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Published in:
BMJ Open

DOI:
10.1136/bmjopen-2022-068721

Publication date:
2023

BMJ Open

Long-term comparative effectiveness of antihypertensive monotherapies in primary prevention of cardiovascular events: a population-based retrospective inception cohort study in the Netherlands

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To cite: Li X, Bijlsma MJ, Bos JHJ, *et al*. Long-term comparative effectiveness of antihypertensive monotherapies in primary prevention of cardiovascular events: a population-based retrospective inception cohort study in the Netherlands. *BMJ Open* 2023;**13**:e068721. doi:10.1136/bmjopen-2022-068721

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-068721).

Received 29 September 2022
Accepted 27 July 2023

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ABSTRACT

Objective To determine the long-term effectiveness of antihypertensive monotherapies in primary prevention of cardiovascular events.

Design Retrospective inception cohort study covering a 25-year study period.

Setting University Groningen IADB.nl pharmacy prescription database with data from 1996 to 2020.

Participants Patients aged 18 years or older, free of any cardiovascular disease (CVD) drug therapies prior to initiation of a preventive antihypertensive monotherapy (ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs) and thiazides).

Outcome measures Primary outcome was the time to first prescription of acute cardiac drug therapy (CDT) measured by valid drug proxies to identify a first major CVD event in patients without a history of CVD.

Results Among 33 427 initiators, 5205 (15.6%) patients experienced an acute CDT. The average follow-up time was 7.9±5.5 years. The 25-year incidence rate per 1000 person-years were 25.3, 22.4, 18.2, 24.4 and 22.0 for ACEI, ARB, BB, CCB and thiazide starters, respectively. Inverse probability of treatment-weighted Cox regression showed that thiazide starters had lower hazards than the reference BB starters (HR: 0.88, 95% CI: 0.81 to 0.95). Among patients on diabetes drugs, risks were lower (HR: 0.49, 95% CI: 0.28 to 0.85). CCB starters had higher hazards than reference BB (HR: 1.21, 95% CI: 1.07 to 1.36). The overall estimated number needed to treat for thiazides compared with BBs to prevent one acute CDT in 25 years was 26, and four among patients on diabetes drugs.

Conclusions After adjustments for confounders, patients starting on monotherapy with thiazides had a lower incidence of CDT compared with those starting on BBs, notably among patients on diabetes drugs. Conversely, patients who began CCB monotherapy had a higher incidence of CDT compared with those starting on BBs. Other monotherapies had comparable incidence of cardiovascular disease compared with BBs.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This comparative effectiveness study tracked a large group of individual patients for up to 25 years.
⇒ In this study, both relative and absolute drug effectiveness estimates were reported to better inform policy guidelines.
⇒ In contrast to clinical trials, our sample matches the target population.
⇒ The analysis is according to intention-to-treat, which may underestimate the actual effects of a class of drugs if taken optimally.
⇒ The first prescription of a combination of drugs for an acute cardiovascular event was used as a highly specific proxy of incident major cardiovascular event, which may have led to an underestimation of the actual number of cardiovascular disease events.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally. An estimated 17.9 million people died from CVD in 2019, accounting for 32% of all deaths worldwide.[1] In 2020, 37 000 deaths out of a total of 168 678 deaths in the Netherlands, that is, 22%, were due to CVD.[2] Hypertension is the main risk factor of CVD[1] and drug treatment is considered most effective for cardiovascular risk reduction.[3 4] However, to date, information is scarce to support which drug should be started, notably when used for a longer time.

ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs) and thiazides are the main five classes of drug therapy for hypertension and CVD prevention.[5–7] Guidelines differ in their recommendations for primary prevention of CVD. For example, the WHO guideline recommends

drugs from any of only four monotherapy classes, namely thiazide and thiazide-like agents, ACEIs, ARBs and CCBs. BBs are only recommended for patients with ischaemic heart disease. The Dutch guideline recommends any of the five monotherapies, whereas the European Society of Cardiology (ESC) prefers a combination therapy and only advices the use of a monotherapy in specific populations. For example, when patients have diabetes, all three guidelines prefer monotherapies with ACEIs or ARBs.

The difference in recommendations may be the result of inconsistent evidence. In several network meta-analyses including clinical trials, thiazide-like diuretics were observed to perform better than most drugs like ACEIs, BBs and CCBs in controlling blood pressure or preventing CVD.[8–11] Importantly, BBs were generally found to be inferior compared with other monotherapies.[9 11 12] Some studies found no differences between these five classes of drugs whereas others found only small differences in preventing cardiovascular (CV) events, and none examined long-term 'real-world' effectiveness.[8 13]

Data to support personalisation of antihypertensive monotherapies according to gender, age, comorbidities and other factors is also lacking. Two studies showed that effects appeared generally similar between men and women, and across different ages.[14 15] Fosinopril (ACEIs) was found better than amlodipine (CCBs) in preventing all CV events in patients with diabetes and captopril (ACEIs) was found to perform better compared with diuretics or BBs.[16] Which monotherapy performs better among risk groups with diabetes, rheumatoid arthritis (RA) or asthma/chronic obstructive pulmonary disease (COPD) is rather uncertain.

To address the aforementioned issues, we performed a long-term comparative effectiveness analysis of monotherapies in the prevention of acute cardiac drug therapy (CDT), and specifically examined large subgroups according to gender, age, drugs for diabetes, drugs for RA, drugs for asthma/COPD and calendar-year periods of drug start (see online supplemental table S1 for the abbreviations of proper nouns).

METHODS

Setting and data source

We used data from the University Groningen IADB.nl pharmacy prescription database which contains prescription data for more than 25 years from 1994 to 2020 in the Netherlands. Each patient is registered with a unique IADB patient number as an identifier and data also contain age, gender, time of prescription and the Anatomical Therapeutic Chemical (ATC) code for drugs (see online supplemental table S2).[17] Records are basically complete because of the high patient-pharmacy commitment in the Netherlands, excluding over-the-counter medications and medications dispensed during hospitalisation.[18]

Study population

All patients in the IADB.nl pharmacy prescription database aged 18 years or older at initiation of the antihypertensive monotherapy (index date) were eligible for inclusion in the analysis. The study period was from 1 January 1996 to 31 December 2020. ACEI, ARBs, BBs, CCBs and thiazides are the main five classes of drug therapy for hypertension and CVD prevention.

Inclusion and exclusion criteria

Eligible patients were required to be in the database at least 2 years before the index date and were present in the database for at least 1 year (365 days) after the index date. To be classified according to exposure category, patients were required to have at least three prescriptions of the same antihypertensive monotherapy class in the year after the index date.

We excluded patients who used antihyperlipidemic drug monotherapies in the year after the index date. We excluded patients who used at least two prescriptions of both antihypertensive drug fixed-dose combinations and antihyperlipidemic drug fixed-dose combinations in the year after the index date. We further excluded patients who had any other acute CDT in the 2 years before or within 90 days after the index date. We also excluded patients on at least two prescriptions of chronic, stable heart failure,[19] migraine, adrenal disease, hyperparathyroidism and thyroid problems drugs in the 2 years before or within 90 days after the index date (see online supplemental table S2).

Exposure

Hypertension monotherapy classes were defined as the use of the following antihypertensive single drug compounds: thiazides (ATC-code: C03AA), CCBs (C08C, C08D, C08E), ACEIs (C09A), ARBs (C09C), BBs (C07A). Individuals in a specific antihypertensive monotherapy group were allowed to use different chemical compounds as long as they were within the same class (ATC code level 3/4).

Primary outcome

Primary outcome was the time to first prescription of acute CDT. Acute CDT is a proxy for an incident major CV event according to Pouwels *et al*.[20] The most accurate combination of acute CDT drugs to identify a CVD is at least two drug prescriptions of either a platelet aggregation inhibitor (B01AC), organic nitrate (C01DA) and/or a vitamin K antagonist (B01AA) or other vasodilators used in acute cardiac disease therapies (C01DX), in a time window of 180 days whichever comes first, after the index date. This proxy was able to identify 85% of patients with a documented history of major CVD in primary care. Importantly, specificity was very high (94%) which is important for causal research.

High-risk comorbidities

Patients who had at least two prescriptions for blood glucose-lowering drugs (A10) in the 2 years before the

index date were defined as patients on diabetes drugs (see online supplemental table S2). Patients with at least two prescriptions for disease-modifying antirheumatic drugs (L04, A07EC01) in the 2 years before the index date were defined as patients on RA drugs. Patients with at least two prescriptions for inhaled steroids (R03BA; R03AK; R03AL)[21] in the 2 years before the index date were defined as patients on asthma or COPD drugs.

Statistical analysis

The data were imported in RStudio for cleaning, handling and analysis. The quantitative variables were expressed by the format of mean±SD, the qualitative variables were expressed by proportion and percentages. All statistical two-sided test levels (α values) were set at 0.05 to indicate statistical significance. No corrections for multiple testing were performed, and results were interpreted as exploratory. The Pearson's χ^2 test, t-test and Welch's analysis of variance test were used to analyse the relationship between the variables and exposure as well as the variables and acute CDT. We calculated the incidence rate per 1000 person-years (py) for each type of antihypertensive monotherapy class. We applied the Kaplan-Meier curve to estimate the survival difference among these different classes of drugs with the occurrence of the outcome acute CDT. We used 'twang'[22] R package of inverse probability weighting (IPW) to balance the baseline confounding variables. Cox regression modelling was used to estimate the relative effectiveness of monotherapies by means of HR and their corresponding 95% CIs. We presented the analyses overall as well as for subgroups according to gender, age, calendar-years periods (according to the year of index date, patients were divided into three periods of calendar-years) and presence of drugs for diabetes, RA, asthma or COPD. We used the Austin method to calculate number needed to treat (NNT) per time window and used Altman's method to calculate 95% CI.[23]

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Baseline characteristics

In all, the average follow-up time was 7.9±5.5 years. Among a total of 33 427 patients, 13 712 (41.0%) patients used BBs at baseline after the longest mean follow-up time of 8.7±5.9 years followed by ACEI and thiazide starters accounting for 21.5% and 20.2%, respectively (see table 1). CCBs and ARBs were the least prescribed, with 9.5% and 7.8%, respectively. Among 33 427 starters, 14 417 (43.1%) were men. The mean age was 54.8±15.2 years, thiazide users were oldest with mean age 60.7±13.4 years while BB users had the lowest mean age of 50.2±15.7 years. At baseline 1471 (4.4%) patients had drugs for diabetes and among ACEI treated patients, drugs for diabetes was most frequent (12.7%). Drugs for asthma or COPD were present in 2567 (7.7%) patients and 275 (0.8%) patients had drugs to treat RA. During the last decade (2010–2020), almost half of the study patients, 16 891 (50.5%), received their first prescription and the distribution of monotherapies was more or less the same across decades.

Acute cardiac drug therapy

In all, 5205/33 427 (15.6%) patients were dispensed acute CDT (see table 2). Among 5205 starters, 2052 BB starters (39.4%) received a first acute CDT. Patients with acute CDT outcome were on average 7 years older than those without outcome. During the second decade (2000–2010), slightly more than half of the total observed acute CDT occurred, 3193/5205 (61.3%). Except for the drugs for comorbidities RA and asthma/COPD, there were statistically significant differences in the distribution across acute CDT outcome between patients with different monotherapy types, gender, age, drugs for diabetes and calendar-year periods (p<0.001).

Incidence rate

Acute CDT incidence rate per 1000 py slightly increased within 5 years, 10 years, 15 years, 20 years and 25 years for all patients across the five different monotherapies (see online supplemental figure 1). Patients who initially started on ACEIs had the highest 5-year incidence rate of 21.5/1000 py among all types of drug starters. On the contrary, BB starters had the lowest 5-year incidence rate of 15.2/1000 py. The same trend can be seen for 10-year, 15-year, 20-year and 25-year periods. The 25-year incidence rate were 25.3/1000 py, 22.4/1000 py, 18.2/1000 py, 24.4/1000 py and 22.0/1000 py for ACEI, ARB, BB, CCB and thiazide starters, respectively (see online supplemental figure 1 and table S3).

Survival analysis

The Kaplan-Meier curves showed that the cumulative survival of five classes of antihypertensive drug monotherapies decreased with increasing follow-up time in 25 years before and after IPW (see figure 1). Before IPW, BB starters had the highest cumulative survival rate compared with other drugs. After IPW adjusted between antihypertensive monotherapies and gender, age, drugs for diabetes, drugs for RA, drugs for asthma/COPD, calendar-year periods, thiazide starters showed higher cumulative survival rate and the baseline characteristics became more similar throughout the follow-up periods. Before IPW, patients who used ACEIs, ARBs, CCBs and thiazides at baseline all had higher hazards of acute CDT than reference BB starters (see table 3). After IPW, CCB starters showed higher hazards compared with BB (HR: 1.21, 95% CI: 1.07 to 1.36, p=0.002), while patients who used thiazides had lower hazards compared with BB starters (HR: 0.88, 95% CI: 0.81 to 0.95, p=0.002).

Subgroup analysis

After IPW adjusted analysis, in men, thiazide starters had lower hazards of acute CDT than reference BB starters

Table 1 Baseline characteristics for population who used antihypertensive drugs monotherapy in different subgroups

Demographics	Total N=33 427 n (%)	ACEIs N=7189 (21.5)* n (%)	ARBs N=2591 (7.8)* n (%)	BBs N=13 712 (41.0)* n (%)	CCBs N=3167 (9.5)* n (%)	Thiazides N=6768 (20.2)* n (%)	P value†
Average follow-up years‡	7.9±5.5	7.0±5.0	7.8±5.2	8.7±5.9	5.9±4.7	8.0±5.1	/
Gender							
Male	14 417 (43.1)	4099 (57.0)	1335 (51.5)	5021 (36.6)	1458 (46.0)	2504 (37.0)	<0.001
Age§ (years)	54.8±15.2	56.6±13.9	57.1±13.1	50.2±15.7	56.5±15.1	60.7±13.4	<0.001¶
18–39	5221 (15.6)	743 (10.3)	223 (8.6)	3435 (25.1)	439 (13.9)	381 (5.6)	<0.001
40–69	22 158 (66.3)	5050 (70.2)	1878 (72.5)	8633 (63.0)	2082 (65.7)	4515 (66.7)	
≥70	6048 (18.1)	1396 (19.4)	490 (18.9)	1644 (12.0)	646 (20.4)	1872 (27.7)	
Drugs for diabetes							
Yes	1471 (4.4)	910 (12.7)	162 (6.3)	167 (1.2)	59 (1.9)	173 (2.6)	<0.001
Drugs for rheumatoid arthritis							
Yes	275 (0.8)	69 (1.0)	28 (1.1)	77 (0.6)	54 (1.7)	47 (0.7)	<0.001
Drugs for asthma/ COPD							
Yes	2567 (7.7)	601 (8.4)	241 (9.3)	781 (5.7)	293 (9.3)	651 (9.6)	<0.001
Calendar-year periods							
1996–2000	2466 (7.4)	464 (6.5)	120 (4.6)	1288 (9.4)	199 (6.3)	395 (5.8)	<0.001
2000–2010	14 070 (42.1)	2470 (34.4)	1081 (41.7)	6561 (47.8)	748 (23.6)	3210 (47.4)	
2010–2020	16 891 (50.5)	4255 (59.2)	1390 (53.6)	5863 (42.8)	2220 (70.1)	3163 (46.7)	

*Row percentage, others are all column percentage.
†P value: significance value of the χ^2 test or ANOVA test, which showed the difference of distribution of patients who used five antihypertensive monotherapies at baseline in different subgroups of covariates.
‡Use mean±SD to describe average follow-up years.
§Use mean±SD to describe continuous age.
¶Welch's ANOVA test to describe whether patients of different classes of antihypertensive monotherapy were different in age (heterogeneity of variance).
ACEIs, ACE inhibitors; ANOVA, analysis of variance; ARBs, angiotensin II receptor blockers; BBs, beta-blockers ; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease.

(HR: 0.86, 95% CI: 0.76 to 0.97), but the point estimate was similar to the overall group. In women, CCB starters had higher hazards than BB (HR: 1.33, 95% CI: 1.13 to 1.56) with a slightly higher point estimate than the overall group. Age did not substantially modify the effects. Among patients with or without diabetes drugs, thiazide starters both had lower hazards compared with BB users (HR: 0.49, 95% CI: 0.28 to 0.85 and HR: 0.91, 95% CI: 0.84 to 0.98), however the point estimate was much lower in the diabetes drug treated group. Among patients without drugs for diabetes, RA and asthma/COPD, the results showed the same pattern as those in all patients. There was no substantial modification by decade (see table 4, online supplemental figure 2).

Absolute drug effectiveness estimates

The NNT for thiazides compared with BBs were 102, 49, 34, 29 and 26 over 5, 10, 15, 20 and 25 study years in preventing one acute CDT, respectively. Among patients on RA drugs, the NNT were the lowest of 11, 6, 6, 3 and 3 over 5, 10, 15, 20 and 25 study years compared with patients in other subgroups, respectively. Among patients on diabetes drugs, the NNT for thiazides compared with BBs were 12, 8, 7, 6 and 4 over 5, 10, 15, 20 and 25 study years, respectively (details see online supplemental figure 3 and table S4).

DISCUSSION

In this long-term 'real-world' analysis using an inception cohort design we found that when patients start on thiazide monotherapy, they had a lower incidence of CDT compared with those started on BBs, notably among patients on diabetes drug treatment. CCB users had a higher incidence of CDT than BB users and there were

Table 2 Distribution of exposures groups and different subgroups according to outcome acute cardiac drug therapy (CDT) (%)

Demographics	Acute CDT N=5205 (15.6)* n (%)	No acute CDT N=28 222 (84.4)* n (%)	P value†
Antihypertensive monotherapies			
ACEIs	1183 (22.7)	6006 (21.3)	<0.001
ARBs	425 (8.2)	2166 (7.7)	
BBs	2052 (39.4)	11 660 (41.3)	
CCBs	420 (8.1)	2747 (9.7)	
Thiazides	1125 (21.6)	5643 (20.0)	
Gender: male	2552 (49.0)	11 865 (42.0)	<0.001
Age (years) ‡	61.0±13.2	53.7±15.3	<0.001§
18–39	292 (5.6)	4929 (17.5)	<0.001
40–69	3419 (65.7)	18 739 (66.4)	
≥70	1494 (28.7)	4554 (16.1)	
Drugs for diabetes: Yes	368 (7.1)	1103 (3.9)	<0.001
Drugs for rheumatoid arthritis: Yes	49 (0.9)	226 (0.8)	0.343
Drugs for asthma/COPD: Yes	426 (8.2)	2141 (7.6)	0.144
Calendar-year periods			
1996–2000	846 (16.3)	1620 (5.7)	<0.001
2000–2010	3193 (61.3)	10 877 (38.5)	
2010–2020	1166 (22.4)	15 725 (55.7)	

*Row percentage, others are all column percentage.
†P value: significance value of the χ^2 test or t-test, which showed the difference of distribution of patients who had acute CDT as outcome or not in different subgroups of covariates.
‡Use mean±SD to describe continuous age.
§Use t-test to describe whether patients who had acute CDT or not were different in age.
ACEIs, ACE inhibitors; ARBs, angiotensin II receptor blockers ; BBs, beta-blockers; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease.

no major differences between the remaining monotherapies. No substantial effect modification by gender, age, other drugs for comorbidities or decade were found.

In our study, BBs were the most frequently prescribed monotherapies (41%) for patients starting on any antihypertensive monotherapy. This is in contrast with the fact that thiazides and ACEIs are currently preferred for the treatment of hypertension and CVD prevention.[6 7 24] Likely, this is because BBs are nevertheless considered an effective treatment for hypertension and CVD reduction in the Netherlands.[25]

We found that all five classes of monotherapies showed a slowly increasing trend in acute CDT incidence rate with increasing follow-up years. The 25-year acute CDT incidence rate for ACEI starters was the highest and for BB starters the lowest. These findings are in accordance with the ALLHAT study,[26] which compared starters with chlorthalidone, amlodipine and lisinopril monotherapies as the representation of thiazide-like diuretic, CCBs and ACEIs, respectively. In this study, increasing cumulative event rates for combined CVD during a follow-up time of on average 4.9 years was observed. Lisinopril had a little bit sharper slope than amlodipine and then chlorthalidone. The ALLHAT study had a similar population size as our study, but their study was limited to high-risk individuals 55 years and older who had a history of CV heart disease. A study by Dahlöf *et al*[27] found a primary composite endpoint morbidity rate per 1000 person-years for losartan-based of 23.8 and for atenolol-based of 27.9 within at least 4 years follow-up time, which were higher event rates than in our study. These two drugs represented the ARB and BB drug classes. In this study 9193 patients aged 55–80 with essential hypertension were included which was similar to our study population. However, death, stroke and myocardial infarction were included in a composite endpoint.

To adjust for baseline differences between the compared groups, we used IPW. After IPW adjustment our analysis showed that thiazide users had a lower incidence of CDT compared with BBs. Our results provide further evidence in support of the ESC/European Society of Hypertension[7] guideline for hypertension diagnosis and treatment, which recommends thiazides as the initial treatment. Furthermore, our results were in accordance with other

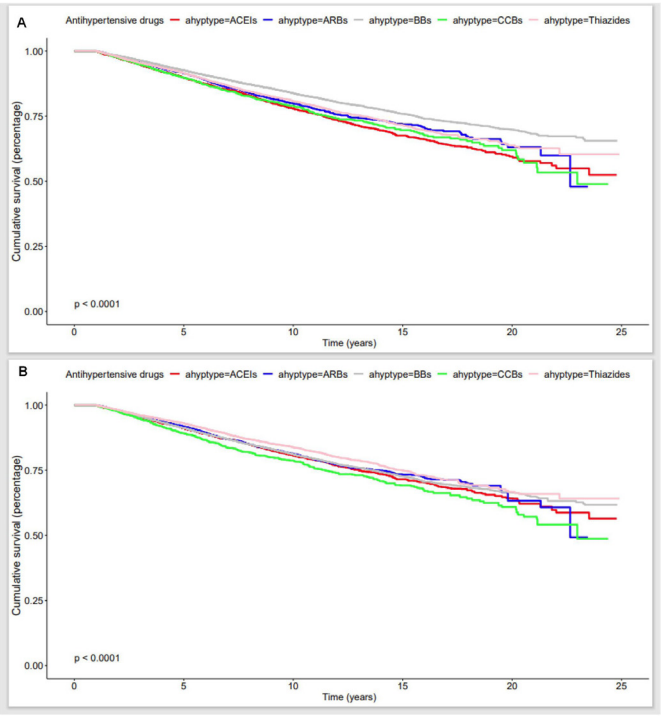

Figure 1 Survival curves for acute cardiac drug therapy in patients treated with five types of antihypertensive monotherapies in 25-year of time before and after IPW. (A) Before IPW, (B) after IPW. ACEIs, ACE inhibitors; ARBs, angiotensin II receptor blockers; BBs, beta-blockers; CCBs, calcium channel blockers; IPW, inverse probability weighting.

studies. A network meta-analysis of 42 trials by Psaty *et al*[10] showed that low-dose diuretic therapy performed better than any classes of antihypertensive drugs. For example, low-dose diuretic therapy had a lower estimate compared with BBs therapy in developing a CVD event (relative risk [RR]: 0.89, 95% CI: 0.80 to 0.98), using CVD events as the outcome. The Fretheim *et al*[9] study included 25 trials, the results of the meta-analysis showed that diuretics had a lower risk of myocardial infarction compared with BBs (RR: 0.82, 95% CI: 0.68 to 0.98), but most of the trials were of low quality.

We also found that CCB users had a higher incidence of CDT compared with BBs, which is different from findings by Zhu *et al*.[11] The investigators showed that CCBs reduced the risk of major CV events compared with BBs (RR: 0.84, 95% CI: 0.77 to 0.92). Their study included three randomised controlled trials (RCTs) for different CVD outcomes and most of the studies had moderate quality. The difference between our study and the others can be explained by many reasons. For example, CCBs and BBs may have differential effects on specific CVD outcomes, BBs have been shown to be beneficial in reducing the risk of heart failure and recurrent myocardial infarction.[28] In contrast, CCBs may have limited efficacy in preventing these specific outcomes. Therefore, when primary prevention of CVD involves targeting these specific endpoints, BBs may be preferred over CCBs. We did not find evidence of differences in effects across other drug monotherapies compared with BBs. However, for example, a study by Dahlöf *et al*[27] showed that losartan-based (ARBs) is superior to atenolol-based (BBs) in reducing a composite of CVD events.

Furthermore, some studies[8 9] showed that thiazide or thiazide-like diuretics performed better than ACEIs and CCBs in preventing separate CVD, and that BBs[9 12] were the least effective compared with other classes of agents in reducing CVD mortality or CV event.

A meta-analysis[13] from Law *et al* included 147 RCTs published between 1966 and 2007 which showed that the relative effectiveness among five classes of antihypertensive drugs in preventing coronary heart disease was almost the same. However, the source of evidence was mostly uninformative.

Subgroup

Diabetes is a risk factor for CVD and thiazide monotherapy had an even lower incidence of CDT compared with BBs in patients on diabetes drugs and the number needed to treat were lower as well. Patients use antidiabetic drugs at the same time as a monotherapy of antihypertensive drugs and adherence to drug regimens may be better in this group. Some studies[16] showed that ACEIs were more

Table 3 Cox regression analysis of acute cardiac drug therapy (CDT) (N=5205)

	Acute CDT			
Antihypertensive monotherapies	**Crude HR (95% CI)**	**P value**	**IPW adjusted* HR (95% CI)**	**P value**
Reference: BBs				
Exposure				
ACEIs	1.42 (1.32 to 1.52)	<0.001	1.04 (0.96 to 1.13)	0.351
ARBs	1.24 (1.12 to 1.37)	<0.001	0.99 (0.88 to 1.10)	0.813
CCBs	1.39 (1.25 to 1.54)	<0.001	1.21 (1.07 to 1.36)	0.002
Thiazides	1.21 (1.13 to 1.31)	<0.001	0.88 (0.81 to 0.95)	0.002

*IPW adjusted between antihypertensive monotherapies and gender, age, drugs for diabetes, drugs for RA, drugs for asthma/COPD, calendar-year periods.
ACEIs, ACE inhibitors ; ARBs, angiotensin II receptor blockers ; BBs, beta-blockers; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; IPW, inverse probability weighting; RA, rheumatoid arthritis.

Table 4 Cox regression analysis of acute cardiac drug therapy (CDT) in different subgroups

	Crude HR (95% CI)				IPW adjusted * HR (95% CI)			
Subgroups	**ACEIs vs BBs**	**ARBs vs BBs**	**CCBs vs BBs**	**Thiazides vs BBs**	**ACEIs vs BBs**	**ARBs vs BBs**	**CCBs vs BBs**	**Thiazides vs BBs**
Gender								
Male	1.22 (1.11 to 1.35)	1.07 (0.93 to 1.23)	1.20 (1.03 to 1.40)	1.12 (1.00 to 1.26)	1.03 (0.92 to 1.15)	0.91 (0.79 to 1.06)	1.07 (0.90 to 1.27)	0.86 (0.76 to 0.97)
Female	1.42 (1.27 to 1.58)	1.29 (1.11 to 1.51)	1.50 (1.30 to 1.74)	1.30 (1.18 to 1.43)	1.05 (0.93 to 1.18)	1.05 (0.89 to 1.23)	1.33 (1.13 to 1.56)	0.90 (0.81 to 1.00)
Age (years)								
18–39	1.76 (1.31 to 2.38)	0.92 (0.49 to 1.74)	1.44 (0.95 to 2.17)	1.14 (0.74 to 1.74)	1.17 (0.78 to 1.75)	1.04 (0.54 to 2.01)	1.49 (0.97 to 2.30)	0.95 (0.59 to 1.51)
40–69	1.21 (1.11 to 1.32)	1.07 (0.94 to 1.21)	1.23 (1.07 to 1.40)	0.93 (0.85 to 1.02)	1.04 (0.94 to 1.14)	0.96 (0.84 to 1.09)	1.22 (1.05 to 1.42)	0.86 (0.78 to 0.95)
≥70	1.08 (0.94 to 1.24)	0.96 (0.78 to 1.17)	1.12 (0.92 to 1.35)	0.90 (0.79 to 1.03)	1.01 (0.86 to 1.17)	0.96 (0.78 to 1.18)	1.12 (0.91 to 1.38)	0.88 (0.76 to 1.01)
Drugs for diabetes								
Yes	1.25 (0.88 to 1.78)	1.05 (0.67 to 1.65)	1.15 (0.60 to 2.22)	0.58 (0.34 to 0.98)	1.10 (0.76 to 1.59)	0.93 (0.59 to 1.48)	0.79 (0.35 to 1.81)	0.49 (0.28 to 0.85)
No	1.32 (1.22 to 1.42)	1.21 (1.09 to 1.35)	1.39 (1.25 to 1.55)	1.23 (1.14 to 1.32)	1.03 (0.95 to 1.12)	0.99 (0.88 to 1.11)	1.23 (1.10 to 1.39)	0.91 (0.84 to 0.98)
Drugs for rheumatoid arthritis								
Yes	0.82 (0.41 to 1.66)	0.54 (0.18 to 1.61)	0.73 (0.33 to 1.63)	0.30 (0.10 to 0.88)	0.78 (0.37 to 1.64)	0.41 (0.14 to 1.22)	1.36 (0.59 to 3.14)	0.35 (0.11 to 1.12)
No	1.42 (1.32 to 1.53)	1.25 (1.12 to 1.38)	1.39 (1.25 to 1.55)	1.22 (1.14 to 1.32)	1.04 (0.96 to 1.13)	0.99 (0.89 to 1.11)	1.20 (1.07 to 1.35)	0.88 (0.82 to 0.96)
Drugs for asthma/ COPD								
Yes	1.76 (1.35 to 2.29)	1.69 (1.19 to 2.39)	1.60 (1.13 to 2.28)	1.33 (1.01 to 1.74)	1.19 (0.89 to 1.60)	1.31 (0.90 to 1.89)	1.29 (0.88 to 1.89)	0.91 (0.68 to 1.22)
No	1.39 (1.29 to 1.49)	1.20 (1.07 to 1.34)	1.37 (1.22 to 1.53)	1.20 (1.11 to 1.30)	1.03 (0.94 to 1.12)	0.96 (0.85 to 1.08)	1.20 (1.06 to 1.36)	0.88 (0.80 to 0.95)
Calendar-year periods								
1996–2000	1.65 (1.38 to 1.96)	1.47 (1.08 to 2.00)	1.60 (1.26 to 2.03)	1.35 (1.11 to 1.63)	1.03 (0.83 to 1.28)	1.06 (0.76 to 1.46)	1.25 (0.97 to 1.62)	0.94 (0.76 to 1.17)

Continued

Table 4 Continued

Subgroups	Crude HR (95% CI)				IPW adjusted * HR (95% CI)			
	ACEIs vs BBs	ARBs vs BBs	CCBs vs BBs	Thiazides vs BBs	ACEIs vs BBs	ARBs vs BBs	CCBs vs BBs	Thiazides vs BBs
2000–2010	1.47 (1.34 to 1.61)	1.19 (1.04 to 1.36)	1.51 (1.30 to 1.75)	1.20 (1.09 to 1.31)	0.99 (0.89 to 1.10)	0.90 (0.78 to 1.03)	1.19 (1.02 to 1.40)	0.85 (0.77 to 0.94)
2010–2020	1.45 (1.24 to 1.69)	1.52 (1.23 to 1.87)	1.41 (1.16 to 1.72)	1.35 (1.14 to 1.59)	1.17 (0.99 to 1.38)	1.23 (0.99 to 1.53)	1.15 (0.94 to 1.41)	0.95 (0.80 to 1.14)

*IPW adjusted between antihypertensive monotherapies and gender, age, drug for diabetes, drug for RA, drug for asthma/COPD, calendar-year periods.
ACEIs, ACE inhibitors ; ARBs, angiotensin II receptor blockers ; BBs, beta-blockers; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; IPW, inverse probability weighting; RA, rheumatoid arthritis.

effective than CCBs and BBs in patients with diabetes. Östergren[29] *et al* found that amlodipine-based treatment (CCBs) was better than atenolol-based regimen (BBs) in patients with type II diabetes for preventing CVD events (unadjusted HR 0.86, 95% CI: 0.76 to 0.98).

Potential limitations and strengths

Although the analysis was according to the intention-to-treat principle, a potential limitation of our study may be that we underestimated the actual effects of a class of drugs if taken optimally. First, we treated drug use as a time-constant variable. However, in practice patients may stop, switch or add on drugs. Second, diagnostic data was not available in the IADB database, the first prescription of a combination of drugs for an acute CV event was used as a highly specific proxy of incident major CV event, which may have led to an underestimation of the actual number of CVD events. However, this is unlikely to affect our estimates of comparative effectiveness and random misclassification will lead to a null finding. Third, some unmeasured confounding may have influenced the result. The WHO considers unhealthy diet, physical inactivity, tobacco use and harmful use of alcohol as important behavioural risk factors of CVD which could not be measured in this database. However, in the Netherlands, the indication did not strongly favour any of the monotherapies, hence it is unlikely that distribution of these risk factors was very different between monotherapy groups. However, some antihypertensive drugs can infrequently be used for other indications which may have caused in part the lower effectiveness estimate as found for CCBs which can be prescribed for migraine or Raynaud disease.

Our study also has some strengths. In contrast to clinical trials, our 'real-world' patient population is representative of the target population. Second, follow-up time was much longer than all trials and cohort studies so far. Since ageing of populations becomes increasingly important in the duration of prevention programmes, it is essential to gather information on longer-term effects. In contrast with earlier reports on this topic, we reported both relative and absolute effectiveness. Finally, despite guidelines on prevention with monotherapies for hypertension have changed over time, no substantial effect modification by decade was observed.

Conclusion

After adjustments for confounders, patients starting on monotherapy with thiazides had a lower incidence of CDT compared with those starting on BBs, notably among patients on diabetes drugs. Conversely, patients who began CCB monotherapy had a higher incidence of CDT compared with those starting on BBs. Other monotherapies had comparable incidence of CDT compared with BBs.

Acknowledgements We thank the pharmacies that supplied data to the University Groningen IADB.nl database.

Contributors XL conceived and EH, MB, CCMS-V and JB designed the study. JB constructed data. XL, MB and EH wrote the first draft. All the authors reviewed and approved the final article. EH is the guarantor.

Funding XL is funded by the China Scholarship Council (file no: 202106070028).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study is based on established database IADB.nl. Data are collected in accordance with the national and European guidelines on privacy requirements for handling human data. The authors have no ethical conflicts to disclose. Ethics approval is not needed and required for this study. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available.

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