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Long-term comparative effectiveness of anti-hypertensive monotherapies in primary prevention of cardiovascular events

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Abstract

Objective: To determine the long-term effectiveness of anti-hypertensive 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 anti-hypertensive monotherapy (Angiotensin-converting enzyme inhibitors [ACEIs], Angiotensin II receptor blockers [ARBs], Beta-blockers [BBs], Calcium Chanel Blockers [CCBs], 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 33427 initiators, 5204 (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 (NNT) for thiazides compared with BBs to prevent one acute CDT in 25 years was 27, and 4 among patients on diabetes drugs.

Conclusions: Starting monotherapy with thiazides appeared to be more effective than BBs in the prevention of acute CDT, notably among patients on diabetes drugs. Other monotherapies had effectiveness profiles comparable to BBs.

Key words: monotherapy, primary prevention, acute cardiac drug therapy, cohort study, comparative effectiveness

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 CVD 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, 37000 deaths out of a total of 168678 deaths in the Netherlands, i.e. 22%, were due to cardiovascular disease.[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.

Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin II receptor blockers (ARBs), Beta-blockers (BBs), Calcium Chanel 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 World Health Organization (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 ischemic 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 BP 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 CV events, and none examined long-term “real-world” effectiveness.[8,13]

Data to support personalization of anti-hypertensive 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 diabetes patients 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 an 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 (OTC) medications and medications dispensed during hospitalization.[18]

Study population

All patients in the IADB.nl pharmacy prescription database aged 18 years or older at initiation of the anti-hypertensive monotherapy (index date) were eligible for inclusion in the analysis. The study period was from January 1, 1996 to December 31, 2020. Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin II receptor blockers (ARBs), Beta-blockers (BBs), Calcium Chanel Blockers (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 two years before the index date and were present in the database for at least one 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 anti-hypertensive monotherapy class in the year after the index date.

We excluded patients who used anti-hyperlipidemic 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 anti-hyperlipidemic drug fixed-dose combinations in the year after the index date. We further excluded patients who had any other acute cardiac drug therapy (CDT) in the two 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 two 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 anti-hypertensive monotherapy group were allowed to use different chemical compounds as long as they were within the same class (ATC code level 4).

Primary outcome

Primary outcome was the time to first prescription of acute cardiac drug therapy (CDT). Acute CDT is a proxy for an incident major cardiovascular 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.

High-risk co-morbidities

Patients who had at least two prescriptions for blood glucose-lowering drugs (A10) in the two 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 anti-rheumatic drugs (DMARDs: L04, A07EC01) in the two years before the index date were defined as patients on rheumatoid arthritis drugs. Patients with at least two prescriptions for inhaled steroids (R03BA; R03AK; R03AL)[21] in the two years before the index date were defined as patients on asthma or COPD drugs.

Statistical analysis

The data were imported in R-studio for cleaning, handling, and analysis. The quantitative variables were expressed by the format of mean ± standard deviations (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. The Pearson's $\chi 2$ test, t-test and Welch's ANOVA test were used to analyze the relationship between the variables and exposure as well as the variables and acute CDT. We calculated the incidence rate per 1000 person-years for each type of anti-hypertensive 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’ R-package of inverse probability weighting (IPW) to balance the baseline confounding variables. Cox regression modeling was used to estimate the relative effectiveness of monotherapies by means of hazard ratio’s (HR) and their corresponding 95% confidence intervals (CI). 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% confidence interval.[22]

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. 13712/33427 (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 starters, 14417/33427 were male (43.1%). 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 was 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, 16891 (50.5%), received their first prescription and the distribution of monotherapies was more or less the same across decades.

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

Demographics	**Total N=33427**	**ACEIs N=7189 (21.5) ***	**ARBs N=2591 (7.8) ***	**BBs N=13712 (41.0) ***	**CCBs N=3167 (9.5) ***	**Thiazides N=6768 (20.2) ***	***P*§**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
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	14417 (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	22158 (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	14070 (42.1)	2470 (34.4)	1081 (41.7)	6561 (47.8)	748 (23.6)	3210 (47.4)	
2010-2020	16891 (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 Chi-squared test or anova test, which showed the difference of distribution of patients who used five anti-hypertensive monotherapies at baseline in different subgroups of covariates

† use mean ± standard deviations to describe average follow up years

†† use mean ± standard deviations to describe continuous age

‡ Welch's anova test to describe whether patients of different classes of anti-hypertensive monotherapy were different in age (Heterogeneity of variance)

Acute cardiac drug therapy

In all, 5204/33427 (15.6%) patients were dispensed acute CDT (see table 2). 2051/5204 (39.4%) BB starters 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, 3192/5204 (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).

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

Demographics	**Acute CDT N=5204 (15.6) ***	**No acute CDT N=28223 (84.4) ***	***P*§**
	n (%)	**n (%)**	
Anti-hypertensive monotherapies			
ACEIs	1183 (22.7)	6006 (21.3)	<0.001
ARBs	425 (8.2)	2166 (7.7)	
BBs	2051 (39.4)	11661 (41.3)	
CCBs	420 (8.1)	2747 (9.7)	
Thiazides	1125 (21.6)	5643 (20.0)	
Gender: male	2552 (49.0)	11865 (42.0)	<0.001
Age(years) †	61.0±13.2	53.7±15.3	<0.001‡
18-39	291 (5.6)	4930 (17.5)	<0.001
40-69	3419 (65.7)	18739 (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)	0.342
Drugs for asthma/COPD:Yes	426 (8.2)	2141 (7.6)	0.143
Calendar-year periods			
1996-2000	846 (16.3)	1620 (5.7)	<0.001
2000-2010	3192 (61.3)	10878 (38.5)	
2010-2020	1166 (22.4)	15725 (55.7)	

* row percentage, others are all column percentage

§ P value: significance value of the Chi-squared 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 ± standard deviations to describe continuous age

‡ use t test to describe whether patients who had acute CDT or not were different in age

Incidence rate

Acute CDT incidence rate per 1000 person-years 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, thiazide starters, respectively (see online supplemental figure 1 and supplemental table S3).

Survival analysis

The Kaplan-Meier curves showed that the cumulative survival of five classes of anti-hypertensive drug monotherapies decreased with increasing follow-up time in 25 years before and after IPW (see figure 1). Before IPW, BB starters had highest cumulative survival rate compared with other drugs. After IPW adjusted between anti-hypertensive 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).

Table 3 Cox regression analysis of acute cardiac drug therapy (CDT) (N=5204)

	Acute CDT			
Anti-hypertensive monotherapies	**Crude HR (95%CI)**	***P***	**IPW ajusted* HR (95%CI)**	***P***
Reference:BBs				
Exposure				
ACEIs	1.42 (1.32 to 1.52)	<0.001	1.04 (0.96 to 1.13)	0.347
ARBs	1.24 (1.12 to 1.38)	<0.001	0.99 (0.88 to 1.10)	0.817
CCBs	1.39 (1.25 to 1.55)	<0.001	1.21 (1.07 to 1.36)	0.002
Thiazides	1.22 (1.13 to 1.31)	<0.001	0.88 (0.81 to 0.95)	0.002

*IPW adjusted between anti-hypertensive monotherapies and gender, age, drugs for diabetes, drugs for RA, drugs for asthma/COPD, calendar-year periods

Subgroup analysis

After IPW adjusted analysis, in males, thiazide starters had lower hazards of acute CDT than reference BB starters (HR: 0.86, 95% CI: 0.76 to 0.97), but the point estimate was similar to overall group. In females, 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).

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

Subgroups	Crude HR (95% CI)				IPW ajusted * 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
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 (0.93 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 (1.28 to 1.59)	1.29 (1.11 to 1.51)	1.51 (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	1.77 (1.31 to 2.40)	0.93 (0.49 to 1.75)	1.44 (0.96 to 2.18)	1.14 (0.75 to 1.76)	1.18 (0.79 to 1.76)	1.04 (0.54 to 2.02)	1.50 (0.98 to 2.31)	0.95 (0.60 to 1.52)
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 1.33)	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)	1.40 (1.25 to 1.55)	1.23 (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)	1.61 (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 1.50)	1.20 (1.07 to 1.34)	1.37 (1.22 to 1.53)	1.20 (1.12 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 (0.81 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 1.29)	1.06 (0.76 to 1.46)	1.25 (0.97 to 1.62)	0.94 (0.76 to 1.17)
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 (1.10 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 (1.15 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 anti-hypertensive monotherapies and gender, age, drug for diabetes, drug for RA, drug for asthma/COPD, calendar-year periods

Absolute drug effectiveness estimates

The NNT for thiazides compared with BBs were 102, 49, 35, 29, and 27 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, 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, online supplemental table S4).

Discussion

In this long-term "real-world" analysis using an inception cohort design we found that when patients start on thiazide monotherapy, this was more effective than when they start with BBs, notably among patients on diabetes drug treatment. CCBs were less effective than BBs and there were 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 anti-hypertensive monotherapy. This is in contrast with the fact that thiazides and ACEIs are currently preferred for the treatment of hypertension and CVD prevention.[6,7,23] Likely, this is because BBs are nevertheless considered an effective treatment for hypertension and CVD reduction in the Netherlands.[24]

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,[25] 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 cardiovascular disease 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 cardiovascular heart disease. A study by Björn et al [26] 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 to 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 inverse probability of treatment weighting (IPW). After IPW adjustment our analysis showed that thiazides were more effective at preventing acute CDT compared to BBs. Our results provide further evidence in support of the ESC/ESH[7] guideline for hypertension diagnosis and treatment, which recommends thiazides as the initial treatment. Furthermore, our results were in

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

We also found that CCBs were inferior at preventing acute CDT compared to BBs, which is different from findings by Zhu et.al.[11] The investigators showed that CCBs reduced the risk of major CV events compared to BBs (RR: 0.84, 95% CI: 0.77 to 0.92). Their study included three randomized controlled trials (RCTs) for different CVD outcomes and most of the studies had moderate quality. We did not find evidence of differences in effects across other drug monotherapies compared with BBs. However, for example, Björn et.al [26] 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 disease, and that BBs[9,12] were the least effective compared to 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 were mostly uninformative.

Subgroup

Diabetes is a risk factor for cardiovascular disease and thiazide monotherapy appeared to perform much better compared with BBs in patients on diabetes drugs and number needed to treat were lower as well. Patients use anti-diabetic 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 effective than CCBs and BBs in diabetes patients. Jan[27] 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 ITT 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, 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 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 behavioral risk factors of CVD which could not be measured in this database. However, the indication was the same for all monotherapies in the vast majority of patients and it is unlikely that distribution of these risk factors was very different between monotherapy groups. However, some anti-hypertensive 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 for 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 programs, 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

Starting monotherapy with thiazides appeared to be more effective than BBs in the prevention of acute CDT. Other drugs had comparable effectiveness profiles. In patients on diabetes drugs, both relative and absolute effectiveness of monotherapy with thiazides were better than BBs in the prevention of acute CDT. In rheumatoid arthritis patients, absolute effectiveness of monotherapy with thiazides was better than BBs in the prevention of acute CDT.

a. Contributorship statement XCL conceived and EH, MJB, CCMSV and JHJ designed the study. JHJ constructed data. XCL, MJB and EH wrote the first draft. All the authors reviewed and approved the final article.

b. Competing interests The authors declare no other competing interests.

c. Funding Xuechun Li is funded by the China Scholarship Council (file no: 202106070028).

d. Data sharing statement The study remains in progress and the data are not currently available for sharing.

e. Ethics approval statement 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.

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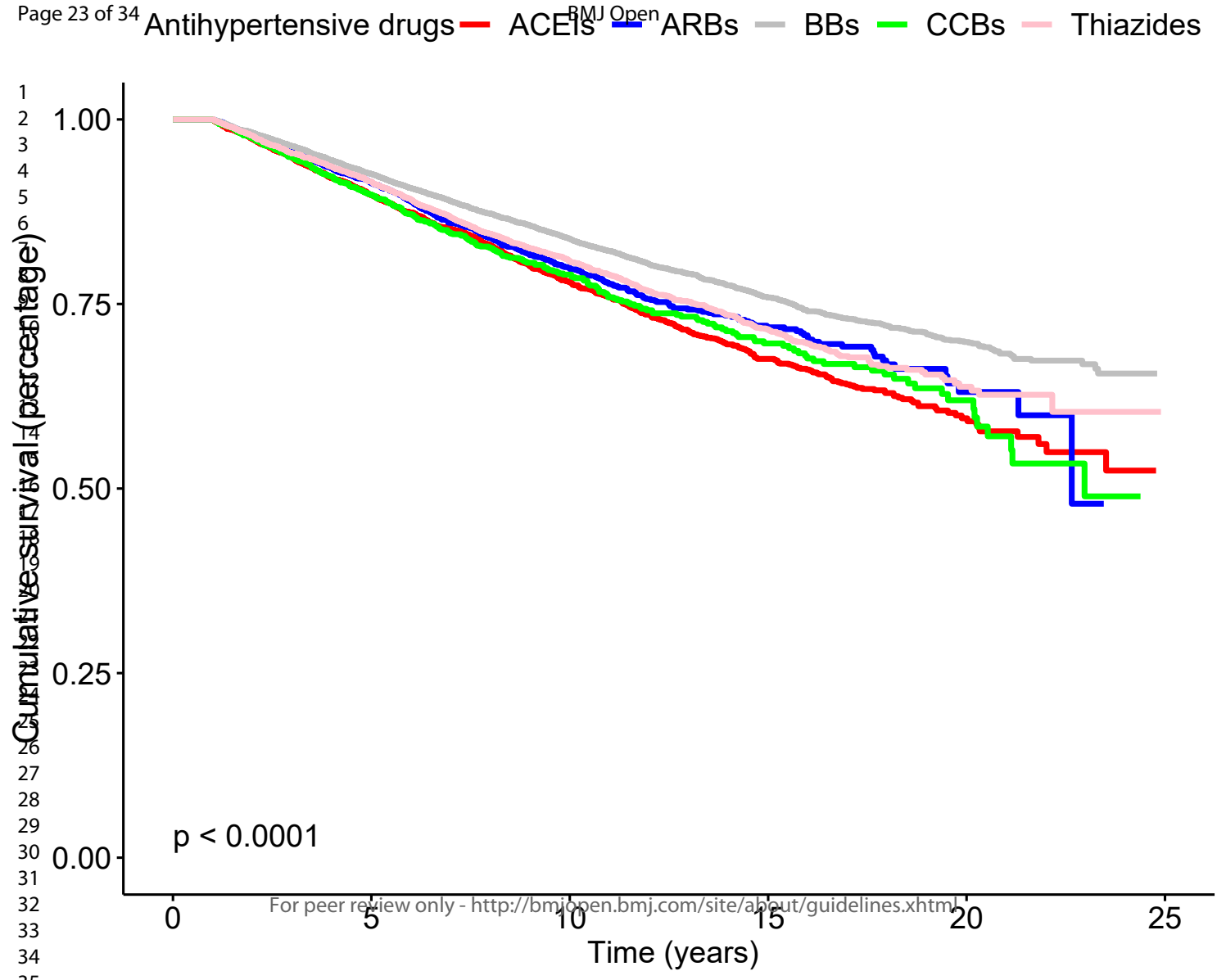
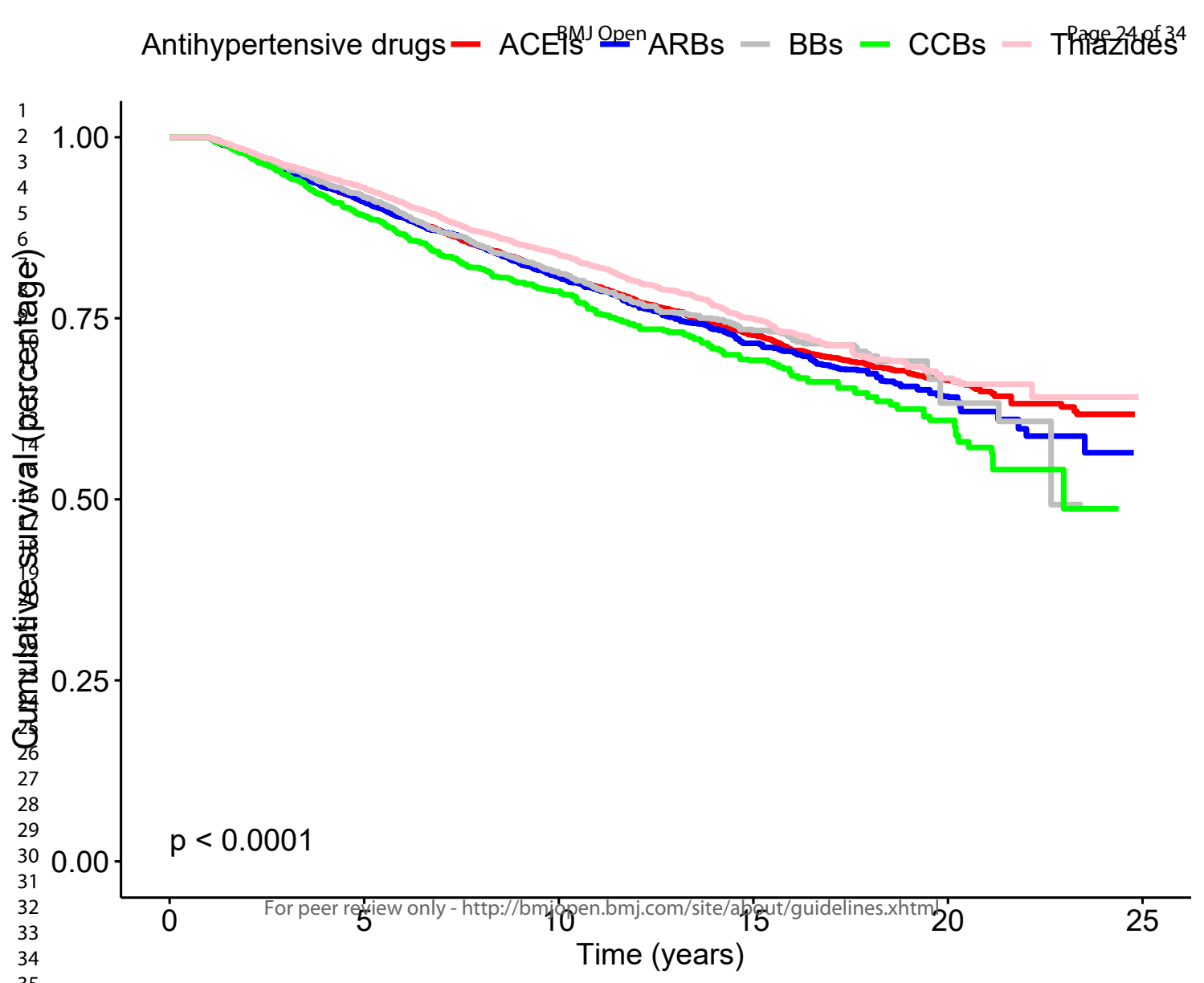
Figure legend

Figure 1 Survival curves for acute CDT in patients treated with 5 types of anti-hypertensive monotherapies in 25-year of time before and after IPW. (A) before IPW, (B) after IPW





Supplemental table S1. List of abbreviations

Full name	Abbreviation
Anatomical therapeutical chemical code	ATC code
Angiotensin converting enzyme inhibitors	ACEIs
Angiotensin II receptor blockers	ARBs
Beta-blockers	BBs
Calcium channel blockers	CCBs
Cardiovascular	CV
Cardiac drug therapy	CDT
Cardiovascular diseases	CVDs
Chronic obstructive pulmonary disease	COPD
Confidence interval	CI
Disease-modifying antirheumatic drug	DMARD
European Society of Cardiology	ESC
Hazard ratio	HR
Inverse probability weighting	IPW
Number needed to treat	NNT
Over-the-counter	OTC
Rheumatoid arthritis	RA
Standard deviations	sd
World Health Organization	WHO

Supplemental table S2. ATC codes used in our study

All mentioned diseases and medications	ATC code
Anti-hypertensive drug monotherapies	
ACEIs	C09A
ARBs	C09C
BBs	C07A
CCBs	C08C, C08D, C08E
Thiazides	C03AA
Anti-hyperlipidemic drug monotherapies	
HMG CoA reductase inhibitors	C10AA
Fibrates	C10AB
Bile acid sequestrants	C10AC
Nicotinic acid and derivatives	C10AD
Other lipid modifying agents	C10AX
Antihypertensive drug fixed-dose combinations	
Thiazides and potassium in combination	C03AB
Thiazides, combinations with psycholeptics and/or analgesics	C03AH
Thiazides, combinations with other drugs	C03AX
Calcium channel blockers and diuretics	C08G
Angiotensin converting enzyme inhibitors and combinations	C09B
Angiotensin II receptor blockers and combinations	C09D
Beta blocking agents and thiazides	C07B
Beta blocking agents and other diuretics	C07C
Beta blocking agents, thiazides and other diuretics	C07D
Beta blocking agents and vasodilators	C07E
Beta blocking agents, other combinations	C07F
Anti-hyperlipidemic drug fixed-dose combinations	
HMG CoA reductase inhibitors in combination with other lipid modifying agents	C10BA
HMG CoA reductase inhibitors, other combinations	C10BX
Secondary prevention	
Platelet aggregation inhibitor	B01AC
Vitamin K antagonist	B01AA
Organic nitrate	C01DA
Other vasodilators used in cardiac diseases	C01DX
Chronic, stable heart failure	
High-ceiling diuretics	C03C
Migraine	
Triptan	N02C
Adrenal disease	
Phentolamine	C04AB01
Tolazoline	C04AB02
Anticorticosteroids	H02CA

Mifeprostone	G03XB
Metyrapone	V04CD
Hyperparathyroidism	
Calcium, combinations with vitamin D and/or other drugs	A12AX
Vitamin D and analogues	A11CC
Thyroid problems	
Thyroid hormones	H03AA
Diabetes	
Blood glucose lowering drugs	A10
Rheumatoid arthritis	
Methotrexate	L04AX03
Sulfasalazine	A07EC01
Leflunomide	L04AA13
Etanercept	L04AB01
Infliximab	L04AB02
Adalimumab	L04AB04
Golimumab	L04AB06
Abatacept	L04AA24
Anakinra	L04AC03
Tocilizumab	L04AC07
Asthma / COPD	
Inhaled steroids	R03BA, R03AK, R03AL

Supplemental table S3. Incidence rate/1000 person-years of acute CDT for anti-hypertensive monotherapies within 5 years, 10 years, 15 years, 20 years and 25 years

Follow-up year	ACEIs	ARBs	BBs	CCBs	Thiazides
5-year					
Cumulative events	591	187	854	237	492
Person years	27435	10404	56076	11132	27815
Incidence rate	21.5	18.0	15.2	21.3	17.7
10-year					
Cumulative events	966	347	1540	352	903
Person years	39740	15801	88490	14955	42957
Incidence rate	24.3	22.0	17.4	23.5	21.0
15-year					
Cumulative events	1127	405	1904	397	1077
Person years	44820	18237	105445	16542	49325
Incidence rate	25.1	22.2	18.1	24.0	21.8
20-year					
Cumulative events	1175	423	2031	413	1122
Person years	46493	18924	111919	17154	50907
Incidence rate	25.3	22.4	18.1	24.1	22.0
25-year					
Cumulative events	1183	425	2051	420	1125
Person years	46675	18964	112734	17222	51022
Incidence rate	25.3	22.4	18.2	24.4	22.0

Supplemental table S4. Number needed to treat for thiazides monotherapy compared with BBs monotherapy to prevent acute CDT in all patients and subgroups.

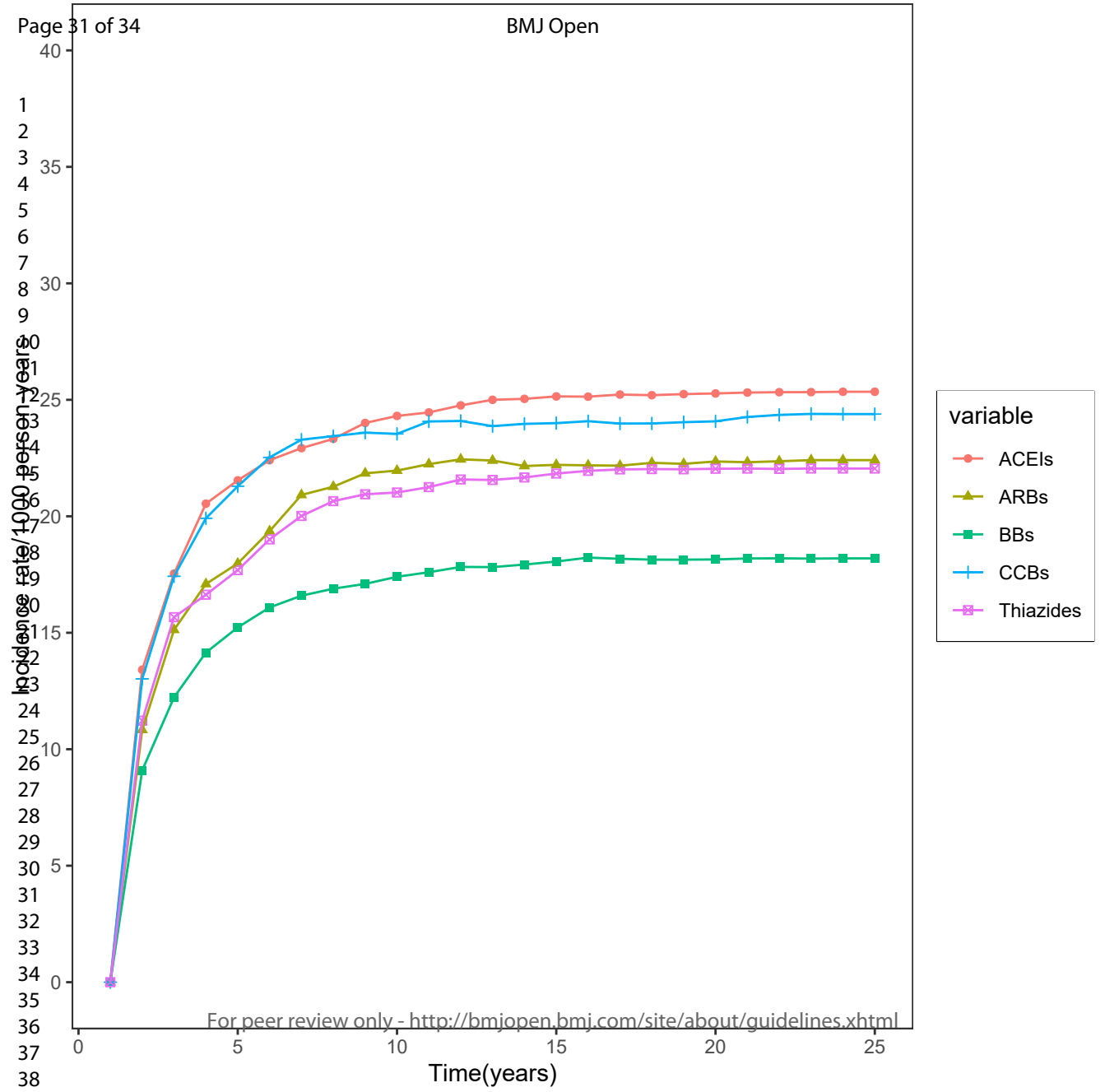
	NNT (95% CI)				
	5-year	**10-year**	**15-year**	**20-year**	**25-year**
All patients	102 (100 to 100)	49 (33 to 100)	35 (25 to 50)	29 (17 to 100)	27 (14 to Inf)
Gender					
Male	71 (50 to 100)	34 (25 to 100)	25 (14 to 50)	21 (11 to 100)	21 (11 to Inf)
Female	144 (100 to Inf)	68 (50 to 100)	47 (25 to 100)	38 (20 to Inf)	34 (-50 to 14)
Age(years)					
18-39	772 (-Inf to 100)	298 (-100 to 100)	168 (-100 to 50)	115 (-50 to 25)	100 (-20 to 14)
40-69	98 (100 to 100)	45 (33 to 100)	31 (20 to 50)	25 (17 to 50)	23 (-Inf to 11)
≥70	52 (33 to Inf)	27 (14 to Inf)	22 (-100 to 10)	21 (-25 to 7)	21 (-13 to 6)
Drugs for diabetes					
Yes	12 (9 to 20)	8 (6 to 13)	7 (5 to 11)	6 (4 to 10)	4 (-13 to 2)
No	136 (100 to Inf)	63 (50 to 100)	44 (25 to 100)	37 (20 to 100)	35 (-100 to 14)
Drugs for rheumatoid arthritis					
Yes	11 (7 to 33)	6 (3 to 17)	6 (3 to 17)	3 (-3 to 1)	3 (-3 to 1)
No	108 (100 to 100)	51 (33 to 100)	36 (25 to 100)	30 (20 to 100)	28 (-Inf to 14)
Drugs for asthma/COPD					
Yes	114 (-100 to 33)	60 (-50 to 20)	46 (-33 to 14)	38 (-17 to 9)	38 (-17 to 9)
No	102 (100 to 100)	48 (33 to 100)	34 (25 to 50)	28 (17 to 100)	26 (13 to Inf)
Calendar years					
1996-2000	140 (-100 to 50)	70 (-50 to 20)	53 (-33 to 17)	45 (-25 to 13)	43 (-25 to 11)
2000-2010	69 (50 to 100)	35 (25 to 50)	26 (20 to 50)	23 (14 to 50)	22 (14 to 50)
2010-2020	354 (-Inf to 100)	171 (-100 to 50)	149 (-50 to 33)	149 (-50 to 33)	149 (-50 to 33)

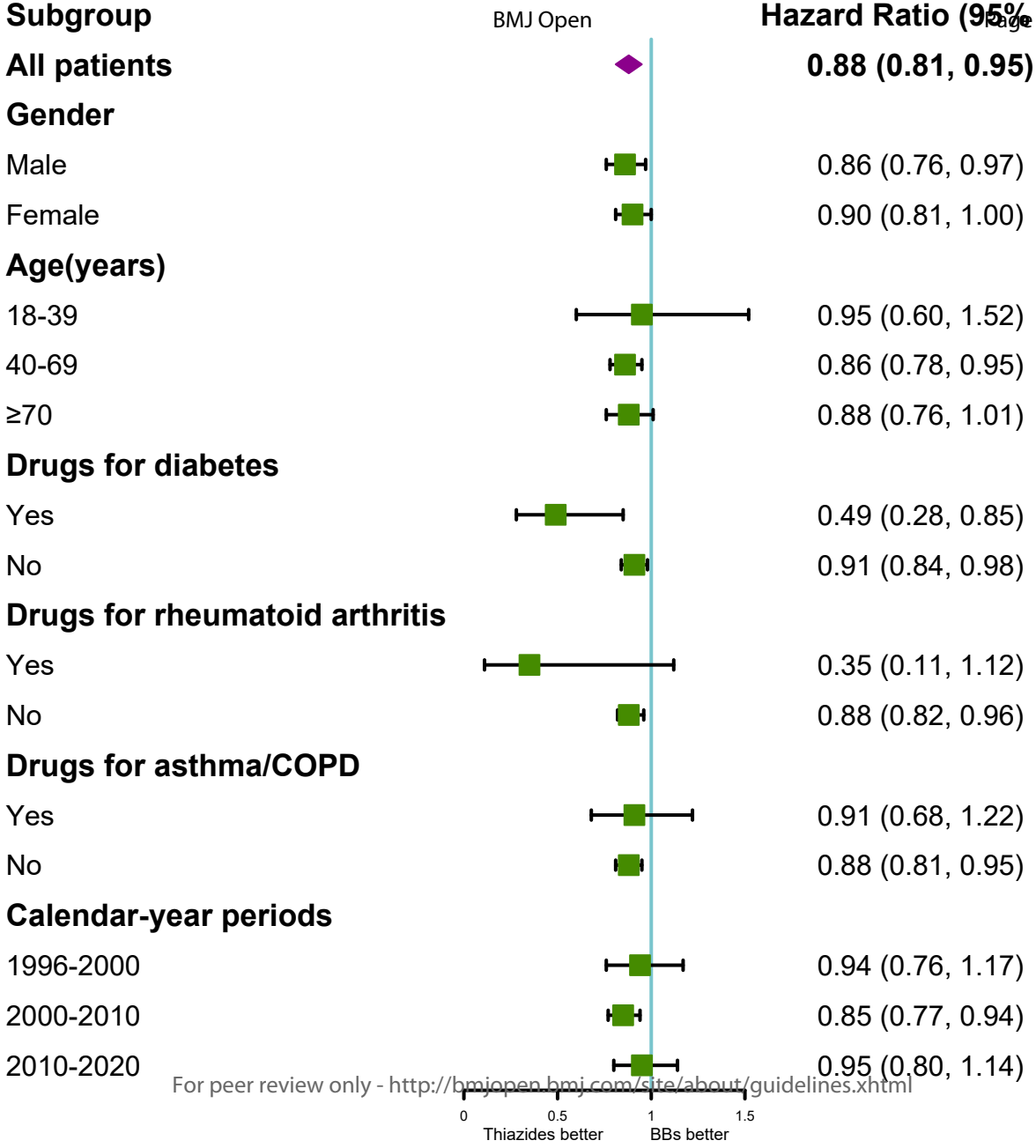
Supplemental figures legend

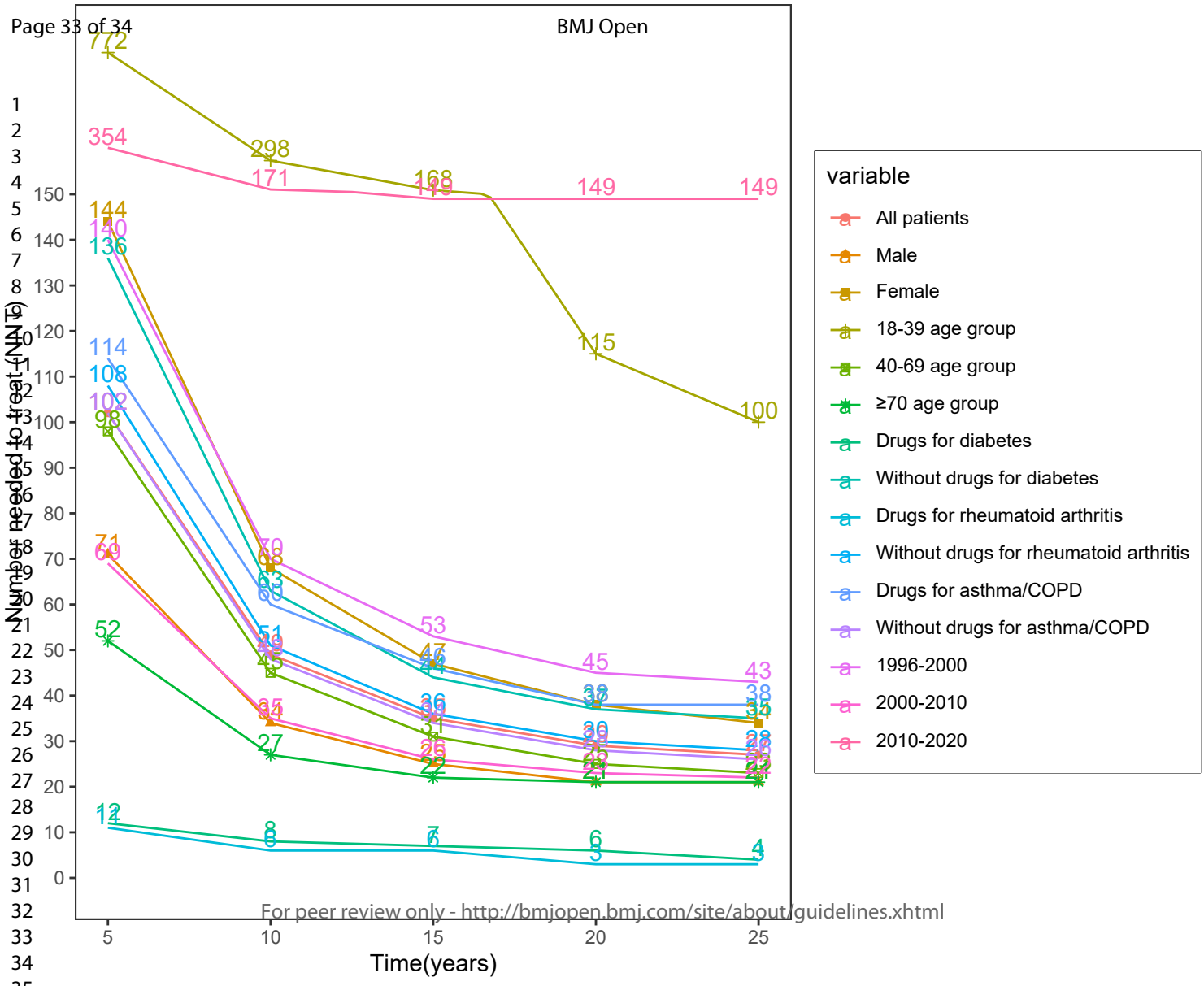
Supplemental figure 1. Incidence rate/1000 person-years of acute CDT for anti-hypertensive monotherapies of 25 years

Supplemental figure 2. Forest plot of subgroup hazard ratios between thiazides and BBs after IPW

Supplemental figure 3. NNT (number needed to treat) for thiazides compared with BBs during 25 years in subgroups







STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6,7 6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7,8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 - -
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 - 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	-
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Long-term Comparative Effectiveness of Anti-hypertensive Monotherapies in Primary Prevention of Cardiovascular Events: A Population-Based Retrospective Inception Cohort Study in the Netherlands

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Keywords:	Cardiac Epidemiology < CARDIOLOGY, PRIMARY CARE, Hypertension < CARDIOLOGY

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Long-term Comparative Effectiveness of Anti-hypertensive Monotherapies in Primary Prevention of Cardiovascular Events: A Population-Based Retrospective Inception Cohort Study in the Netherlands

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Abstract

Objective: To determine the long-term effectiveness of anti-hypertensive 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 anti-hypertensive monotherapy (Angiotensin-converting enzyme inhibitors [ACEIs], Angiotensin II receptor blockers [ARBs], Beta-blockers [BBs], Calcium Chanel Blockers [CCBs], 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 33427 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 (NNT) for thiazides compared with BBs to prevent one acute CDT in 25 years was 26, and 4 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 CDT compared to BBs.

Key words: monotherapy, primary prevention, acute cardiac drug therapy, cohort study, comparative effectiveness

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 CVD 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, 37000 deaths out of a total of 168678 deaths in the Netherlands, i.e. 22%, were due to cardiovascular disease.[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.

Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin II receptor blockers (ARBs), Beta-blockers (BBs), Calcium Chanel 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 World Health Organization (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 ischemic 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 BP 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 CV events, and none examined long-term “real-world” effectiveness.[8 ,13]

Data to support personalization of anti-hypertensive 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 diabetes patients 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 an 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 (OTC) medications and medications dispensed during hospitalization.[18]

Study population

All patients in the IADB.nl pharmacy prescription database aged 18 years or older at initiation of the anti-hypertensive monotherapy (index date) were eligible for inclusion in the analysis. The study period was from January 1, 1996 to December 31, 2020. Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin II receptor blockers (ARBs), Beta-blockers (BBs), Calcium Chanel Blockers (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 two years before the index date and were present in the database for at least one 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 anti-hypertensive monotherapy class in the year after the index date.

We excluded patients who used anti-hyperlipidemic 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 anti-hyperlipidemic drug fixed-dose combinations in the year after the index date. We further excluded patients who had any other acute cardiac drug therapy (CDT) in the two 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 two 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 anti-hypertensive 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 cardiac drug therapy (CDT). Acute CDT is a proxy for an incident major cardiovascular 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 cardiovascular disease in primary care. Importantly, specificity was very high (94%) which is important for causal research.

High-risk co-morbidities

Patients who had at least two prescriptions for blood glucose-lowering drugs (A10) in the two 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 anti-rheumatic drugs (DMARDs: L04, A07EC01) in the two years before the index date were defined as patients on rheumatoid arthritis drugs. Patients with at least two prescriptions for inhaled steroids (R03BA; R03AK; R03AL)[21] in the two years before the index date were defined as patients on asthma or COPD drugs.

Statistical analysis

The data were imported in R-studio for cleaning, handling, and analysis. The quantitative variables were expressed by the format of mean ± standard deviations (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 $\chi 2$ test, t-test and Welch's ANOVA test were used to analyze the relationship between the variables and

exposure as well as the variables and acute CDT. We calculated the incidence rate per 1000 person-years for each type of anti-hypertensive 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' R-package of inverse probability weighting (IPW) to balance the baseline confounding variables. Cox regression modeling was used to estimate the relative effectiveness of monotherapies by means of hazard ratio's (HR) and their corresponding 95% confidence intervals (CI). 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% confidence interval.[22]

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. 13712/33427 (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 starters, 14417/33427 were male (43.1%). 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 was 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, 16891 (50.5%), received their first prescription and the distribution of monotherapies was more or less the same across decades.

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

Demographics	**Total N=33427**	**ACEIs N=7189 (21.5) ***	**ARBs N=2591 (7.8) ***	**BBs N=13712 (41.0) ***	**CCBs N=3167 (9.5) ***	**Thiazides N=6768 (20.2) ***	***P*§**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
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	14417 (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	22158 (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	14070 (42.1)	2470 (34.4)	1081 (41.7)	6561 (47.8)	748 (23.6)	3210 (47.4)	
2010-2020	16891 (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 Chi-squared test or anova test, which showed the difference of distribution of patients who used five anti-hypertensive monotherapies at baseline in different subgroups of covariates

† Use mean ± standard deviations to describe average follow up years

†† Use mean ± standard deviations to describe continuous age

‡ Welch's anova test to describe whether patients of different classes of anti-hypertensive monotherapy were different in age (Heterogeneity of variance)

Acute cardiac drug therapy

In all, 5205/33427 (15.6%) patients were dispensed acute CDT (see table 2). 2052/5205 (39.4%) BB starters 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).

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

Demographics	**Acute CDT N=5205 (15.6) ***	**No acute CDT N=28222 (84.4) ***	***P*§**
	n (%)	**n (%)**	
Anti-hypertensive monotherapies			
ACEIs	1183 (22.7)	6006 (21.3)	<0.001
ARBs	425 (8.2)	2166 (7.7)	
BBs	2052 (39.4)	11660 (41.3)	
CCBs	420 (8.1)	2747 (9.7)	
Thiazides	1125 (21.6)	5643 (20.0)	
Gender: male	2552 (49.0)	11865 (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)	18739 (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)	10877 (38.5)	
2010-2020	1166 (22.4)	15725 (55.7)	

* Row percentage, others are all column percentage

§ P value: significance value of the Chi-squared 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 ± standard deviations to describe continuous age

‡ Use t test to describe whether patients who had acute CDT or not were different in age

Incidence rate

Acute CDT incidence rate per 1000 person-years 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, thiazide starters, respectively (see online supplemental figure 1 and supplemental table S3).

Survival analysis

The Kaplan-Meier curves showed that the cumulative survival of five classes of anti-hypertensive drug monotherapies decreased with increasing follow-up time in 25 years before and after inverse probability weighting (IPW) (see figure 1). Before IPW, BB starters had highest cumulative survival rate compared with other drugs. After IPW adjusted between anti-hypertensive 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).

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

	Acute CDT			
Anti-hypertensive monotherapies	**Crude HR (95%CI)**	***P***	**IPW adjusted* HR (95%CI)**	***P***
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 anti-hypertensive monotherapies and gender, age, drugs for diabetes, drugs for RA, drugs for asthma/COPD, calendar-year periods

Subgroup analysis

After IPW adjusted analysis, in males, thiazide starters had lower hazards of acute CDT than reference BB starters (HR: 0.86, 95% CI: 0.76 to 0.97), but the point estimate was similar to overall group. In females, 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).

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

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
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)
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 anti-hypertensive monotherapies and gender, age, drug for diabetes, drug for RA, drug for asthma/COPD, calendar-year periods

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, 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, online supplemental 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 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 anti-hypertensive 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 ,23] Likely, this is because BBs are nevertheless considered an effective treatment for hypertension and CVD reduction in the Netherlands.[24]

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,[25] 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 cardiovascular disease 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 cardiovascular heart disease. A study by Björn et al [26] 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 to 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 inverse probability of treatment weighting (IPW). After IPW adjustment our analysis showed that thiazide users had a lower incidence of CDT compared to BBs. Our results provide further evidence in support of the ESC/ESH[7] guideline for hypertension diagnosis and treatment, which

recommends thiazides as the initial treatment. Furthermore, our results were in accordance with other studies. A network meta-analysis of 42 trials by Bruce et.al[10] showed that low-dose diuretic therapy performed better than any classes of antihypertensive drugs. For example, low-dose diuretic therapy had lower estimate compared to BBs therapy in developing a CVD event (RR: 0.89, 95%CI: 0.80 to 0.98), using CV disease events as the outcome. The Atle et.al[9] study included 25 trials, the results of the meta-analysis showed that diuretics had a lower risk of myocardial infarction compared to 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 to BBs, which is different from findings by Zhu et.al.[11] The investigators showed that CCBs reduced the risk of major CV events compared to BBs (RR: 0.84, 95% CI: 0.77 to 0.92). Their study included three randomized 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[27]. 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, Björn et.al [26] 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 disease, and that BBs[9 ,12] were the least effective compared to 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 were mostly uninformative.

Subgroup

Diabetes is a risk factor for cardiovascular disease and thiazide monotherapy had an even lower incidence of CDT compared with BBs in patients on diabetes drugs and number needed

to treat were lower as well. Patients use anti-diabetic 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 effective than CCBs and BBs in diabetes patients. Jan[28] 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 ITT 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 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 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 behavioral risk factors of CVD which could not be measured in this database. However, in the Netherlands, the indication did not strongly favor any of the monotherapies, hence it is unlikely that distribution of these risk factors was very different between monotherapy groups. However, some anti-hypertensive 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 for 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 programs, 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 to BBs.

a. Contributorship statement XCL conceived and EH, MJB, CCMSV and JHJ designed the study. JHJ constructed data. XCL, MJB and EH wrote the first draft. All the authors reviewed and approved the final article.

b. Competing interests The authors declare no other competing interests.

c. Funding Xuechun Li is funded by the China Scholarship Council (file no: 202106070028).

d. Data sharing statement The study remains in progress and the data are not currently available for sharing.

e. Ethics approval statement 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.

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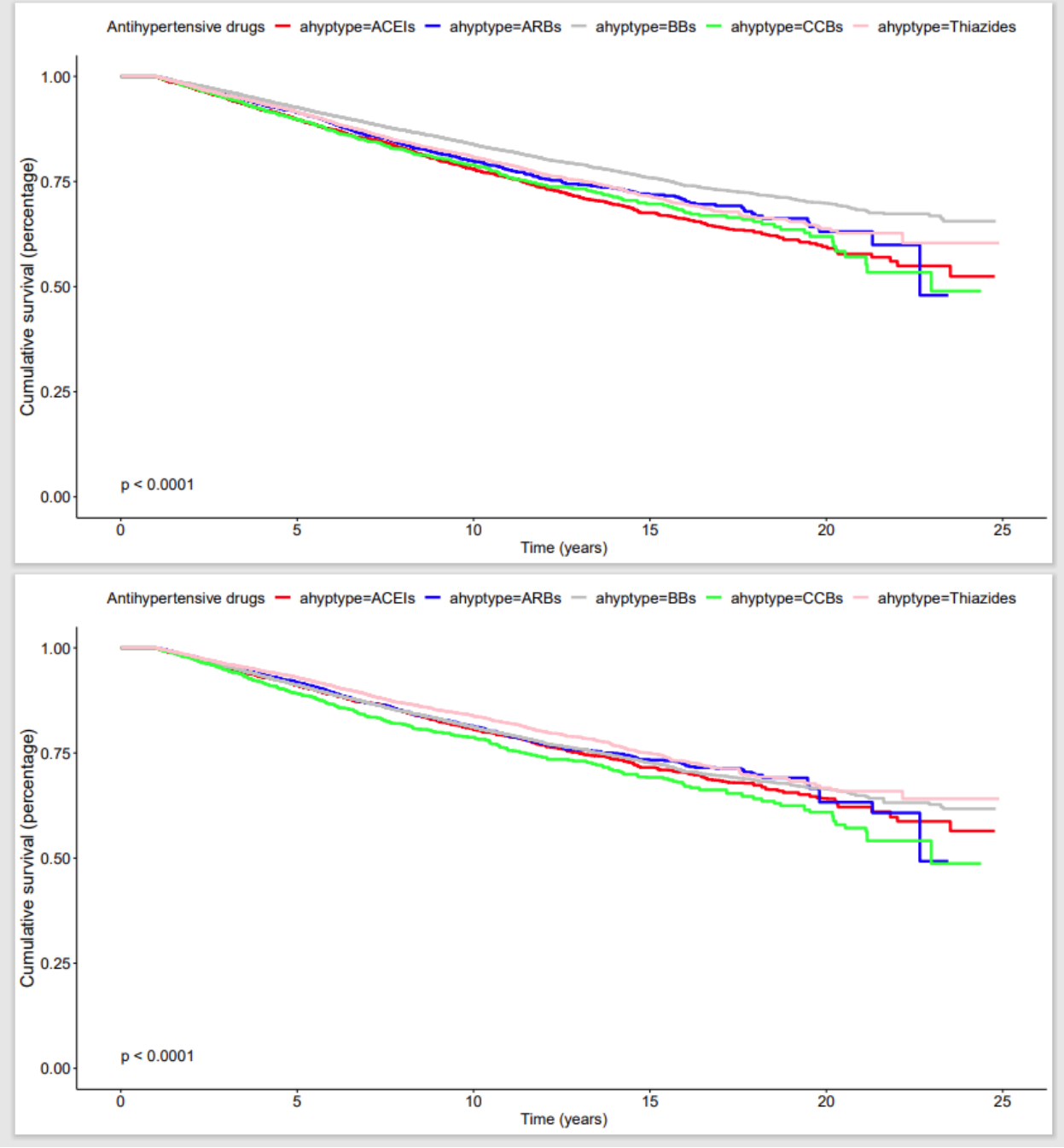
Figure legend

Figure 1 Survival curves for acute CDT in patients treated with 5 types of anti-hypertensive monotherapies in 25-year of time before and after IPW. (A) before IPW, (B) after IPW



Supplemental table S1. List of abbreviations

Full name	Abbreviation
Anatomical therapeutical chemical code	ATC code
Angiotensin converting enzyme inhibitors	ACEIs
Angiotensin II receptor blockers	ARBs
Beta-blockers	BBs
Calcium channel blockers	CCBs
Cardiovascular	CV
Cardiac drug therapy	CDT
Cardiovascular diseases	CVDs
Chronic obstructive pulmonary disease	COPD
Confidence interval	CI
Disease-modifying antirheumatic drug	DMARD
European Society of Cardiology	ESC
Hazard ratio	HR
Inverse probability weighting	IPW
Number needed to treat	NNT
Over-the-counter	OTC
Person-years	py
Rheumatoid arthritis	RA
Standard deviations	sd
World Health Organization	WHO

Supplemental table S2. ATC codes used in our study

All mentioned diseases and medications	ATC code
Anti-hypertensive drug monotherapies	
ACEIs	C09A
ARBs	C09C
BBs	C07A
CCBs	C08C, C08D, C08E
Thiazides	C03AA
Anti-hyperlipidemic drug monotherapies	
HMG CoA reductase inhibitors	C10AA
Fibrates	C10AB
Bile acid sequestrants	C10AC
Nicotinic acid and derivatives	C10AD
Other lipid modifying agents	C10AX
Antihypertensive drug fixed-dose combinations	
Thiazides and potassium in combination	C03AB
Thiazides, combinations with psycholeptics and/or analgesics	C03AH
Thiazides, combinations with other drugs	C03AX
Calcium channel blockers and diuretics	C08G
Angiotensin converting enzyme inhibitors and combinations	C09B
Angiotensin II receptor blockers and combinations	C09D
Beta blocking agents and thiazides	C07B
Beta blocking agents and other diuretics	C07C
Beta blocking agents, thiazides and other diuretics	C07D
Beta blocking agents and vasodilators	C07E
Beta blocking agents, other combinations	C07F
Anti-hyperlipidemic drug fixed-dose combinations	
HMG CoA reductase inhibitors in combination with other lipid modifying agents	C10BA
HMG CoA reductase inhibitors, other combinations	C10BX
Secondary prevention	
Platelet aggregation inhibitor	B01AC
Vitamin K antagonist	B01AA
Organic nitrate	C01DA
Other vasodilators used in cardiac diseases	C01DX
Chronic, stable heart failure	
High-ceiling diuretics	C03C
Migraine	
Triptan	N02C
Adrenal disease	
Phentolamine	C04AB01
Tolazoline	C04AB02
Anticorticosteroids	H02CA

Mifeprostone	G03XB
Metyrapone	V04CD
Hyperparathyroidism	
Calcium, combinations with vitamin D and/or other drugs	A12AX
Vitamin D and analogues	A11CC
Thyroid problems	
Thyroid hormones	H03AA
Diabetes	
Blood glucose lowering drugs	A10
Rheumatoid arthritis	
Methotrexate	L04AX03
Sulfasalazine	A07EC01
Leflunomide	L04AA13
Etanercept	L04AB01
Infliximab	L04AB02
Adalimumab	L04AB04
Golimumab	L04AB06
Abatacept	L04AA24
Anakinra	L04AC03
Tocilizumab	L04AC07
Asthma / COPD	
Inhaled steroids	R03BA, R03AK, R03AL

Supplemental table S3. Incidence rate/1000 person-years of acute CDT for anti-hypertensive monotherapies within 5 years, 10 years, 15 years, 20 years and 25 years

Follow-up year	ACEIs	ARBs	BBs	CCBs	Thiazides
5-year					
Cumulative events	591	187	854	237	492
Person years	27435	10404	56076	11132	27815
Incidence rate	21.5	18.0	15.2	21.3	17.7
10-year					
Cumulative events	966	347	1540	352	903
Person years	39740	15801	88490	14955	42957
Incidence rate	24.3	22.0	17.4	23.5	21.0
15-year					
Cumulative events	1127	405	1905	397	1077
Person years	44820	18237	105441	16542	49325
Incidence rate	25.1	22.2	18.1	24.0	21.8
20-year					
Cumulative events	1175	423	2032	413	1122
Person years	46493	18924	111911	17154	50907
Incidence rate	25.3	22.4	18.2	24.1	22.0
25-year					
Cumulative events	1183	425	2052	420	1125
Person years	46675	18964	112726	17222	51022
Incidence rate	25.3	22.4	18.2	24.4	22.0

Supplemental table S4. Number needed to treat for thiazides monotherapy compared with BBs monotherapy to prevent acute CDT in all patients and subgroups.

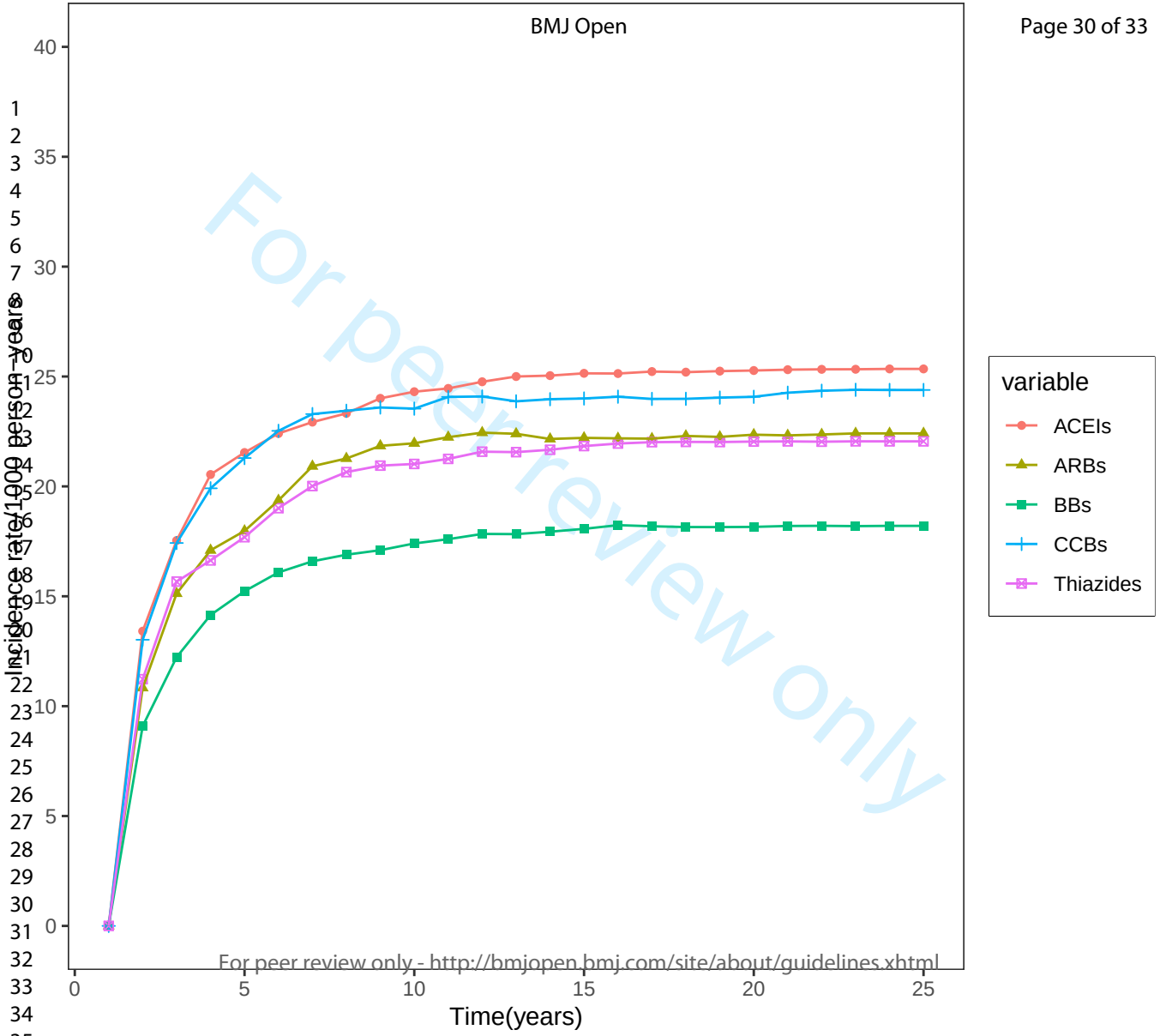
	NNT (95% CI)				
	5-year	**10-year**	**15-year**	**20-year**	**25-year**
All patients	102 (100 to 100)	49 (33 to 100)	34 (25 to 50)	29 (17 to 100)	26 (14 to Inf)
Gender					
Male	71 (50 to 100)	34 (25 to 100)	25 (14 to 50)	21 (11 to 100)	21 (11 to Inf)
Female	143 (100 to Inf)	67 (50 to 100)	47 (25 to 100)	38 (20 to Inf)	34 (-50 to 14)
Age(years)					
18-39	720 (-Inf to 100)	278 (-100 to 100)	156 (-100 to 33)	107 (-50 to 25)	93 (-25 to 14)
40-69	98 (100 to 100)	45 (33 to 100)	31 (20 to 50)	25 (17 to 50)	23 (-Inf to 11)
≥70	52 (33 to Inf)	27 (14 to Inf)	22 (-100 to 10)	21 (-25 to 7)	21 (-13 to 6)
Drugs for diabetes					
Yes	12 (9 to 20)	8 (6 to 13)	7 (5 to 11)	6 (4 to 10)	4 (-13 to 2)
No	135 (100 to Inf)	63 (50 to 100)	44 (25 to 100)	37 (20 to 100)	34 (-100 to 14)
Drugs for rheumatoid arthritis					
Yes	11 (7 to 33)	6 (3 to 17)	6 (3 to 17)	3 (-3 to 1)	3 (-3 to 1)
No	107 (100 to 100)	51 (33 to 100)	36 (25 to 100)	30 (20 to 100)	28 (-Inf to 14)
Drugs for asthma/COPD					
Yes	114 (-100 to 33)	60 (-50 to 20)	46 (-33 to 14)	38 (-17 to 9)	38 (-17 to 9)
No	101 (100 to 100)	48 (33 to 100)	34 (25 to 50)	28 (17 to 100)	26 (13 to Inf)
Calendar years					
1996-2000	140 (-100 to 50)	70 (-50 to 20)	53 (-33 to 17)	45 (-25 to 13)	43 (-25 to 11)
2000-2010	69 (50 to 100)	35 (25 to 50)	26 (20 to 50)	23 (14 to 50)	22 (14 to 50)
2010-2020	354 (-Inf to 100)	171 (-100 to 50)	149 (-50 to 33)	149 (-50 to 33)	149 (-50 to 33)

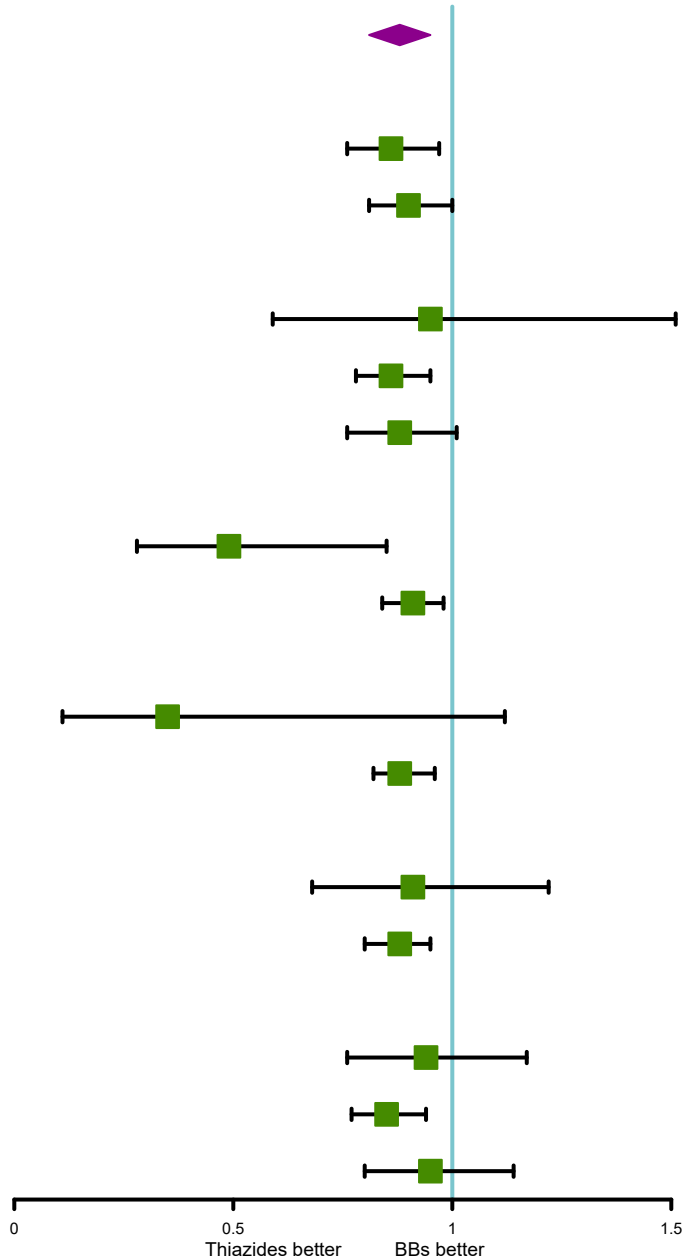
Supplemental figures legend

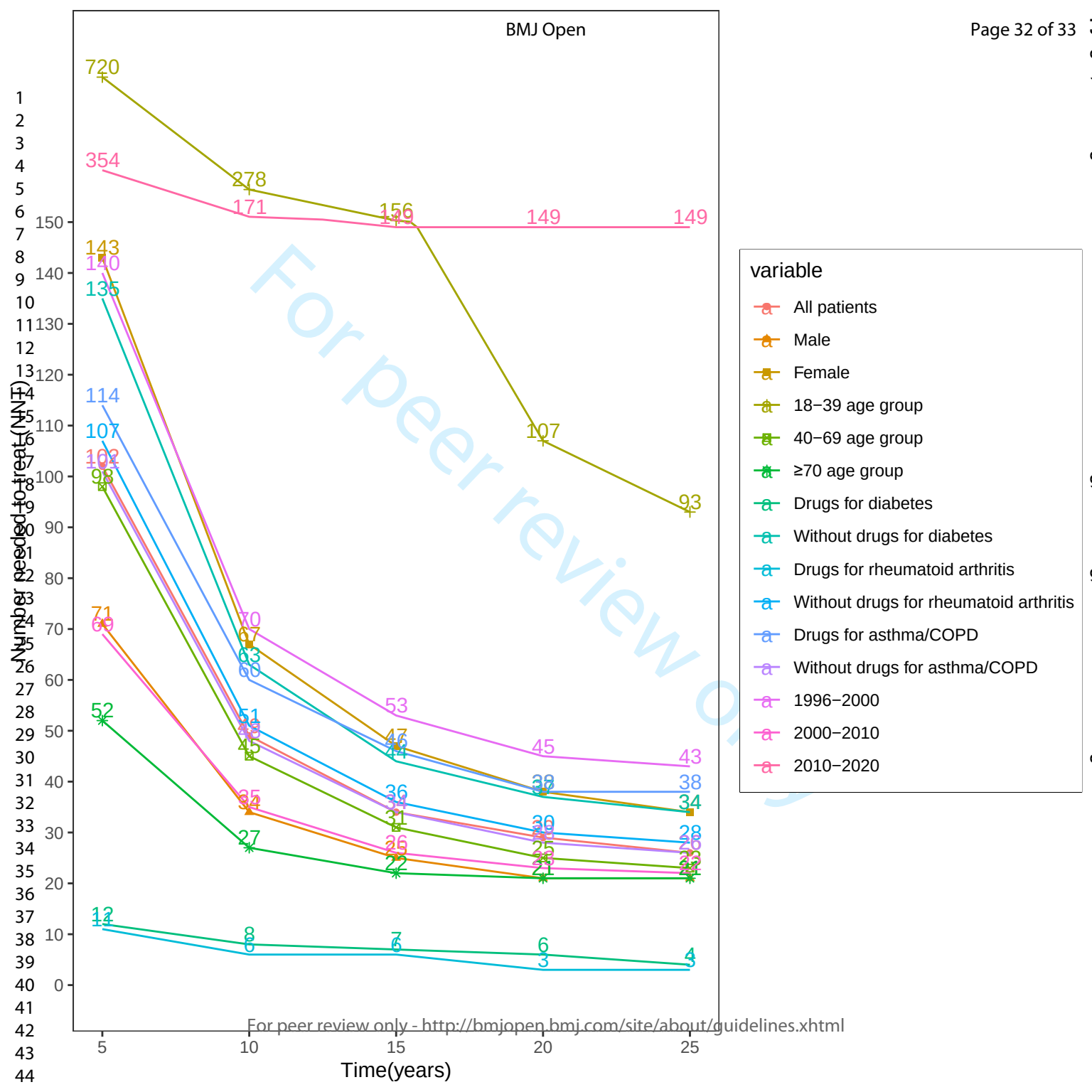
Supplemental figure 1. Incidence rate/1000 person-years of acute CDT for anti-hypertensive monotherapies of 25 years

Supplemental figure 2. Forest plot of subgroup hazard ratios between thiazides and BBs after IPW

Supplemental figure 3. NNT (number needed to treat) for thiazides compared with BBs during 25 years in subgroups







STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6,7 6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7,8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 - -
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 - 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	-
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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

Li X, Bijlsma M, Bos J, *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;0:e068721. doi:10.1136/bmjopen-2022-068721

This article has been corrected since it was published online. We identified a small error in the syntax defining the outcome in our study. The outcome definition is defined as '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.' In the current published version, we observed 5205 patients who had an outcome. However, due to an overseen error in the SQL syntax used to define an outcome, we set the end date of the first prescription of any of these four classes of proxy prescription, even if the second prescription was not within 180 days after this first date. We further treated these patients as without an outcome. However, after this prescription, a new episode could have occurred that fulfilled this definition and could have led to observing an outcome as defined. After correcting the syntax, it appeared that 5770 instead of 5205 patients had an outcome both in the abstract and results.

We subsequently reanalyzed the data using the updated syntax and it appeared that the outcome associations barely changed which means that our main conclusions remain the same. However, the updated numbers and percentages have changed for abstract, table1-4, figure1, Supplementary table S3/S4, supplementary figure 1-3, including also the text, see in the changed track changes text:

1. The results part in the abstract has been updated to

'**Results:** Among 33 427 initiators, 5770 (17.3%) patients experienced an acute CDT. The average follow-up time was 7.8±5.4 years. The 25 year incidence rate per 1000 person-years were 28.4, 25.2, 20.1, 28.4 and 25.2 for ACEI, ARB, BB, CCB, and thiazide starters, respectively. Inverse probability weighted Cox regression showed that thiazide starters had lower hazards than the reference BB starters (HR: 0.88, 95%confidence interval: 0.82 to 0.96). Among patients on diabetes drugs, risks were lower (HR: 0.58, 95%confidence interval: 0.34 to 0.96). CCB starters had higher hazards than reference BB (HR: 1.26, 95% CI: 1.13 to 1.41). The overall estimated number needed to treat for thiazides compared with BBs to prevent one acute CDT in 25 years was 26, and five among patients on diabetes drugs.'

2. 'Results' has been updated to the following content, including tables 1–4.

RESULTS

Baseline characteristics

In all, the average follow-up time was 7.8±5.4 years. Among a total of 33 427 patients, 13712 (41.0%) patients used BBs at baseline after the longest mean follow-up time of 8.6±5.8 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, 14417 (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),

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

Demographics	Total n=33 427	ACEIs n=7189 (21.5) *	ARBs n=2591 (7.8) *	BBs n=13712 (41.0) *	CCBs n=3167 (9.5) *	Thiazides n=6768 (20.2) *	P value†
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Average follow-up years‡	7.8±5.4	6.9±5.0	7.7±5.2	8.6±5.8	5.8±4.6	7.9±5.0	/
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 $\chi 2$ 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.

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, 5770/33427 (17.3%) patients were dispensed acute CDT (see table 2). Among 5770 starters, 2245 BB starters (38.9%) received a first acute CDT. Patients with acute CDT outcome were on average 8 years older than those without outcome. During the second decade (2000–2010), slightly more than half of the total observed acute CDT occurred, 3549/5770 (61.5%). Except for the drugs for comorbidities RA, there were statistically significant differences in the distribution across acute CDT outcome between patients with different monotherapy types, gender, age, drugs for diabetes, drugs for asthma/COPD and calendar-year periods ($p<0.05$).

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 CCBs had the highest 5 year incidence rate of 24.0/1000 py among all types of drug starters. On the contrary,

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

Demographics	Acute CDT n=5770 (17.3) *	No acute CDT n=27657 (82.7) *	P value†
	n (%)	n (%)	
Anti-hypertensive monotherapies			
ACEIs	1307 (22.7)	5882 (21.3)	<0.001
ARBs	473 (8.2)	2118 (7.7)	
BBs	2245 (38.9)	11 467 (41.5)	
CCBs	480 (8.3)	2687 (9.7)	
Thiazides	1265 (21.9)	5503 (19.9)	
Gender: male	2778 (48.1)	11 639 (42.1)	<0.001
Age(years) ‡	61.5±13.3	53.5±15.2	<0.001§
18–39	312 (5.4)	4909 (17.7)	<0.001
40–69	3709 (64.3)	18 449 (66.7)	
≥70	1749 (30.3)	4299 (15.5)	
Drugs for diabetes:Yes	408 (7.1)	1063 (3.8)	<0.001
Drugs for rheumatoid arthritis:Yes	54 (0.9)	221 (0.8)	0.334
Drugs for asthma/COPD:Yes	491 (8.5)	2076 (7.5)	0.010
Calendar-year periods			
1996–2000	940 (16.3)	1526 (5.5)	<0.001
2000–2010	3549 (61.5)	10 521 (38.0)	
2010–2020	1281 (22.2)	15 610 (56.4)	

*Row percentage, others are all column percentage.
†P value: significance value of the χ2test 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, chronicobstructive pulmonary disease.

BB starters had the lowest 5 year incidence rate of 16.7/1000 py. The same trend can be seen for 10 year, 15 year, 20 year and 25 year periods. The 25 year incidence rate were 28.4/1000 py, 25.2/1000 py, 20.1/1000 py, 28.4/1000 py and 25.2/1000 py for ACEI,

Table 3 Cox regression analysis of acute cardiac drug therapy (CDT) (n=5770)

	Acute CDT			
Antihypertensive monotherapies	Crude HR (95%confidence interval)	P value	IPW adjusted* HR (95%confidence interval)	P value
Reference:BBs				
Exposure				
ACEIs	1.44 (1.35 to 1.55)	<0.001	1.06 (0.98 to 1.14)	0.158
ARBs	1.27 (1.15 to 1.40)	<0.001	0.99 (0.89 to 1.11)	0.920
CCBs	1.48 (1.34 to 1.63)	<0.001	1.26 (1.13 to 1.41)	< 0.001
Thiazides	1.26 (1.18 to 1.35)	<0.001	0.88 (0.82 to 0.96)	0.002

*IPW adjusted between anti-hypertensive 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, chronicobstructive pulmonary disease; IPW, inverse probability weighting; RA, rheumatoid arthritis.

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

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
Gender								
Male	1.24 (1.13 to 1.36)	1.07 (0.93 to 1.23)	1.28 (1.11 to 1.48)	1.14 (1.03 to 1.27)	1.03 (0.93 to 1.14)	0.91 (0.78 to 1.05)	1.11 (0.95 to 1.31)	0.86 (0.76 to 0.97)
Female	1.48 (1.33 to 1.64)	1.36 (1.18 to 1.57)	1.60 (1.39 to 1.83)	1.36 (1.25 to 1.49)	1.08 (0.96 to 1.22)	1.07 (0.92 to 1.24)	1.40 (1.20 to 1.62)	0.91 (0.82 to 1.00)
Age(years)								
18–39	1.79 (1.34 to 2.39)	0.96 (0.52 to 1.76)	1.52 (1.03 to 2.25)	1.07 (0.70 to 1.64)	1.36 (0.92 to 2.02)	1.06 (0.57 to 2.00)	1.55 (1.03 to 2.34)	0.89 (0.56 to 1.42)
40–69	1.21 (1.11 to 1.32)	1.07 (0.95 to 1.21)	1.28 (1.13 to 1.46)	0.95 (0.87 to 1.04)	1.04 (0.94 to 1.14)	0.96 (0.84 to 1.09)	1.29 (1.12 to 1.48)	0.87 (0.79 to 0.96)
≥70	1.09 (0.96 to 1.25)	0.98 (0.82 to 1.18)	1.20 (1.00 to 1.42)	0.91 (0.80 to 1.03)	1.04 (0.90 to 1.20)	0.98 (0.81 to 1.19)	1.18 (0.98 to 1.43)	0.88 (0.77 to 1.00)
Drugs for diabetes								
Yes	1.28 (0.91 to 1.79)	1.10 (0.71 to 1.69)	1.28 (0.70 to 2.37)	0.68 (0.42 to 1.11)	1.12 (0.78 to 1.60)	0.97 (0.62 to 1.51)	0.91 (0.42 to 1.94)	0.58 (0.34 to 0.96)
No	1.34 (1.25 to 1.45)	1.24 (1.12 to 1.37)	1.48 (1.34 to 1.63)	1.27 (1.19 to 1.37)	1.05 (0.97 to 1.14)	0.99 (0.89 to 1.11)	1.29 (1.15 to 1.44)	0.90 (0.84 to 0.98)
Drugs for rheumatoid arthritis								
Yes	0.84 (0.42 to 1.66)	0.51 (0.17 to 1.51)	0.87 (0.41 to 1.83)	0.35 (0.13 to 0.95)	0.76 (0.37 to 1.58)	0.38 (0.13 to 1.15)	1.65 (0.78 to 3.48)	0.42 (0.15 to 1.16)
No	1.45 (1.35 to 1.55)	1.27 (1.15 to 1.41)	1.48 (1.34 to 1.64)	1.27 (1.18 to 1.36)	1.06 (0.98 to 1.15)	1.00 (0.90 to 1.11)	1.26 (1.13 to 1.41)	0.89 (0.82 to 0.96)
Drugs for asthma/COPD								
Yes	1.72 (1.34 to 2.21)	1.70 (1.23 to 2.35)	1.69 (1.22 to 2.34)	1.38 (1.07 to 1.77)	1.13 (0.86 to 1.49)	1.30 (0.92 to 1.83)	1.38 (0.97 to 1.95)	0.90 (0.68 to 1.18)
No	1.41 (1.32 to 1.52)	1.22 (1.10 to 1.36)	1.45 (1.31 to 1.61)	1.24 (1.16 to 1.34)	1.05 (0.97 to 1.14)	0.97 (0.87 to 1.08)	1.25 (1.11 to 1.41)	0.88 (0.81 to 0.96)
Calendar-year periods								
1996–2000	1.75 (1.48 to 2.06)	1.39 (1.03 to 1.88)	1.61 (1.28 to 2.03)	1.39 (1.16 to 1.67)	1.10 (0.90 to 1.35)	0.99 (0.72 to 1.36)	1.21 (0.95 to 1.55)	0.95 (0.77 to 1.17)
2000–2010	1.52 (1.39 to 1.65)	1.23 (1.09 to 1.40)	1.70 (1.48 to 1.95)	1.26 (1.15 to 1.37)	1.02 (0.92 to 1.13)	0.92 (0.80 to 1.05)	1.30 (1.12 to 1.51)	0.86 (0.78 to 0.95)
2010–2020	1.38 (1.19 to 1.60)	1.54 (1.26 to 1.87)	1.40 (1.16 to 1.68)	1.34 (1.15 to 1.57)	1.11 (0.95 to 1.30)	1.24 (1.01 to 1.52)	1.12 (0.92 to 1.36)	0.93 (0.79 to 1.10)

*IPW adjusted between anti-hypertensive 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, chronicobstructive pulmonary disease; IPW, inverse probability weighting; RA, rheumatoid arthritis.

ARB, BB, CCB, thiazide starters, respectively (see online supplemental figure 1 and supplemental 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 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: 1.26, 95% CI: 1.13 to 1.41, p<0.001), while patients who used thiazides had lower hazards compared with BB starters (HR: 0.88, 95% CI: 0.82 to 0.96, p=0.002).

Subgroup analysis

After IPW adjusted analysis, in men, thiazide starters had lower hazards of acute CDT than reference BB starters (HR: 0.86, 95% CI: 0.76 to 0.97), but the point estimate was similar to overall group. In women, CCB starters had higher hazards than BB (HR: 1.40, 95% CI: 1.20 to 1.62) 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: 0.58, 95% CI: 0.34 to 0.96 and HR: 0.90, 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 98, 47, 33, 28 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 13, 7, 5, 4 and 4 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 14, 9, 7, 7 and 5 over 5, 10, 15, 20 and 25 study years, respectively (details see online supplemental figure 3 and online supplemental table S4).

3. In 'Discussion' part, the third paragraph.

'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' has been updated to 'The 5 year acute CDT incidence rate for CCB starters was the highest and for BB starters the lowest. These findings are little difference compared with the ALLHAT study.'

4. The Figure 1 and Supplementary table S3/S4, Supplementary figure 1-3 has been updated.

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