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ORIGINAL REPORT

Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study†

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SUMMARY

Objective The objective of the study is to investigate factors related to treatment persistence among users of antihypertensive (AHT) drugs in daily practice.

Methods Data for this study were obtained from the PHARMO database including pharmacy records and hospitalizations in the Netherlands ($n = 950\,000$). Patients who newly received AHT therapy ($n = 17\,113$) between 1997 and 2001 were selected. Of these patients, random samples of 500 patients per drug class were drawn. One-year persistence was defined as (1) the percentage of patients using AHTs at least 270 days and receiving AHT in 3 months after the 1-year follow-up period, and (2) Catalan method (Kaplan–Meier curves). Gender specific persistence rates per drug class were adjusted for significant factors including age, use of antidiabetics and lipid lowering drugs, and prior cardiovascular hospitalizations (OR and 95%CI).

Results Persistence was highest in users of angiotensin II receptor blockers (ARBs) (62.0%), progressively lower in users of angiotensin converting enzyme inhibitors (ACE-inhibitors, 59.7%), betablockers (35.0%), calcium channel blockers (34.7%), and diuretics (33.0%), resulting in the highest OR of 3.4 [95%CI: 2.6–4.5] for ARBs compared to diuretics. The persistence of AHT use in women was substantially lower (40.1% vs. 50.2%, OR 0.7 [95%CI: 0.6–0.8]) and differences between drug classes were larger than in men.

Conclusions These results demonstrate marked differences in persistence between AHT classes, with the highest persistence for ARBs and lowest for diuretics. Women were less persistent with their AHT compared to men. This low persistence leads to suboptimal treatment with a potential for substantial clinical consequences. Especially in women, more attention paid to AHT persistence patterns could improve their cardiovascular outcome. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — hypertension; persistence; switching; antihypertensive drugs

INTRODUCTION

Hypertension is a major risk factor for vascular disease[1] and effective blood pressure treatment has been shown to reduce both cardiovascular and cerebrovascular events.[2] Despite the availability of effective treatment, hypertension persists in a substantial proportion of the population due to a combination of under-diagnosis and undertreatment leading to poor blood pressure control.[3,4] The percentage of patients in whom blood pressure control is achieved varies by country. For example, the US National Health and Nutrition Examination Survey (NHANES III) documented a control rate of 25%,[5] while the Canada heart health survey found that only about 13% of Canadians with hypertension were adequately

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controlled.[6] In the Netherlands, it was demonstrated that 30% of the hypertensive women and 46% of hypertensive men aged 20–59 years were undertreated for hypertension explained by uncontrolled blood pressure and inappropriate treatment.[7] One explanation for uncontrolled blood pressure, despite treatment, is poor compliance or poor persistence with antihypertensive (AHT) therapy.[8] The availability of different classes of AHT drugs and the need to tailor treatment to meet patients' needs and characteristics, makes treatment decisions a challenging process. A physician may opt to prescribe the drug that in large clinical trials has been shown to result in the lowest number needed to treat (NNT) to prevent one major cardiovascular event. However, in landmark trials drug use is highly controlled and compliance is usually higher than that observed in ''real life'' medical practice. Indeed, the persistence levels of AHT drug therapy reported for such trials do not reflect the persistence observed in average daily care.[9–11] Mainly due to side effects, drug persistence in daily practice may be lower and differ between AHT drug classes compared with persistence observed in controlled trials. This may justify an altered (initial) AHT drug choice for hypertension treatment.

In this study, factors related to treatment persistence among users of AHT drugs are investigated in daily practice. The results of this study may provide useful insights in everyday use of AHT drugs, which, in turn, may contribute to making optimal choices in therapy.

MATERIALS AND METHODS

Data sources

Data for this study were obtained from the PHARMO medical record linkage system in the Netherlands. The PHARMO medical record linkage system includes the drug-dispensing records from community pharmacies and hospital discharge records of all 950 000 community-dwelling inhabitants of 25 medium-sized cities in the Netherlands.[12] For all residents, the drug-dispensing histories are linked to the hospital discharge records of the same patient based on characteristics such as date of birth, gender, and a code for the general practitioner. The computerized drug-dispensing histories contain data concerning the dispensed drug, type of prescriber, dispensing date, dispensed amount, prescribed dose regimens, and the legend duration (prescription length). The hospital records include detailed information concerning the primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the ICD-9-CM (*International Classification of Diseases, 9th Revision, Clinical Modification*). Drug names are coded according to the Anatomical Therapeutic Chemical (ATC) Classification.

Selection of patients

From the PHARMO system, a retrospective cohort study was performed by selecting all patients using AHT drugs between 1997 and 2001 (base cohort, $n = 48\,234$). Patients were included in the base cohort if they: (1) did not use AHT drugs in the year before the index date, as a proxy for incident users, (2) were registered at least 1 year in PHARMO RLS before and at least 15 months after the first prescription of AHT drugs, and (3) received at least two prescriptions for AHT drugs ($n = 17\,113$). From the base cohort, a random sample of 500 incident (new) patients per drug class was drawn for the analyses. After sampling patients using fixed combinations were excluded. The different classes of AHT drugs included diuretics, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin-2 antagonists (ARBs), calcium-channel blockers (CCBs), and miscellaneous AHT drugs (mainly α-blockers). Because of the small number ($n = 236$) and heterogeneity of the miscellaneous AHT group, we excluded this group from further analyses. Furthermore, patients on fixed combinations were used for further analyses. If two AHT drugs were used concurrently at the start of AHT treatment, these drugs were excluded from further analyses.

The use of AHT drugs was converted into treatment episodes of uninterrupted use. Patients may have had one or several treatment episodes during their follow-up. The follow-up of the patients ended if the patient died, moved out of the PHARMO area or the end of the data collection period (31 December 2001) was reached, whichever of these events came first.

Definition of persistence

The index date of treatment was defined as the date of the first prescription of AHT drug. The use of AHT drugs was followed during a 15 months period from the index date for all patients in the persistence cohort.

Persistence was analyzed using two methods: 1-year persistence rates and the Kaplan–Meier method. Firstly, 1-year persistence rates of AHT drugs were defined as the percentage of patients that used AHT drugs for at least 270 days and had an additional drug dispensing in the 3 months after the follow-up period of 1 year adapted from other studies.[13–15] Secondly,

persistence was analyzed in accordance with the method of Catalan *et al.*[16] as the number of days from the date of start of the index date to the date of the first failure to continue renewals of AHT with a permissible gap between renewals. Non-persistence of therapy was defined as a drug holiday of at least 30 days in this method. For patients continuously treated during the 1-year period, the duration of treatment was censored at 1 year. Persistence was presented in Kaplan–Meier survival curves for the different treatment cohorts.

Definition of treatment episodes and switching

The dispensing patterns for AHT were ascertained for each incident patient in their follow-up period. For each dispensing, the legend duration of use was calculated by dividing the number of units dispensed by the number of units to be used per day as defined in the pharmacies. All prescriptions were subsequently converted into episodes of consecutive use of AHT. A treatment episode was defined as a period of time in which a continuous specific pharmacotherapeutic treatment took place. An episode was measured as the time span between the starting date of the first dispensing until the expiry date of the final dispensing. The end date of an episode was set at half the legend-duration time after the last dispensing date, assuming that patients stop their medication somewhere in time after the last dispensing. In case of interruptions between two prescriptions of less than 30 days, the episode was considered uninterrupted.[16] Consequently, patients may have had multiple treatment episodes in their life, but only first episodes were used for the analyses. Patients may switch from therapy during or between treatment episodes. Episodes of mutual exclusive drugs (single AHT drug use within one drug class) were immediately ended at the start of a new AHT drug, irrespective of the number of assumed unused tablets (in stock) of the foregoing prescription. When the start of a new AHT occurred during the episode of the former AHT drug and the new AHT episode ended after the end date of the former AHT drug episode, it was considered to be a between episode switch and was classified as non persistent with the patient's initial therapy from that moment. Subjects who switch from one therapy to another and who stop AHT treatment were considered non-persistent.

Covariates of AHT treatment and persistence

Persistence per drug class and gender were analyzed. Several potential confounding factors associated with persistence were studied including co-medication (antiasthmatic drugs, antidiabetic drugs, lipid lowering drugs), monotherapy, age, and history of diabetes and/or cardiovascular diseases, and stratified by AHT drug class. Co-medication was measured in the year before the index date, whereas prior cardiovascular hospitalizations were measured in the available history before the index date. Prior cardiovascular hospitalizations were defined by the following discharge diagnoses: ischemic heart disease (ICD-9-CM: 410–414), congestive heart failure (ICD-9CM: 428), arrhythmia (ICD-9-CM: 426–427), peripheral vascular disease (ICD-9-CM: 441, 443.9, 785.4), cerebrovascular disease (ICD-9-CM: 430–438) and hypertension (ICD-9-CM: 401–405).

Data analysis

Persistence was presented as 1-year persistence rates. Odds ratios (ORs) and 95% confidence intervals (95%CI), crude and adjusted for several potential confounders, were calculated to estimate the associations between factors and persistence by drug class and gender using logistic regression analyses. The Kaplan–Meier curves permit therapy failure rates (stop rates) per day since start of therapy. Co-morbidity and adverse events (based on hospitalizations) were investigated using the drug records linked to hospitalization admission data.

RESULTS

Description of cohort

After sampling and exclusion of patients, the study population consisted of 2243 patients who were eligible for the study. The general characteristics of incident users of AHT drugs are presented in Table 1. Most of the subjects were aged between 40 and 79 years (80%), and 57% were female. The first prescription of AHT medication was mainly prescribed by a general practitioner (85%), followed by an internist or a cardiologist (6% and 4%, respectively). Antiasthmatic drugs, antidiabetic drugs, and lipid lowering drugs were observed in, respectively, 14.2%, 11.3%, and 9.4% of the patients. About 8% of the patients were hospitalized prior to the index date for cardiovascular disease, mainly for ischemic heart diseases (4%).

In Table 2, the crude persistence rates are shown with regard to demographics, class of AHT drugs, and medical history. Factors significantly related to persistence were gender, age, starting year of therapy, AHT drug class, antiasthmatic drugs, lipid lowering drugs,

Table 1. General characteristics of users of antihypertensive drugs

Characteristics	*n* (%)
Patients	2243 (100.0)
Gender	
Male	967 (43.1)
Female	1276 (56.9)
Age (years)	
0–19	35 (1.6)
20–39	257 (11.5)
40–59	955 (42.6)
60–79	831 (37.0)
≥80	165 (7.4)
Starting year of therapy	
1997	525 (23.4)
1998	522 (23.3)
1999	561 (25.0)
2000	454 (20.2)
2001	181 (8.1)
Prescriber of first AHT prescription	
General practitioner	1907 (85.0)
Internist	130 (5.8)
Cardiologist	90 (4.0)
Other	116 (5.2)
Antihypertensive drugs[#]	
Diuretics	458 (20.4)
Beta-blockers	471 (21.0)
Calcium-antagonists	455 (20.3)
ACE-inhibitors	412 (18.4)
ARBs	447 (19.9)
Co-medication*	
Antidiabetic drugs	253 (11.3)
Lipid lowering drugs	211 (9.4)
Antiasthmatic drugs	318 (14.2)
Prior cardiovascular hospitalizations[$]	185 (8.2)
Ischemic heart disease	89 (4.0)
Congestive heart failure	6 (0.3)
Arrhythmia	32 (1.4)
Peripheral vascular disease	15 (0.7)
Cerebrovascular disease	52 (2.3)
Hypertension	3 (0.1)

AHT, antihypertensive; ACE-inhibitors, angiotensin converting enzyme inhibitors; ARBs, angiotensin-2 receptor blockers; DDDeq, fraction of DDD per day; index date, date of the first AHT prescription; SD, standard deviation.

[#]The number does not add up to 100% as the groups are not mutually exclusive.

*Co-medication was measured in the year before the index date.

[$]Prior hospitalizations were measured before the index date.

prior cardiovascular events (total) and prior ischemic heart disease. Persistence of AHT therapy in general was highest with ARBs and ACE inhibitors (62.0% and 59.7%, respectively), was lower among women than men (respectively, 50.2% and 40.1%; OR crude 0.7 [95%CI: 0.6–0.8]), and increased with age from 17.1% for patients aged <20 years to 50.4% for patients aged 60–79 years. Patients using antidiabetic or lipid lowering drugs concurrently were more persistent than those not using these drugs (respectively, 56.5% was persistent; OR crude 1.7 [95%CI: 1.3–2.2], and 63.5% was persistent; OR crude 2.4 [95%CI: 1.8–3.2]). A 1.4-fold higher persistence was observed in patients who had prior cardiovascular hospitalizations compared to patients who had no cardiovascular hospitalizations (52.4% was persistent; OR crude 1.4 [95%CI: 1.0–1.9]).

Furthermore, we found that users of angiotensin converting enzyme inhibitors (ACE-inhibitors) switched more frequently (16.5%; $p < 0.001$) compared to ARBs (9.6%) and diuretics users (8.3%). Most of the switches to ARBs were switches from ACE-inhibitors (66%).

In Table 3, the differences in persistence overall and by gender between drug classes are shown. Substantially higher persistence with ACE-inhibitors and ARBs in comparison to diuretics was observed regardless of gender, respectively, OR adjusted 2.8 [95%CI: 2.1–3.8] and OR adjusted 3.4 [95%CI: 2.6–4.5]). The difference between ACE-inhibitors and ARBs in men were similar (for men OR 3.0 [95%CI: 1.9–4.7] and OR 3.0 [95%CI: 1.9–4.7], but was higher in women for ARBs than ACE-inhibitors (OR 3.9 [95%CI: 2.7–5.6] and OR 2.7 [95%CI: 1.8–3.9], respectively). Figure 1 demonstrates Kaplan–Meier curves by gender according to the Catalan method.[16] Figure 1 and Table 3 demonstrate that there was also a strong trend for persistence among users of CCBs and β-blockers to be lower than among users of ARBs and ACE inhibitors.

DISCUSSION

The results of the current study suggest that there is a difference in persistence between AHT drug classes. After correction for confounding factors, users of ARBs and ACE-inhibitors were the most persistent with their treatment. Furthermore, a lower persistence in women compared to men and increasing persistence over the years were observed. Other factors influencing persistence were concurrent use of antidiabetic or lipid lowering drugs and the occurrence of prior cardiovascular hospitalizations.

Duration and persistence of AHT drug therapy affects blood pressure control and thereby the risk of cardiovascular morbidity and mortality induced by hypertension. Thus AHT persistence is an important issue regarding health resource utilization and costs.[17,18] Discontinuation of treatment represents a common problem in clinical practice and was confirmed in our study. Our findings of persistence rates between 33 and 62% are in line with earlier studies demonstrating persistence rates between 20 and

Table 2. Factors related to persistence rates with AHT drugs

Characteristics		*n*	Non-persistent users (% of total patients)	Persistent users (% of total patients)	Odds ratios (95% CI)
			n (%)	*n* (%)	
	N	2243	1246 (55.6)	997 (44.4)	
Gender	Men	967	482 (49.8)	485 (50.2)	1.0 (Reference)
	Women	1276	764 (59.9)	512 (40.1)	0.7 (0.6–0.8)
Age (years)	0–19	35	29 (82.9)	6 (17.1)	0.3 (0.1–0.7)
	20–39	257	197 (76.7)	60 (23.3)	0.4 (0.3–0.6)
	40–59	955	515 (53.9)	440 (46.1)	1.1 (0.8–1.5)
	60–79	831	412 (49.6)	419 (50.4)	1.3 (0.9–1.8)
	≥80	165	93 (56.4)	72 (43.6)	1.0 (Reference)
Starting year of therapy	1997	525	322 (61.3)	203 (38.7)	1.0 (Reference)
	1998	522	298 (57.1)	224 (42.9)	1.2 (0.9–1.5)
	1999	561	298 (53.1)	263 (46.9)	1.4 (1.1–1.8)
	2000	454	236 (52.0)	218 (48.0)	1.4 (1.1–1.9)
	2001	181	92 (50.8)	89 (49.2)	1.5 (1.1–2.2)
AHT drug[#]					
Diuretics		458	307 (67.0)	151 (33.0)	1.0 (Reference)
Beta-blockers		471	306 (65.0)	165 (35.0)	1.1 (0.9–1.5)
Calcium-antagonists		455	297 (65.3)	158 (34.7)	1.1 (0.8–1.4)
ACE-inhibitors		412	166 (40.3)	246 (59.7)	3.0 (2.3–4.0)
ARBs		447	170 (38.0)	277 (62.0)	3.3 (2.5–4.4)
Co-medication**					
Antidiabetic drugs		253	110 (43.5)	143 (56.5)	1.7 (1.3–2.2)
Lipid lowering drugs		211	77 (36.5)	134 (63.5)	2.4 (1.8–3.2)
Antiasthmatic drugs		318	189 (59.4)	129 (40.6)	0.8 (0.7–1.1)
Prior cardiovascular event[$]		185	88 (47.6)	97 (52.4)	1.4 (1.0–1.9)
Ischaemic heart disease		89	36 (40.4)	53 (59.6)	1.9 (1.2–2.9)
Congestive heart failure		6	2 (33.3)	4 (66.7)	2.5 (0.5–13.6)
Arrhythmia		32	17 (53.1)	15 (46.9)	1.0 (0.5–2.1)
Peripheral vascular disease		15	9 (60.0)	6 (40.0)	0.8 (0.3–2.3)
Cerebrovascular disease		52	29 (55.8)	23 (44.2)	1.0 (0.6–1.7)
Hypertension		3	2 (66.7)	1 (33.3)	0.6 (0.1–6.8)

ACE-inhibitors, angiotensin converting enzyme inhibitors; ARBs, angiotensin-2 receptor blockers; CI, confidence interval.
Odds ratios were measured with univariate analyses using logistic regression analysis (with data based on Monane).
[#]The number does not add up to 100% as the groups are not mutually exclusive.
**Co-medication was measured in the year before the index date.
[$]Prior hospitalizations were measured before the index date.

67%.[13,14,19–21] While most studies determine persistence patterns over a relatively short period of time (e.g., 6 or 12 months), Conlin *et al.*[19] determined that persistence patterns were maintained over a 4-year time period. The largest decline in persistence occurred in the first 12 months after initiation of therapy, with a subsequent slowing of discontinuation rate up to 4 years. Esposti *et al.*[22] reported that persistence on initial AHT therapy was 58% after a 3-year period, with 35% discontinuing the treatment and 8% were recommenced on a treatment in the third year.

Even when correcting for significant factors determining persistence, such as co-medication and prior events, we were still able to confirm earlier results concerning the association between persistence and the different AHT drug classes.[13,14,19,23] In general, the newer AHT drug classes, such as ARBs and ACE-inhibitors, showed larger persistence rates in comparison with the older drug classes, such as diuretics.

Previous studies have demonstrated that the choice of the initial AHT drug has an impact on the persistence rates.[14,19,20,22,23] This difference may be explained, at least in part, by differences in adverse effects (safety) and tolerability.[24,25] Indeed, in our study, patients treated with ARBs demonstrated the greatest persistence in comparison with the other AHT classes. ACE-inhibitors have a bothersome adverse effect of coughing that occurs more often in women than in men,[26]

Table 3. Persistence overall and by gender for AHT drug users

Type of AHT drug	Gender	Persistent users (% of total $n = 2243$)	Odds ratios (95%CI)	Adjusted odds ratios (95%CI)*
		n (%)		
Diuretics	Both	151 (33.0)	1.0 (Reference)	1.0 (Reference)
Beta-blockers		165 (35.0)	1.1 (0.9–1.5)	1.3 (1.0–1.7)
Calcium-antagonists		158 (34.7)	1.1 (0.8–1.4)	1.1 (0.8–1.4)
ACE-inhibitors		246 (59.7)	3.0 (2.3–4.0)	2.8 (2.1–3.8)
ARBs		277 (62.0)	3.3 (2.5–4.4)	3.4 (2.6–4.5)
	Men			
Diuretics		53 (37.9)	1.0 (Reference)	1.0 (Reference)
Beta-blockers		82 (41.2)	1.2 (0.7–1.8)	1.3 (0.8–2.1)
Calcium-antagonists		85 (42.7)	1.2 (0.8–1.9)	1.2 (0.8–2.0)
ACE-inhibitors		138 (62.7)	2.8 (1.8–4.3)	3.0 (1.9–4.7)
ARBs		127 (60.8)	2.6 (1.6–4.0)	3.0 (1.9–4.7)
	Women			
Diuretics		98 (30.8)	1.0 (Reference)	1.0 (Reference)
Beta-blockers		83 (30.5)	1.0 (0.7–1.4)	1.2 (0.8–1.8)
Calcium-antagonists		73 (28.5)	0.9 (0.6–1.3)	0.9 (0.6–1.3)
ACE-inhibitors		108 (56.3)	2.9 (2.0–4.2)	2.7 (1.8–3.9)
ARBs		150 (63.0)	3.8 (2.7–5.5)	3.9 (2.7–5.6)

ACE-inhibitors, angiotensin converting enzyme inhibitors; ARBs, angiotensin-2 receptor blockers; CI, confidence interval.
*Adjusted for age, use of antidiabetics, use of lipid lowering drugs, and prior cardiovascular hospitalizations.

possibly explaining why the persistence with ARBs and ACE inhibitors is equal in men, but not equal in women. Other factors such as convenience, polypharmacy, and cost in the choice of AHT are also critically important issues in the treatment of hypertension.

In line with other studies, persistence was associated with patient-related factors such as age, concurrent treatment for other chronic diseases, prior hospitalization for cardiovascular complications, as well as the number of drug changes during the first months of treatment.[13,15,20,22] These studies also found that men had a better persistence with AHT therapy than women.[13,15,20,22] In general, women report higher rates of adverse events than men.[27,28] This may explain why the present study demonstrated a lower persistence rate among women than among men (40.1% vs. 50.2%, respectively). This suggests that monitoring persistence by gender may identify potential problems that lead to treatment discontinuation.

Patients who switched or stopped AHT therapy were all considered as non-persistent. About 10% of the patients on AHT therapy switched from one AHT drug to another, meaning that the major part of the patients who were non-persistent were patients who stopped their therapy completely, and therefore were not protected for long-term cardiovascular complications at all.

A limitation of our study was that we could not confirm that tolerability or side effects were actually the reason for early discontinuation. Others found, however, that tolerability and minor adverse effects are likely to drive switches and discontinuations during follow-up both reported by patients and by clinicians.[29] In a cross-sectional study of Wallenius *et al.*,[30] it was found that patients try to manage their hypertension with a lower dosage and/or fewer drugs than prescribed. In the current study, we lack information on the indication for which the AHT drugs were prescribed. For instance, diuretics are prescribed for ankle edema in women, whereas for men this occurs probably far less often.[31] However, as we selected patients who used more than one AHT prescription, and as the prescription of diuretics for ankle edema is not intended to be chronic and the same association was found in men, it is unlikely that this explains the observed differences between men and women. Other indications may also differ between men and women such as history of myocardial infarction or angina. However, we adjusted for cardiovascular hospitalizations in the analyses.

The findings of the current study confirm that results from randomized clinical controlled trials do not reflect the persistence patterns observed in daily clinical practice. Hence, estimates of NNT from clinical trial are apt to overestimate the effectiveness and subsequently the cost-effectiveness of some AHT drug classes. Moreover, as actual use in practice differs for different classes of AHTs, cost-effectiveness

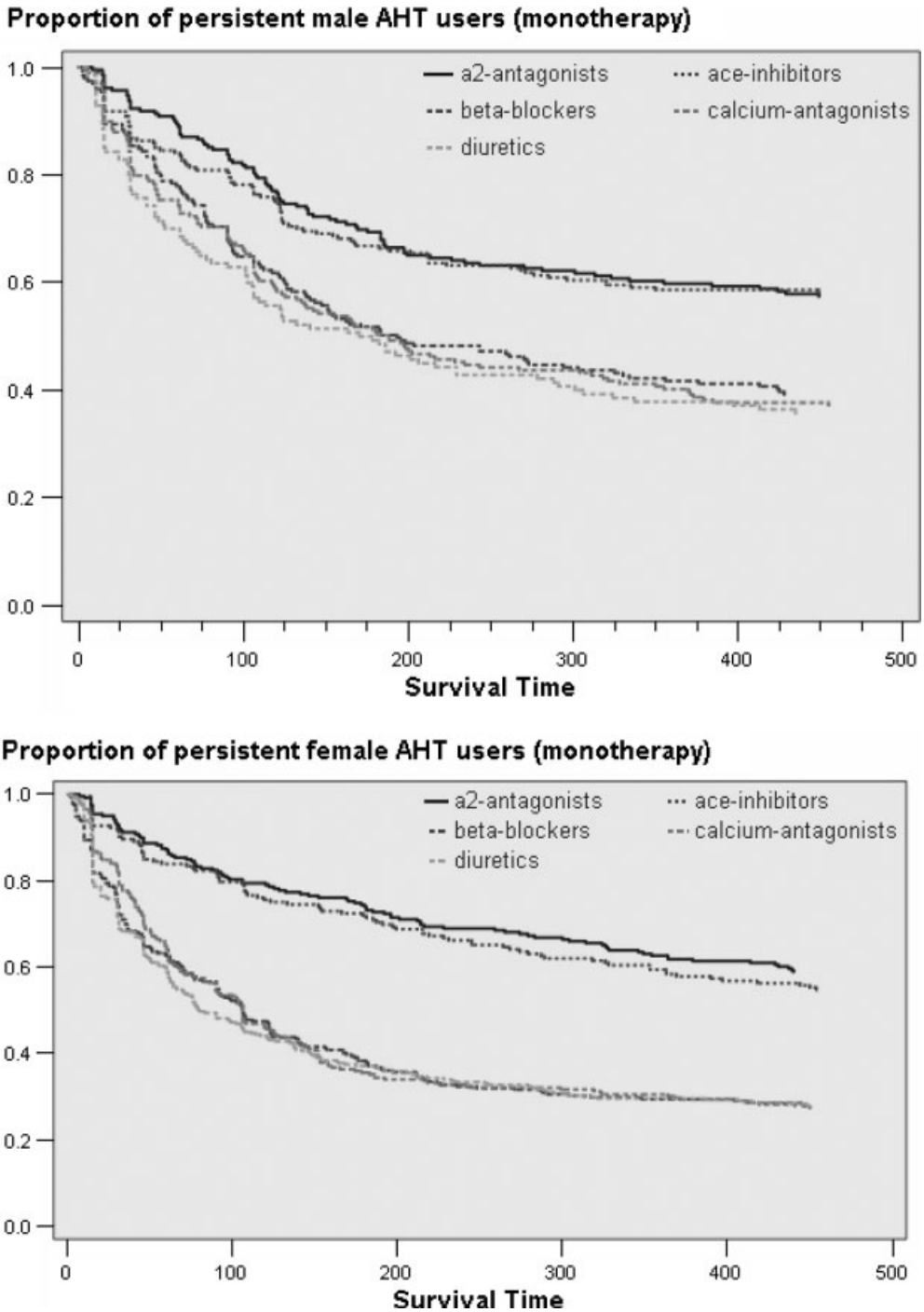

Figure 1. Kaplan–Meier survival curve for persistence of male and female AHT users during 15 months

estimates are biased and result in differential misclassification of cost-effectiveness. A study based on a meta-analysis of 15 major clinical trials of hypertension reported that diuretics remain cost-effective, even under the assumption that newer drugs are 50% more effective (half of the NNT of diuretics). Since in this study the persistence was more than twice higher among ACE inhibitors and ARBs, this criterion may actually be met.[32] The results of the current study suggest that the differences in cost-effectiveness between, for example, ARBs and diuretics may be less than expected and that this difference may vary for men and women. Formulary decisions based purely on numbers needed to treat as obtained from clinical trials and/or on the cost of drugs (e.g., inexpensive diuretics) suggest that cost savings may be overestimated due to the lack of persistence observed in daily practice.

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