0.99	0.93–1.05	0.94	0.90–0.98
TZs+ARBs combined	0.93	0.84–1.02	1.00	0.91–1.10	0.97	0.90–1.04
Age per 10 years	0.90	0.88–0.92	0.84	0.82–0.85	0.86	0.85–0.87
Women vs. men					1.15	1.10–1.20

Data are presented as separate models in men and women and one with both genders

95% CI, 95% Confidence interval

Sweden and Denmark in 2004 [24]. It has been suggested that Norwegian physicians are early adopters of the newest medications and interventions and that they have a limited awareness of the costs of drug therapy to society on a whole. [25]

The incident usage of TZs seems to be relatively high, given the availability of the newer drug classes, i.e. ACE inhibitors and calcium channel blockers in addition to ARBs. It should be noted that new reimbursement rules were implemented in Norway in 2004 which implied that TZs should, if possible, be the first-line therapy for uncomplicated hypertension. This decision might have influenced the choice of initial therapy [26]. However, the use of TZs was already on the rise in Norway in the years preceding the introduction of the 2004 regulations. One possible reason for this high use of TZs may be due to the publication of results from studies conducted in preceding years that compared new and old drugs (TZs and beta-blockers) and reported largely comparable results in the study groups [4, 27–31].

Recent hypertension studies have indicated that new therapeutic approaches might be favourable, not least the combination of ACE inhibitors or ARBs with calcium channel blockers [32]. In accordance with newly revised reimbursement regulations in Norway, most drug classes may be selected as first-choice therapy. It remains to be seen how the incident prescribing pattern will be in coming years.

A sizable proportion of the patients in our study started with the combination of ARBs and TZs . This prescribing

Table 5 Number of main antihypertensive drug groups[a] used by individuals 4 years after treatment initiation[b] among persistent users of men and women in relation to initial choice of drug

Initial drug 2005	Number of drug groups[a] after 4 years	Men		Women	
		n	%	n	%
Plain TZs	1	1,139	41	1,898	48
	2	1,179	43	1,553	39
	3	361	13	440	11
	4	80	3	57	1
	5	4	0	2	0
	Total	2,763	100	3,950	100
Plain ARBs	1	2,173	46	2,174	52
	2	1,771	38	1,464	35
	3	652	14	461	11
	4	113	2	73	2
	5	8	0	5	0
	Total	4,717	100	4,177	100
TZs and ARBs combined	1	134	11	148	15
	2	733	60	623	63
	3	305	25	184	19
	4	47	4	38	4
	5	6	0	0	0
	Total	1,225	100	993	100

[a]Drug groups: thiazides, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II-receptor blockers

[b]Drugs dispensed during 3.5–4 years after treatment initiation

behaviour is in accordance with guidelines where starting with two drugs is an option, particularly in patients with the most severe form of hypertension [5]. The persistence of patients starting with such combinations was comparable with that of individuals starting with plain TZs or ARBs, but a somewhat higher proportion of the former needed at least three drugs, indicating that more severe hypertension was, in fact, present.

Gender differences in this study were minor, although TZs were slightly more common as the first choice in women than in men and were slightly more common as TZ monotherapy in women after 4 years. There is no obvious reason for these gender differences. Persistence increased with age in both men and women, probably because of more severe hypertension and increasing health problems among the elderly. This is in accordance with other study findings [8, 10]. Stratified analyses of users below and above 70 years of age showed a similar pattern of persistence and change of therapy as the main analysis (data not shown).

There are a number of possible limitations to our study. First, the lack of information on diagnoses in 2005 may be a limitation. It was only in 2009 that reimbursement codes were fully implemented. We did use the 2009 codes as proxy for the diagnoses. As we do not have information suggesting that the distribution of diagnoses underlying the prescribing of the actual drug classes has changed from 2005 to 2009, we believe that the 2009 codes reflect the diagnoses in the 2005 incident users. Secondly, the absence of data on possible confounding factors in NorPD, such as co-morbidities, socioeconomic status, severity of concomitant diseases, and other risk factors for cardiovascular diseases, might be a limitation in the evaluation of persistence. However, it is likely that the results largely would have been the same even were this information to be available because (1) the aim of the reimbursement policy in Norway is that all individuals with chronic diseases should have the same access to pharmaceuticals, independent of socioeconomic status; (2) mortality was similar in the initial treatment groups, suggesting that there were no major health differences among the groups; (3) adjusting for use of antidiabetics and antithrombotic agents did not change the estimates. The third limitation may be associated with the accuracy—or lack thereof—of the disease codes used on the prescriptions, ICD 10 in hospitals and ICPC-2 in primary care. This accuracy has not been established. We have, however, no indication that this influenced the users of ARBs and TZs differentially. Also of note, in Norway, reimbursement is not obtained without a disease code.

The main strength of the study is the completeness of the NorPD registry for patients in ambulatory care. All pharmacies in Norway are obliged to send prescription data on all dispensed drugs to the NorPD. In reality, the patients will not obtain drugs from unregistered sources. There is no selective reporting, although we cannot be sure that the dispensed drugs were actually taken. It should also be noted that information on drug use in hospitals and nursing homes is not registered in the NorPD and that the persistence might have been underestimated in patients who were admitted to nursing homes. This group of patients constitutes, however, a very low proportion of the total population.

The completeness and quality of the data allowed us to undertake an extensive analysis of drug use, including changes in drug use over a long period. We were able to provide more comprehensive results than just follow-up of persistence in a limited cohort, which is the approach used in most comparable studies. To the best of our knowledge, our study is the first to show types and number of drugs used during a long (4 years) follow-up in the general population.

In conclusion, high persistence of antihypertensive therapy can be achieved in the general population. TZs and ARBS were most often used as first-line antihypertensives in incident users. In men, persistence to antihypertensive medication was somewhat better among initial ARBs users than among initial TZs users, but the differences were small. Continuation on ARBs, alone or in combination with other antihypertensive drugs, was more common than continuation on TZs, both in men and women. A sizeable proportion of patients started on two drugs, and these patients more frequently needed at least three drugs during follow-up.

Conflict of interest The authors declare no conflict of interest.

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