Does comorbidity explain trends in prescribing of newer antihypertensive agents?

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Published in:
Journal of Hypertension

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Objective **Concerns exist about heavily prescribing of new drugs when the evidence on hard outcomes is still limited. This has been the case for the newer classes of antihypertensives, especially in hypertensive patients without additional comorbidity. The association between comorbidity and trends in prescribing of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) was examined for the period 1996–2000.**

Design and methods **Data were obtained from the Integrated Primary Care Information database, which contains medical records from more than 100 general practitioners in the Netherlands. Prevalent drug use in hypertensive patients was determined per calendar year. As initial treatment, the first antihypertensive drug prescribed within 1 year after diagnosis of hypertension was considered. Logistic regression was used to estimate the likelihood of receiving either ACE-I or ARBs.**

Results **The overall prevalent ACE-I use remained stable (31%), but it increased from 33 to 41% in hypertensive patients with diabetes, heart failure, proteinuria and/or renal insufficiency. ARB use increased significantly from 2 to 12%; this trend did not differ between patients with or without specific comorbidities. Initial ACE-I use slightly decreased (from 29% to 24%), whereas initial ARB use significantly increased (from 4% to 12%). ACE-I were more likely to be the first treatment in patients with diabetes [odds ratio (OR) = 3.9; 95% confidence interval (CI) 3.2–4.9] or hypercholesterolemia (OR = 1.4; 95% CI 1.1–1.8). ARBs were more likely to be the initial treatment in patients with asthma/chronic obstructive pulmonary disease (OR = 1.6; 1.2–2.3), diabetes (OR = 2.1; 1.5–2.9) or hypercholesterolemia (OR = 1.7; 1.2–2.4).**

Conclusions **The increased use of ACE-I is mostly restricted to hypertensive patients with comorbidities for which their use has been recommended. Trends in prescribing of ARBs are not related to relevant comorbidities. *J Hypertens* 22:2209–2215 © 2004 Lippincott Williams & Wilkins.**

Journal of Hypertension 2004, **22**:2209–2215

Keywords: antihypertensive agents, comorbidity, drug utilization review, evidence-based medicine, hypertension, primary health care

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Sponsorships: This research project was supported by an unconditional research grant by Health Care Insurance Board, The Netherlands.

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Received 30 January 2004 **Revised** 31 May 2004
Accepted 24 June 2004

Introduction

There is an ongoing debate regarding which drug class should be preferred for treating hypertension [1,2]. Over the years, most national and international guidelines have recommended diuretics and β-blockers as first-choice agents for the treatment of hypertension without comorbidity because benefits on hard outcomes have been demonstrated for these drugs [3–5]. One of the debated issues is the role that angiotensin-converting enzyme inhibitors (ACE-I) and, more recently, angiotensin II receptor blockers (ARBs) have in treating uncomplicated hypertension. The first studies showing benefits in terms of cardiovascular morbidity and mortality in hypertension patients were published in 1999 for ACE-I [6–8], and in 2002 for ARBs [9] (Fig. 1). However, during the preceding years in which the cardiovascular disease outcomes of these newer antihypertensive drugs were largely unknown, large shifts were observed in the use of these drugs in hypertensive patients [10–15].

However, evidence that ACE-I are effective in reducing morbidity and mortality in patients with heart failure or diabetes mellitus was available several years earlier [16–18]. Based on this evidence, ACE-I have been recommended in the Dutch hypertension guidelines since 1997 as first-choice agents for hypertensive patients who also have heart failure or diabetes mellitus, especially in the presence of proteinuria [3,4]. ARBs, which were introduced in the Netherlands in 1995, were first mentioned in a Dutch hypertension guideline in 2000, and

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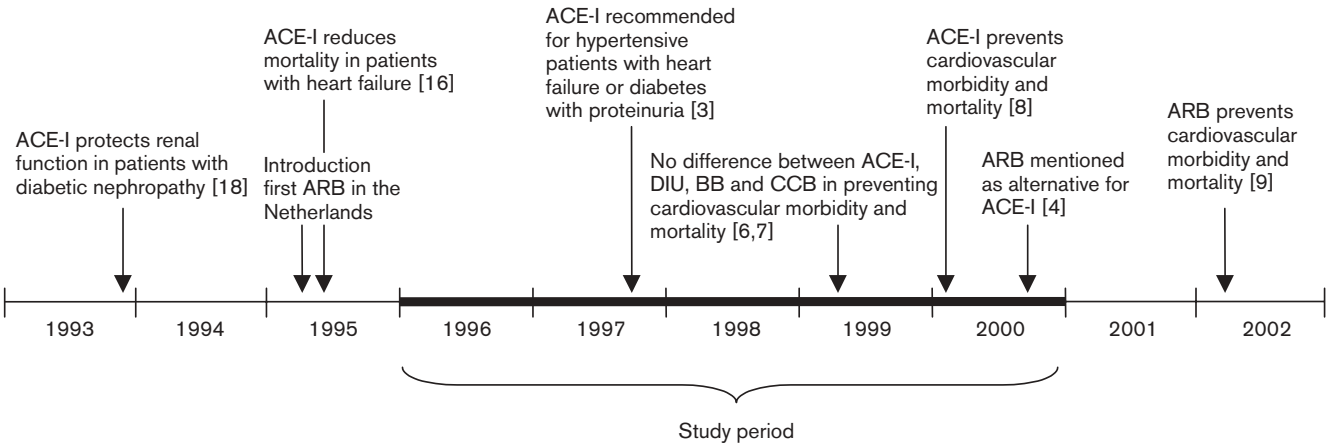
Fig. 1



Relevant trial results and Dutch guideline recommendations regarding ACE inhibitors and angiotensin II receptor blockers before, during and after the study period. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DIU, diuretic; BB, β-blocker; CCB, calcium channel blocker.

are recommended as alternative for ACE-I when these drugs are not well tolerated [4]. It might be expected that increases in the use of ACE-I and ARBs have been the largest in these specific patient groups for which they have been recommended. In a survey conducted in the USA in 1997, primary care physicians reported that they increased the use of ACE-I as initial therapy for hypertensive patients with heart failure or diabetes [19]. Cross-sectional analyses of prescription data showed that ACE-I were more likely to be prescribed in hypertensive patients with certain comorbidities, such as diabetes, hypercholesterolemia, heart failure, history of myocardial infarction or angina pectoris [11–13]. There are also some descriptive studies indicating that increased ACE-I use is influenced by the presence of comorbidities, such as diabetes [20,21]. However, these studies do not rigorously analyse the effect of comorbidity on changes in ACE-I and ARB prescribing over time. Given the difference in available evidence and recommendations on hard outcomes, it is important to analyse trends in the prescribing of ARBs separate from ACE-I.

The aim of this study was to examine the trends in prevalent and initial use of ACE-I and ARBs in comparison with other drug classes for the treatment of hypertension from 1996 to 2000, and to clarify the role of comorbidity in explaining these trends. The findings will shed new light regarding the extent that physicians anticipate on or follow the available scientific evidence and guideline recommendations.

Methods

Setting

In this study, data from the Integrated Primary Care Information (IPCI) database from the Erasmus Medical Center were used. This is a longitudinal general practice research database containing the complete electronic medical records from more than 100 Dutch general practitioners (GPs) participating on a voluntary basis, receiving a yearly financial reward. In the Netherlands, patients are registered to a single GP who has a gatekeeper role in coordinating their medical care. GPs contributing to the IPCI database are not permitted to use paper-based records in addition to their electronic medical records. They all prescribe electronically using a uniform coding system, and use the International Classification for Primary Care (ICPC) for diagnosis coding [22]. Information on drug prescriptions comprises brand name, quantity, strength, indication, prescribed daily dose and the anatomical therapeutical chemical classification (ATC) code [23]. The computer records further contain information on patient demographics, referrals, and textual medical data entered by the GP. Thus, the records can be considered to contain all drug prescriptions, and all clinical information considered relevant by the GPs for providing adequate care for their patients. The database complies with European Union guidelines on the use of medical data for medical research, and has been proven valid using different reference methods for pharmaco-epidemiological research [24].

Study period and population

The 5-year study period started on 1 January 1996 and ended on 31 December 2000. The source population comprised all individuals aged more than 18 years who had at least 6 months registration with their GP in the IPCI database during the study period. All patients with either a ICPC-coded diagnosis of hypertension or hypertension in the patient diary as free text were

selected. This latter group was manually evaluated to include only those patients where hypertension was mentioned as their diagnosis.

For hypertensive patients, all prescriptions written after diagnoses of hypertension for any of the five main antihypertensive drug classes were selected. This includes diuretics, β-blockers, calcium channel blockers, ACE-I and ARBs. Furthermore, for each patient, the presence of specific comorbidities using the ICPC-codes and free text or, when possible, the ATC-code for indication-specific drugs were identified. The following comorbidities that might influence the choice of hypertension treatment were included: angina pectoris, ankle oedema, arrhythmia, asthma and/or chronic obstructive pulmonary disease (COPD), diabetes mellitus, gout, heart failure, hypercholesterolemia, myocardial infarction, proteinuria and/or renal insufficiency, and stroke. Data were also collected on referrals to an internist or cardiologist because patients with comorbidities are more likely to be referred to a specialist, and specialists have been found to prescribe more ACE-I than GPs [25].

Estimation of antihypertensive drug use

To be able to look at trends in use of antihypertensives in independent groups of patients, 20% of all patients registered in the IPCI database in each calendar year were randomly sampled. For each calendar year, prevalent antihypertensive drug use was estimated on the first Wednesday in October. A hypertensive patient was defined as prevalent user of a certain class of antihypertensive drugs based on the last prescription in the 6 months before the index date. Initial drug use was assessed for all newly diagnosed hypertensive patients as the first antihypertensive drug prescribed within 1 year after the diagnosis, excluding patients who used any antihypertensive drugs in the 6 months before initiation of hypertension therapy.

Statistical analysis

The outcome variables studied were prevalent and initial use of ACE-I and ARBs, including monotherapy as well as combination therapy containing an ACE-I or ARB. The likelihood of receiving ACE-I or ARB was estimated through logistic regression analysis. As a reference category, users of classic antihypertensives (i.e. diuretics, β-blockers and calcium channel blockers) were chosen. In all models, an adjustment was made for sex and age (categorized as 18–50, 50–59, 60–69, 70–79, 80 years and above), because substantial sex and age differences have been found in antihypertensive drug choice [11]. First, the effect of comorbidity or referrals to a cardiologist or internist were explored in separate univariate models, that include also year, sex and age. To verify whether a specific comorbidity explained the time trend in the likelihood of receiving an ACE-I or ARB, an interaction term consisting of the comorbidity in question and calendar year was added in each univariate regression model. If this interaction term was significant and the stratified analysis showed a trend over the years than this comorbidity would partly explain trends in prescribing of newer antihypertensives. Next, all significant factors were included in the final multivariate logistic regression model using a stepwise procedure.

Results

The number of individuals aged more than 18 years who were registered for at least 6 months in the IPCI database increased from 95 974 in 1996 to 160 397 in 2000. In our random samples in each calendar year, a total of 115 344 patients were selected and 10 706 patients with a diagnosis of hypertension were identified. Hypertensive patients had a mean ± SD age of 63 ± 14 years, and 61% were women (ranging from 54% in the lowest age group to 77% in the highest age group). Of these patients, 54% had hypertension with at least one comorbidity; 1774 (17%) had diabetes, 1835 (17%) had hypercholesterolemia and 553 (5.2%) had heart failure. The average number of comorbidities increased from 0.4 in the lowest age group to 1.4 in the highest age group.

Prevalent antihypertensive drug use

In the 10 706 patients with a hypertension diagnosis, 7550 hypertensive patients who were prevalent users of any antihypertensive drug were identified. From 1996 to 2000, prevalent antihypertensive drug use varied from 68 to 73% in all hypertensive patients. Prevalent use of the five antihypertensive drug classes differed between various patient subgroups (e.g. sex, age, referrals and comorbidities) (Table 1). Time trends showed that there was a significant increase in prevalent use of β-blockers (from 38 to 43%) and ARBs (from 2 to 11%), whereas prevalent use of calcium channel blockers somewhat decreased (from 22 to 21%), and prevalent use of diuretics (41%) and ACE-I (31%) remained stable over the years. Overall, the average number of antihypertensives prescribed per patient increased from 1.4 to 1.5.

Prevalent ACE-I use

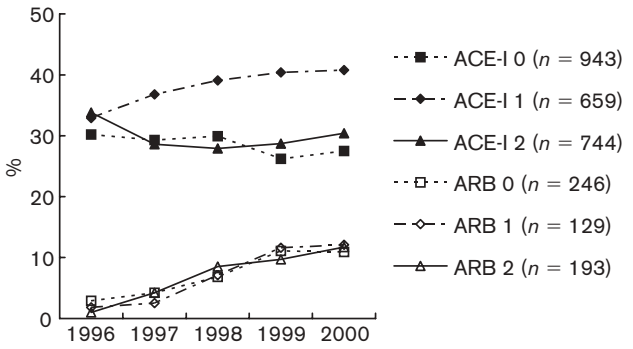
In hypertensive patients without any comorbidity, approximately 29% were treated with an ACE-I. In hypertensive patients who also suffered from diabetes, heart failure, proteinuria and/or renal insufficiency, the prevalent use of ACE-I increased from 32.9 to 40.8% (Fig. 2). The univariate analysis confirmed that diabetes, heart failure and proteinuria and/or renal insufficiency were the strongest predictors of ACE-I use [odds ratios (OR) = 1.7, 1.4 and 1.4, respectively]. Other significant comorbidities were hypercholesterolemia (OR = 1.2), angina pectoris (OR = 0.8) and ankle

Table 1 Prevalent use of diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs) in 7550 treated hypertensive patients

	n	(%)	% Diuretics	% β-blockers	% CCB	% ACE-I	% ARBs
Period of time							
1996	1044	(14)	41.0	38.2	22.1	31.8	2.1
1997	1499	(20)	42.3	41.3	20.1	30.8	3.8
1998	1786	(24)	41.6	41.7	21.1	31.2	7.4
1999	1903	(25)	39.9	41.3	18.5	30.4	10.8
2000	1318	(17)	41.3	42.9	20.6	31.6	11.5
Sex							
Male	2776	(37)	31.7	41.0	24.3	36.7	8.2
Female	4774	(63)	46.7	41.4	18.0	27.8	7.1
Age							
< 50 years	929	(12)	27.2	46.3	14.7	32.7	8.1
50–59 years	1625	(22)	35.1	48.4	18.3	32.0	8.3
60–69 years	1920	(25)	39.5	42.8	21.5	31.9	7.2
70–79 years	2083	(28)	46.3	37.1	22.9	29.8	7.9
80 years and above	993	(13)	56.4	30.5	21.1	29.2	5.5
Referral							
Internist	1784	(20)	40.8	36.2	26.0	34.3	9.1
Cardiologist	1532	(24)	37.2	42.6	28.8	31.3	9.7
Comorbidity							
No comorbidity	3306	(44)	40.7	46.0	15.4	28.5	7.4
Angina pectoris	878	(12)	37.4	47.3	32.5	26.4	7.2
Ankle oedema	691	(9)	57.3	30.8	22.9	25.6	7.5
Arrhythmia	691	(9)	41.1	38.8	23.7	31.1	9.4
Asthma/COPD	669	(9)	46.5	22.6	26.0	33.2	11.8
Diabetes	1308	(17)	44.0	33.3	22.6	39.8	7.0
Gout	389	(5)	40.1	41.4	25.4	37.3	6.7
Heart failure	454	(6)	62.3	21.1	17.8	36.1	8.6
Hypercholesterolemia	1344	(18)	35.0	43.1	26.9	34.3	8.8
Myocardial infarction	482	(6)	36.1	51.0	32.2	31.7	6.0
Proteinuria/renal insufficiency	185	(2)	44.3	31.9	28.6	37.3	11.4
Stroke	560	(7)	40.5	36.1	28.0	31.1	8.9

CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker;

Fig. 2



Prevalent use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) in 7550 treated hypertensive patients grouped by comorbidity (group 0 = no comorbidity; group 1 = diabetes, heart failure, proteinuria and/or renal insufficiency; group 2 = other comorbidity).

oedema (OR = 0.8). Multivariate logistic regression showed that ACE-I were significantly more likely to be prescribed than classic antihypertensives to patients with diabetes, heart failure, hypercholesterolemia or patients referred to an internist (Table 2). Patients with angina pectoris or ankle oedema were less likely to be prescribed ACE-I. No significant interactions were detected between individual comorbidities and trends in prevalent use of ACE-I, although the interaction between diabetes and trends in prevalent ACE-I use was of borderline significance (test for interaction, $P = 0.058$). In 2000, hypertensive patients with diabetes were more likely to be prescribed ACE-I than in 1996 [OR = 1.8; 95% confidence interval (CI) 1.2–2.8]. When combining patients with at least one comorbidity for which ACE-I are recommended (i.e. diabetes, heart failure, proteinuria and/or renal insufficiency), a significant interaction between these comorbidities and trends in prevalent ACE-I use was found (test for interaction, $P = 0.030$). In 2000, hypertensive patients with diabetes, heart failure, proteinuria and/or renal insufficiency were more likely to be prescribed ACE-I than in 1996 (OR = 1.7; 95% CI 1.1–2.6).

Initial ACE-I use

From 1996 to 2000, 3973 newly treated hypertensive patients were identified. More than one-quarter of these patients were younger than 50 years of age and 40% had at least one comorbidity. The percentage of initial ACE-I use in newly treated hypertensive patients decreased from 28.7 to 23.5%. In hypertensive patients who also had diabetes, heart failure, proteinuria and/or renal insufficiency, the percentage starting

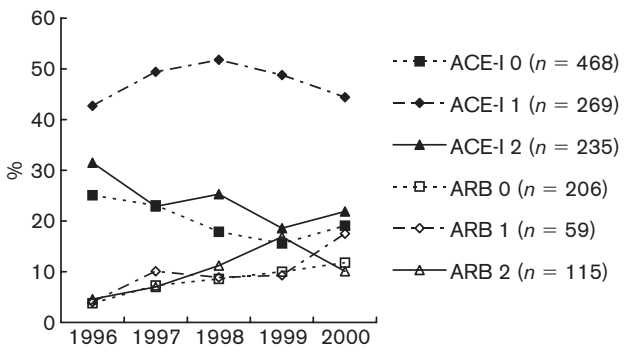
Table 2 Patient characteristics independently associated with prevalent use or initial use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) in treated hypertensive patients

	ACE-I; OR (95% CI)		ARB; OR (95% CI)	
Characteristics	Prevalent use	Initial use	Prevalent use	Initial use
Year				
1996		Reference	Reference	Reference
1997	–	0.9 (0.7–1.2)	1.7 (1.1–2.9)	1.9 (1.1–3.2)
1998	–	0.8 (0.6–1.0)	3.8 (2.4–6.0)	2.3 (1.4–3.8)
1999	–	0.7 (0.5–0.9)	5.5 (3.5–8.7)	2.9 (1.8–4.6)
2000	–	0.8 (0.6–1.0)	6.0 (3.8–9.5)	3.1 (1.9–5.0)
Age				
< 50 years			Reference	
50–59 years	–	–	1.0 (0.7–1.3)	–
60–69 years	–	–	0.9 (0.6–1.2)	–
70–79 years	–	–	0.9 (0.7–1.2)	–
80 years and above	–	–	0.6 (0.4–0.9)	–
Sex				
Female	0.6 (0.6–0.7)	0.6 (0.6–0.8)	0.8 (0.6–0.9)	0.8 (0.6–1.0)
Referral				
Internist	1.2 (1.1–1.4)	1.3 (1.1–1.6)	1.3 (1.1–1.6)	–
Cardiologists	–	1.4 (1.1–1.7)	1.6 (1.2–2.0)	–
Comorbidity				
Angina pectoris	0.7 (0.6–0.8)	–	0.7 (0.5–1.0)	–
Ankle oedema	0.7 (0.6–0.9)	–	–	0.4 (0.2–0.8)
Asthma/COPD	–	–	1.8 (1.4–2.3)	1.6 (1.2–2.3)
Diabetes	1.6 (1.4–1.8)	3.9 (3.2–4.9)	–	2.1 (1.5–2.9)
Heart Failure	1.4 (1.1–1.7)	–	–	–
Hypercholesterolemia	1.2 (1.1–1.4)	1.4 (1.1–1.8)	–	1.7 (1.2–2.4)
Myocardial Infarction	–	–	0.6 (0.4–1.0)	–

COPD, chronic obstructive pulmonary disease; OR, odds ratio; 95% CI, 95% confidence interval.

on an ACE-I was much higher, and increased from 42.7 to 51.8% in 1998 but decreased again to 44.4% in 2000 (Fig. 3). Multivariate logistic regression showed that ACE-I were more likely to be the initial therapy compared with classic antihypertensives for patients with diabetes or hypercholesterolemia (Table 2). No significant interaction between comorbidity and trends in initial use of ACE-I was found. However, initial ACE-I use and year tended to be related among hypertensive patients with diabetes (test for interaction, $P = 0.057$), and among hypertensive patients with at least one of the comorbidities diabetes, heart failure, proteinuria and/or renal insufficiency (test for interaction, $P = 0.060$).

Fig. 3



Initial use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) in 3973 newly treated hypertensive patients grouped by comorbidity (group 0 = no comorbidity; group 1 = diabetes, heart failure, proteinuria and/or renal insufficiency; group 2 = other comorbidity).

Prevalent ARB use

Trends in prevalent use of ARB did not differ between patients with or without comorbidities (Fig. 2). In the univariate analysis, asthma and/or COPD, and proteinuria and/or renal insufficiency were the strongest predictors of ARB use (OR = 1.8 and 1.8, respectively). Multivariate analysis showed that prevalent ARB use was more likely in patients with asthma and/or COPD and patients referred to a cardiologist or internist (Table 2). Patients with a history of myocardial infarction were less likely to be prescribed an ARB. No significant interactions were detected between individual comorbidities and trends in prevalent use of ARBs.

Initial ARB use

Initial ARB use increased significantly from 4.0 to 12.2%, mostly at the expense of initial ACE-I use (28.7 to 23.5%) and calcium channel blocker use (11.6 to 6.2%). Increases in initial ARB use did not differ between patients with or without comorbidities (Fig. 3). ARBs were more likely to be initially prescribed to

patients with diabetes, hypercholesterolemia, asthma and/or COPD than classic antihypertensives (Table 2). Patients with ankle oedema were less likely to be prescribed an ARB as initial therapy. We found no significant interaction between comorbidity and trends in initial use of ARBs.

Discussion

This study showed significant trends in the choice of antihypertensive treatment in the period from 1996 to 2000, which correspond with the general trends in antihypertensive prescriptions in the Netherlands [26,27]. There is an increased use of antihypertensive drug treatment in general, and specific increases in the use of β-blockers and ARBs. Although the overall use of ACE-I had stabilized, we observed an increased use of ACE-I in patients for which such drugs were recommended (i.e. hypertensive patients with diabetes, heart failure, proteinuria and/or renal insufficiency). ARB use increased significantly in all hypertensive patients, but this trend did not differ between patients with or without specific comorbidities. Initial treatment with an ARB increased from 4% in 1996 to 12% in 2000, mostly at the expense of ACE-I and calcium channel blockers. In all years, approximately 30% of the newly treated hypertensive patients without any relevant comorbidity received an ACE-I or an ARB as initial treatment. These findings confirm that these antihypertensive drugs are used whereas long-term benefits are still uncertain and sufficient evidence-based alternatives are available. On the other hand, the differences in prescribing patterns between ACE-I and ARBs suggest that increases in use of new drugs shortly after their introduction are largely not specific but, in later years, are confined to patients for whom this is more evidence-based.

Previous studies demonstrated that, between 1980 and 1998, the use of diuretics and β-blockers declined whereas the use of ACE-I (sometimes including ARBs) increased for treatment of hypertension [10–15]. Our study shows that this pattern is more complicated when differentiating for ACE-I and ARBs, and also for specific subgroups of patients. The relevance of these subgroups was already supported by studies indicating that ACE-I were more commonly prescribed to hypertensive patients with diabetes, hypercholesterolemia, heart failure, history of myocardial infarction or angina pectoris [11–13,20,21]. Looking at the influence of comorbidity during our whole study period, we could confirm some of these associations. Diabetes was the most important predictor, especially for initial ACE-I and ARB use. Hypertensive patients with diabetes were almost four-fold more likely to receive an initial treatment with ACE-I, and two-fold more likely to receive initial ARB treatment. ACE-I use was also higher in patients with heart failure, proteinuria and/or renal insufficiency, but this association diminished after adjusting for specialists' influences. Previous studies that did not correct for this influence may therefore have overestimated the actual influence of some of these comorbidities. By contrast to previous studies, we found a negative association with ACE-I use for patients with a history of myocardial infarction or angina pectoris. This is not surprising because we compared ACE-I users with all users of classic antihypertensives, including β-blockers, whereas other studies used only diuretics as reference category [11–13]. The positive association between patients with hypercholesterolemia and the use of ACE-I and ARB is consistent with previous findings [11]. There are no specific recommendations for the hypertension treatment of this group of patients, and there is no clear reason for especially prescribing ACE-I in patients with this additional risk factor. One possible explanation might be that thiazide diuretics are less favoured for these patients based on reports that they could induce small increases in cholesterol levels [28]. Finally, where other studies already reported that hypertensive patients with asthma and/or COPD were less likely to receive β-blockers [11,12], it became clear from our study that ARBs are used more often as an (initial) antihypertensive treatment for these patients. Although none of the guidelines recommend ARBs for these patients, physicians may be more inclined to use these drugs to avoid bronchospasm caused by β-blockers [29].

An important strength of our study is that we used data from a large, longitudinal database comprising information about diagnoses and prescriptions on a patient level. This allowed us to look at the influence of various patient characteristics on both initial and prevalent use of ACE-I and ARBs. In addition, we adjusted for referrals to disentangle the effect of specialists' prescribing from the effect of comorbidity on prescribing patterns in general practice. This is relevant because we observed that patients who were referred to an internist or cardiologist were more likely to be prescribed ACE-I and ARBs, and medication initiated by specialists is frequently continued by GPs [30].

A limitation of this study is the lack of a specific diagnosis for each medication. As with many cardiovascular drugs, the agents followed in this study may be indicated for the treatment of various diseases. From the GP records, it was not always possible to ascertain the cardiovascular diagnosis for which a particular drug was being used, and one drug may be prescribed to simultaneously treat more than one cardiovascular disease in an individual patient. However, each of the patients included in this study had a diagnosis of hypertension registered in their GP record. Given this, we can assume that the cardiovascular medications

included in this study were either prescribed directly for hypertension or to treat a combination of hypertension and some coexisting conditions.

In conclusion, the use of ACE-I and ARBs is partly related to several comorbidities, only some of which are clearly evidence-based. Although, ACE-I use was similar in the different patient groups in 1996, it increased by the year 2000 in hypertensive patients with comorbidities for which its use has been recommended. By contrast, trends in prescribing of ARBs are not in agreement with evidence-based guidelines at that time. ARB use significantly increased immediately after its introduction in 1995 in hypertensive patients with and without comorbidities. Apparently, these newer antihypertensive agents are considered as a first-choice drug in a non-selective group of hypertensive patients. The steep rise in ARB use might be caused by specific GPs and related to a greater reliance on drug company information or susceptibility to follow the specialists' lead in the use of new drugs, as suggested previously [31].

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Appendix

The ICPC codes [22] and ATC codes [23] shown in the following table were used to assess presence of (co)morbidity.

	ICPC codes	ATC codes
Angina pectoris	K74	
Ankle oedema	K09	
Arrhythmia	K78, K79, K80, K84.3, K84.4	C01B
Asthma/COPD	R95, R96	
Diabetes	T90	A10
Gout	T92	M04
Heart failure	K77	
Hypercholesterolemia	T93	B04, C10
Hypertension	K85, K86, K87	
Myocardial infarction	K75, K76	
Proteinuria/renal insufficiency	U98.1, U99.1	
Stroke	K89, K90	

COPD, chronic obstructive pulmonary disease; ICPC, International Classification for Primary Care; ATC, anatomical therapeutical chemical classification.