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RESEARCH PAPER

Antihypertensive drug classes and risk of incident dementia: a multinational population-based cohort study

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Abstract

Background: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers (ARBs) are first-line antihypertensive drugs for many patients, and influencing angiotensin systems may play a role in dementia risk. This study aimed to investigate whether exposure to different antihypertensive drug classes compared with ACEI affects the risk of dementia and pathological dementia subtypes in a large multinational database study.
Methods: This was a multinational population-based cohort study using electronic health databases in Hong Kong, the UK, Sweden and Australia. A common protocol was used to harmonise the study design. An active comparator, a new user design, was applied to compare the risk of all-cause dementia between different antihypertensive drug classes, with secondary

outcomes of Alzheimer's disease (AD) and vascular dementia (VaD). Adjusted Cox proportional hazards models with inverse probability of treatment weighting were used to generate results in each study site and were pooled in meta-analysis.
Results: One million nine hundred twenty-five thousand, five hundred sixty-three individuals were included across the four databases with a median follow-up ranging from 5.6 to 8.4 years. Compared to ACEI, initiation with ARB was associated with a reduced risk of incident all-cause dementia [hazard ratio (HR): 0.92, 95% confidence interval (CI): 0.89–0.94] and VaD (HR 0.87, 95% CI 0.78–0.96) but not AD.
Conclusions: This is the largest multinational cohort study conducted to date investigating different classes of antihypertensive drugs and the risk of incident dementia. When initiating antihypertensives, physicians and patients should consider the reduced risk of all-cause dementia and VaD with ARB compared with ACEI in their risk–benefit assessment.

Keywords: dementia; antihypertensive drugs; multinational cohort study; older people

Key points

- Multinational population-based cohort study that included almost 2 million adults.
- Angiotensin-II receptor blockers associated with a reduced risk of incident all-cause dementia and vascular dementia.
- Influencing angiotensin systems with different antihypertensive classes may play a role in dementia risk.

Introduction

Dementia is a global health challenge, currently affecting >50 million people worldwide. This number is set to increase with global estimates projected to reach over 150 million by 2050 [1].

In 2020, the Lancet Commission published 12 modifiable risk factors that may prevent or delay dementia [2]. One of these risk factors is hypertension, particularly in those diagnosed from mid-adult life, and its association with dementia has been studied widely [3–5]. Hypertension increases the risk of both Alzheimer's disease (AD) and vascular dementia (VaD) [6]. However, whether antihypertensive drugs, prescribed for the management of hypertension (and other cardiovascular diseases), can reduce the risk of dementia is largely unknown. Previous randomised controlled trials and observational studies investigating the impact of antihypertensive drugs on dementia and AD risk have shown inconsistent findings, and any observed effects may be drug class dependent [7–10].

There is convincing evidence from randomised controlled trials that lowering of blood pressure prevents the development of dementia or cognitive impairment [11]. However, relatively short follow-up time in clinical trials, low recorded incidence of dementia and small effect size often reduce the power to detect differences in treatment effect within these trials compared to observational studies. Recent systematic reviews and meta-analyses containing both trials and observational studies have also presented mixed findings regarding the preferred antihypertensive treatment in the context of dementia risk [12–16]. In the current literature, the heterogeneity of study designs and populations between studies published on the association between use of antihypertensive drugs and risk of dementia make comparison of findings difficult between different countries [17–21]. A large multinational study conducted with a harmonised study design can be an important step forward in generating generalizable evidence on this topic. With the advancement of technology, electronic patient health records containing anonymous real-world data on millions of patients are available for research. This source of data can be effectively used to characterise the real-world use of medications outside the constraints of a clinical trial and include a diverse, representative population to investigate if the impact of antihypertensive drugs is also influenced by ethnicity or geography.

Furthermore, there have been no head-to-head clinical trials of antihypertensives to investigate which drug class may offer the greatest risk reduction for incident dementia. Such an investigation is of importance, as the emergence of the angiotensin hypothesis has been increasingly recognised in the discussion of AD pathology [22]. The angiotensin-converting enzyme (ACE) has been shown *in vitro* to degrade the amyloid beta peptide [23, 24], which is a hallmark feature in the pathogenesis of AD. Previous Mendelian randomisation studies [25, 26] have suggested that genetically proxied ACEI exposure may be linked to an increased risk of AD with any potential effect likely independent of blood pressure lowering. Therefore, there is a need to disentangle the relationship between the use of different antihypertensive drug classes and the development of dementia and AD with direct comparisons with ACEI based on this hypothesis. Such findings would be of great value in clinical practice when clinicians need to decide which antihypertensive to initiate in order to most effectively reduce dementia risk.

The aim of this study was to compare the risk of incident dementia between individuals who are prescribed different antihypertensive drug classes using four electronic health record databases from Hong Kong, the UK, Sweden and Australia with a harmonised study design and pooled results. We sought to understand whether exposure to distinct classes of antihypertensives compared with ACEI is associated with a differential risk of dementia diagnosis.

Methods

This population-based cohort study utilised electronic patient health records, without direct patient contact. A

total of four databases from four countries or regions were used in this study, including data from Hong Kong, the UK, Sweden and Australia. A common protocol approach was used to harmonise the study design and analyses across the databases. All raw data were retrieved and analysed within the collaborating institute without the need to transfer the data, with the purpose of protecting the confidentiality of data and to ensure high scientific standards. Such an approach has been previously used and published [27–29]. Each participating site conducted the analysis within their database according to a common protocol to generate standardised results, which were then pooled from all the collaborating sites.

Data sources

Longitudinal data were retrieved from the four databases: Hospital Authority Data (Hong Kong), IQVIA Medical Research Database (IMRD-UK) (United Kingdom), Swedish Prescribed Drug Register and the Swedish National Patient Registry (Sweden) and the Pharmaceutical Benefits Scheme 10% sample (Australia) provided by Services Australia. These databases have been validated in previous studies [30–33] and are described in Appendix 1. All collaborating sites obtained ethical or governance approval to have their data included in this study.

Study design

Participants and eligibility criteria

To explore the effect of antihypertensive drug exposure on the risk of incident dementia, individuals aged 40 years or older, who were new users of antihypertensive drugs, were included in the study. The definitions of new antihypertensive users, cohort entry period and follow-up period were applied in each of the different databases listed in Appendix 2.

Individuals with any records of all-cause dementia, mild cognitive impairment, head injury or trauma, memory symptoms and confusion, any specific subtypes of dementia syndrome (Parkinson's disease, Huntington's disease, Creutzfeldt–Jacob disease) or prescription records of dementia symptomatic treatment (donepezil, rivastigmine, galantamine, memantine) prior to study entry were excluded.

Exposures

Participants who received at least two consecutive prescriptions of antihypertensive drugs of the same class within 90 days were considered as exposed. This requirement was to ensure that individuals were stable users of their antihypertensive drug class. The index date was the prescription start date of the second antihypertensive prescription that qualified them for study entry, i.e. the date that confirmed exposure ascertainment. Only prescription-naïve antihypertensive users were considered, i.e. those who did not meet the consecutive prescription criteria with their first antihypertensive prescription were excluded, even if they met the criteria at a later point. Antihypertensive drug classes and their prescription codes are listed in Appendix 3.

Outcomes

The outcome of interest was incident all-cause dementia defined by diagnostic or prescription codes depending on the database, with secondary outcomes of diagnoses of AD and VaD. Dementia subtypes and their diagnosis codes are listed in Appendix 4.

Follow-up

Follow-up started from the index date and ended at the occurrence of the primary outcome or censor date (death, transfer out/no more data collection from the database or end of study period, whichever occurred first). Individuals were not censored by a change in antihypertensive treatment to analyse the observational analogue of the clinical trials' intention-to-treat effect. The definitions of eligibility, exposure, outcome and follow-up are illustrated in Figure 1.

Selection of the comparison groups

An active comparator, a new user study design [34] was employed in this study. The exposure groups were classified as: ACE inhibitors (ACEI), angiotensin-II receptor blockers (ARB), beta-blockers, calcium channel blockers (CCB), diuretics and two or more coprescribed classes of antihypertensive drugs (combination).

The ACEI group was the reference exposure group and was compared with the other antihypertensive groups individually. ACEI was selected as the reference group based on our hypothesis of the potential role of ACE in AD pathogenesis and the hypothesised increased risk of AD following ACEI exposure.

Concurrent use of two or more classes of antihypertensive was defined as a combination group for those who had at least two consecutive prescriptions of the same two or more classes of antihypertensive drugs or codrugs started on the same day. New users of two or more classes of antihypertensive combinations that included an ACEI or codrug containing an ACEI were excluded because comparison with ACEI monotherapy as the reference group was not possible for these individuals. Alpha-1 blockers, centrally acting alpha-2 agonists and vasodilators were not included as comparison groups due to relatively small numbers of new users in each database, and the results of grouping them with other antihypertensive classes would have had limited generalisability.

Statistical analyses

To assess the association between different classes of blood pressure-lowering drugs and incident dementia, survival time analysis was conducted using Cox proportional

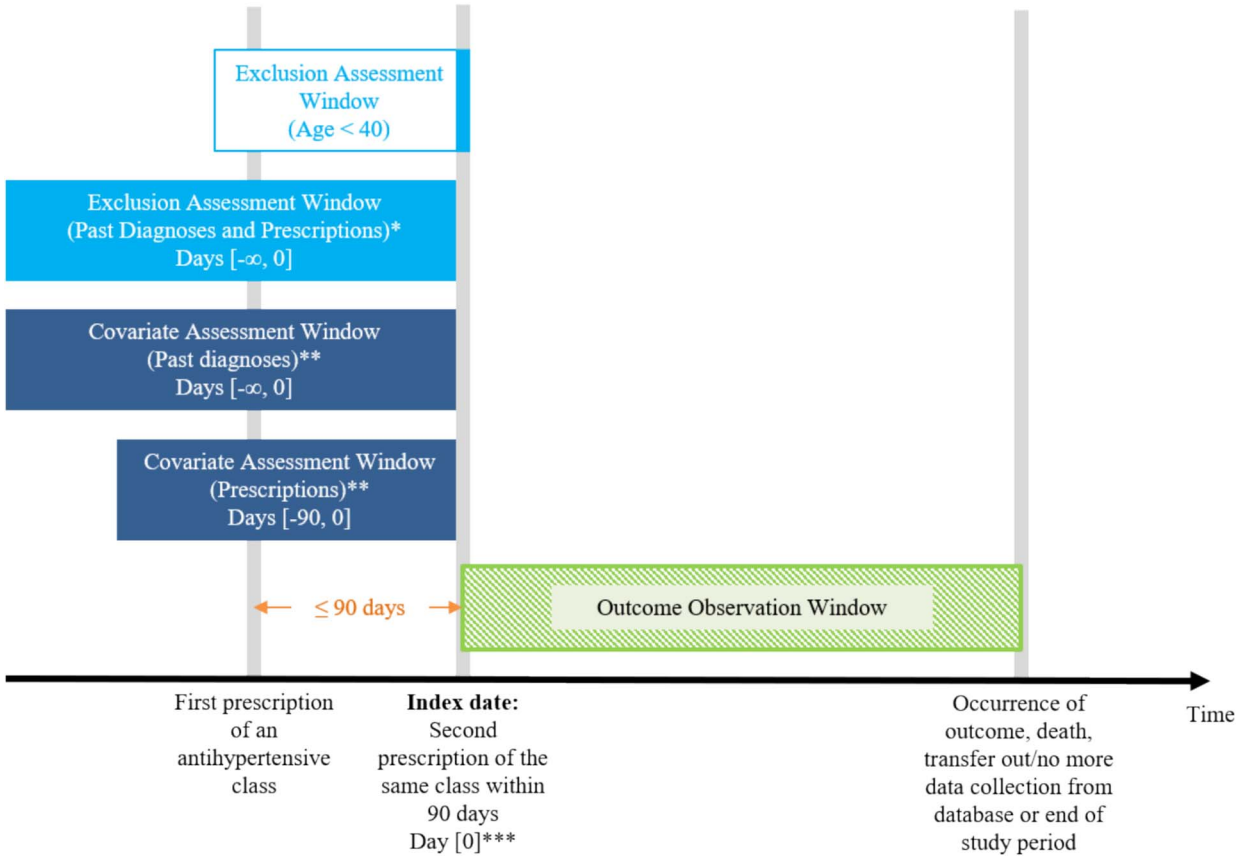

Figure 1. Exposure, outcome and follow-up diagram for eligible patients. *Any records of all-cause dementia, mild cognitive impairment, head injury or trauma, memory symptoms and confusion, any specific subtypes of dementia syndrome (Parkinson's disease, Huntington's disease, Creutzfeldt–Jacob disease), Human Immunodeficiency Virus (HIV) infection or prescription records of dementia symptomatic treatment (donepezil, rivastigmine, galantamine, memantine) **Covariates considered in the propensity score and for regression adjustment. ***Day 0 (Index date) not included when considering exclusion/covariate assessment and outcome observation windows.

hazards regression to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards assumptions were checked with a visual assessment of Schoenfeld residuals.

Propensity score inverse probability of treatment weighting (IPTW) was used to address differences in baseline characteristics between the comparison groups. A propensity score is defined as the probability of receiving the treatment of interest and is a common method to minimise selection bias [35]. The covariates were identified based on medical records prior to the index date. The covariates included in the model varied for each database depending on data availability. The list of covariates available and included in the model for each database is shown in Appendix 5 and included parameters such as age, sex assigned at birth, calendar year at entry, baseline comorbidities and recent drug history. Multinomial logistic regression was used to estimate the propensity score for each individual with consideration of all parameters at the index prescription date (baseline). Absolute standardised differences were estimated to assess covariate balance between groups before and after IPTW. A threshold of 0.1 was considered negligible. To reduce the variance in the effect estimate, stabilised inverse proportional treatment weights were calculated by using the crude probability of receiving the exposure group. Potential confounders unbalanced after IPTW were adjusted for in the regression model. The covariates for IPTW and adjustment in Cox regression are listed in Appendix 5.

The standardised results from each collaborating site were meta-analysed using the random effect model, an approach that has been used to synthesise results in a multinational cohort study setting [36]. A significance level of 0.05 was used in all statistical analyses. All analyses were conducted in R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria), Stata 17 (StataCorp, College Station, TX), Statistical Analysis System (SAS) v9.4 (SAS Institute, Cary, NC) and Review Manager (RevMan) 5.4 (The Cochrane Collaboration, London, UK).

Sensitivity and subgroup analyses

To ensure the robustness of the study findings, sensitivity and subgroup analyses were conducted. The detailed analysis plan is included in Appendix 6.

Results

A total of 1 925 563 new users of antihypertensives were included in this study: 434 506 from Hong Kong, 744 307 from the UK, 301 461 from Sweden and 445 289 from Australia (Figure 2). Baseline characteristics of all individuals from each database are described in Table 1, while characteristics by antihypertensive class for each database are shown in Appendix 7. The mean (standard deviation) age of the four study populations ranged from 61.8 (11.7) in Hong Kong to 74.4 (7.2) in Sweden. The median [interquartile range] follow-up was >5 years across all databases, ranging from 5.6 [2.5–9.3] years in Sweden to 8.4 [4.4–9.9] years in Australia. The most commonly prescribed class of antihypertensive agents varied per country. In Hong Kong, the CCB was most often (57%) prescribed at antihypertensive initiation. In the UK and Sweden, it was the ACEI (27% and 28%, respectively). In Australia, ARB users (40%) represented the highest proportion of new users. After IPTW, there was a general good overlap of propensity score distributions and improved covariate balance (Appendices 8 and 9). The pooled meta-analytic hazard ratios from each database for the overall analyses are presented for interpretation below.

Primary and secondary outcomes

ARB initiation was associated with a lower risk of incident all-cause dementia when compared with ACEI (HR: 0.92, 95% CI: 0.89–0.94) in the overall analyses. No statistically significant association was observed for the risk of all-cause dementia with the other antihypertensive classes (Table 2).

For the secondary outcomes of dementia subtypes, beta-blocker initiation was associated with a lower risk of AD (HR: 0.94, 95% CI: 0.90–0.99), while both ARB and beta-blocker initiation was associated with a lower risk of VaD when compared with ACEI (ARB HR: 0.87, 95% CI: 0.78–0.96, Beta-blocker HR: 0.91, 95% CI: 0.86–0.97). No statistically significant associations were observed for the risk of the dementia subtypes for the other classes (Table 3). Class comparisons for each individual site for primary and secondary outcomes are shown in Appendices 10 and 11, and meta-analysis forest plots are shown in Appendix 12.

Sensitivity and subgroup analysis

Most sensitivity and subgroup analyses have a consistent conclusion as the primary and secondary analyses. The results are detailed in Appendix 13.

Discussion

To our knowledge, this is the largest population-based multi-country study investigating the association between different classes of antihypertensive drugs and the risk of incident dementia in ethnically diverse populations. A common protocol was used to harmonise the study design, enabling direct comparison of the results across databases from different countries/regions. Initiation of ARB was associated with a lower risk of incident all-cause dementia and VaD but not AD compared with ACEI. The results suggest that, compared with ACEI, there was evidence that ARB was associated with a lower dementia risk, while other classes did not seem to have an increased risk of dementia compared with ACEI. These findings were consistent in most of the sensitivity analyses that tested the robustness of the results.

This study highlights some of the differences in prescribing practices for antihypertensive classes across the databases as observed in the distribution of proportions across classes. Current guidelines suggest that ACEIs and ARBs are typically the first-line choice for pharmacological treatment in mid-life hypertension, with CCBs recommended for those aged over 55 [37]. CCBs were the preferred antihypertensives in Hong Kong with a higher proportion of initiators compared with the other databases where ACEI and ARB initiation were more prevalent. The findings of this study provide great value in clinical practice when presented with a choice of oral pharmacological treatment options involving antihypertensives.

Both ARB and ACEI are common antihypertensive classes with similar efficacy for managing hypertension and cardiovascular disease. The observed lower risk of all-cause dementia and VaD may be explained by the underlying difference in the mechanism of ACEI and ARBs. ACEIs reduce levels of angiotensin II by inhibiting its formation from angiotensin I [38], whereas ARBs selectively inhibit 'type 1' angiotensin II receptors (AT1Rs) [39]. The inhibition of AT1R by ARBs leads to greater circulating levels of angiotensin II that are available for activation of 'type 2' and 'type 4' angiotensin II receptors (AT2R and AT4R). Activation of these receptors has been shown to reduce oxidative stress and neuroinflammation and improve cerebral blood flow in animal models [40–42]. Our study supports the use of ARBs compared with ACEI when considering the risk of cognitive decline and dementia, based on a multi-ethnic cohort with a long median follow-up time. Although an HR of 0.92 may suggest a modest risk reduction, even small changes in dementia incidence can have a large impact on relieving the growing burden of dementia [43].

The association of ARB and lower risk of all-cause dementia compared with ACEI may be driven in part by the association between use of ARB and the lower risk of VaD; however, the proportion of dementia diagnoses that was VaD varied from 11% to 16% in Hong Kong to 30%–35% in the UK (Appendix 9).

Our secondary analyses of different types of dementia might have been influenced by our inability to differentiate dementia subtypes in the Australian data. We found differences in the results with the all-cause dementia outcome compared with different subtypes. For example, the new use of beta-blockers was associated with a reduced risk of the AD and VaD subtypes of dementia, but no statistically significant association was identified for all-cause dementia. Because of

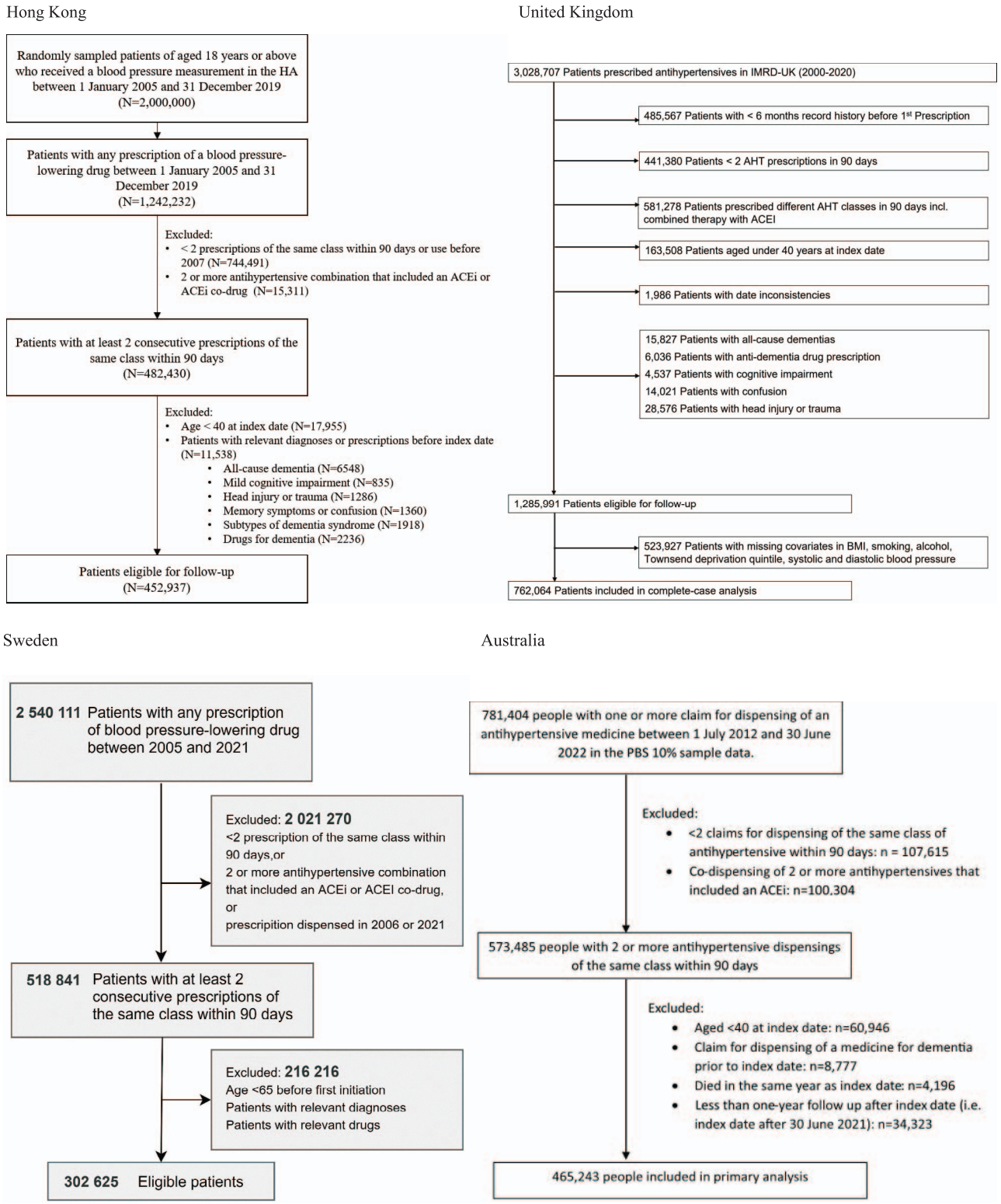

Figure 2. Cohort identification flowchart for each database Abbreviations: HA, Hospital Authority (Hong Kong); ACEI, angiotensin-converting enzyme inhibitor; IMRD-UK, IQVIA Medical Research Database–United Kingdom; AHT, antihypertensive; BMI, body mass index; PBS, Pharmaceutical Benefits Scheme (Australia).

Table 1. Baseline characteristics of new users of antihypertensives for all classes by country/region

Baseline characteristics	Hong Kong *N* = 434 506	UK *N* = 744 307	Sweden *N* = 301 461	Australia *N* = 445 289
Age (mean, SD)	61.8 (11.7)	64 (12.0)	74.4 (7.2)	63.8 (12.3)
Age group (*N*, %)		–		
40–49	65 541 (15.1)	103 924 (14.0)	–	63 186 (14.2)
50–59	133 851 (30.8)	176 628 (23.7)	–	111 253 (25.0)
60–69 (65–69 for Sweden)	127 193 (29.3)	212 029 (28.5)	102 086 (33.9)	132 751 (29.8)
70–79	70 331 (16.2)	173 386 (23.3)	134,257 (44.5)	94 231 (21.2)
≥80	37 590 (8.7)	78 331 (10.5)	65 118 (21.6)	52 918 (11.9)
Female (*N*, %)	221 638 (51.0)	391 502 (52.6)	164 248 (54.5)	234 493 (52.7)
Follow-up years (median, IQR)	6.4 [3.1, 9.7]	7.4 [3.2–11.4]	5.6 [2.5–9.3]	8.4 [4.4–9.9]
Antihypertensive drug class (*N*, %)				
ACE inhibitors	64 470 (14.2)	202 716 (27.2)	83 884 (27.8)	121 971 (27.4)
Angiotensin-II receptor blockers	8992 (2.0)	35 305 (4.7)	38 451 (12.8)	179 628 (40.3)
Beta-blockers	64,785 (14.9)	164 143 (22.1)	68 079 (22.6)	66 292 (14.9)
Calcium channel blockers	246 423 (56.7)	158 810 (21.3)	50 237 (16.7)	64 861 (14.6)
Diuretics	29 963 (6.9)	172 177 (23.1)	41 656 (13.8)	21 537 (4.8)
Combination	19 873 (4.6)	11 147 (1.5)	19 154 (6.4)	–
Baseline comorbidities (*N*, %)				
Chronic obstructive pulmonary disease	9250 (2.1)	30 440 (4.1)	10 718 (3.6)	74 451 (16.7)
Dyslipidaemia	62 834 (14.5)	111 549 (15.0)	12 036 (4.0)	195 993 (44.0)
Diabetes	68 398 (15.7)	119 908 (16.1)	15 668 (5.4)	65 007 (14.6)
Thyroid disorders	13 086 (3.0)	54 114 (7.3)	10 359 (3.1)	33 250 (7.5)
Hypertension	242 391 (55.8)	625 336 (84.0)	35 689 (11.8)	–
Heart failure	3195 (0.7)	30 389 (4.1)	8255 (3.0)	23 407 (5.3)
Cerebrovascular diseases/stroke	24 035 (5.5)	54 072 (7.3)	19 494 (8.3)	–
Ischaemic heart disease	15 863 (3.7)	175 526 (23.6)	21 967 (7.3)	–
Peripheral vascular disease	1646 (0.4)	19 557 (2.6)	1564 (0.5)	–
Arrhythmia and conduction disorders	12 902 (3.0)	52 937 (7.1)	34 599 (11.4)	21 127 (4.7)
Liver disease	10 622 (2.4)	13 908 (1.9)	1721 (0.5)	3344 (0.8)
Renal disease	8583 (2.0)	49 080 (6.6)	3044 (1.0)	2506 (0.6)
Schizophrenia and psychosis	6487 (1.5)	6640 (0.9)	2334 (0.7)	9305 (2.1)
Bipolar disorder	866 (0.2)	4338 (0.6)	1424 (0.5)	1341 (0.3)
Depression	9291 (2.1)	170 926 (23.0)	5658 (1.9)	92 528 (20.8)
Anxiety disorder	5145 (1.2)	83 212 (11.2)	3558 (1.2)	33 421 (7.5)
Concurrent or previous use of drugs (90 days before index) (*N*, %)				
Anticholinergics	71 627 (16.5)	56 553 (7.6)	–	–
Antipsychotics	10 000 (2.3)	9612 (1.3)	6840 (2.3)	9305 (2.1)
Antidepressants	14 870 (3.4)	18 867 (2.5)	31 013 (10.3)	92 528 (20.8)
Oral anticoagulants	2653 (0.6)	28 819 (3.9)	31 537 (10.4)	34 369 (7.5)
Antiplatelet drugs	46 547 (10.7)	182 441 (24.5)	72 175 (23.9)	53 621 (11.8)
Insulins	7428 (1.7)	18 460 (2.5)	7696 (2.5)	65 007 (14.6)
Noninsulin antidiabetic drugs	65 046 (15.0)	72 485 (9.7)	20 697 (6.9)	
Lipid-regulating drugs	54 740 (12.6)	236 772 (31.8)	74 304 (24.6)	195 993 (44.0)
Thyroid and antithyroid drugs	11 522 (2.7)	6594 (0.9)	24 949 (8.3)	33 250 (7.5)
Other characteristics (mean, SD)				
Mean systolic BP—12 months prior to index date (mmHg)	151 (17)	148 (19)	–	–
Mean diastolic BP—12 months prior to index date (mmHg)	85 (10)	85 (11)	–	–
Smoking history	10 202 (2.3)	–	–	10,123 (2.3)
Alcohol abuse history	2987 (0.7)	–	–	866 (0.2)
BMI category (*N*, %)				
Underweight (<18.59 kg/m^2)	–	9457 (1.3)	–	–
Healthy weight (18.6–24.9 kg/m^2)	–	198 698 (26.7)	–	–
Overweight (25–29.9 kg/m^2)	–	292 519 (39.3)	–	–
Obese (30–39.9 kg/m^2)	–	214 484 (28.8)	–	–
Severely obese (≥40 kg/m^2)	–	29 140 (3.9)	–	–
Alcohol status (*N*, %)				
Drinker	–	582 402 (78.2)	–	–
Ex-drinker	–	16 351 (2.2)	–	–
Nondrinker	–	145 545 (19.6)	–	–

(continued)

Table 1. Continued.

Baseline characteristics	Hong Kong *N* = 434 506	UK *N* = 744 307	Sweden *N* = 301 461	Australia *N* = 445 289
Smoking status (*N*, %)				
Current	–	125 862 (16.9)	–	–
Ex-smoker	–	219 528 (29.5)	–	–
Never	–	398 908 (53.6)	–	–
Calendar year at entry (*N*, %)				
2000	–	16 161 (2.2)	–	–
2001	–	20 845 (2.8)	–	–
2002	–	23 818 (3.2)	–	–
2003	–	217 782 (29.3)	–	–
2004	–	39 689 (5.3)	–	–
2005	–	33 226 (4.5)	–	–
2006	–	31 159 (4.2)	–	–
2007	32 023 (7.4)	29 502 (4.0)	34 938 (11.6)	–
2008	31 014 (7.1)	27 558 (3.7)	28 851 (9.6)	–
2009	32 326 (7.4)	73 625 (9.9)	25 076 (8.3)	–
2010	32 748 (7.5)	26 438 (3.6)	22 455 (7.4)	–
2011	33 757 (7.8)	24 444 (3.3)	21 199 (7.0)	–
2012	34 709 (8.0)	24 662 (3.3)	20 599 (6.8)	248 595 (55.8)
2013	35 782 (8.2)	23 953 (3.2)	19 314 (6.4)	37 208 (8.4)
2014	34 457 (7.9)	53 291 (7.2)	18 412 (6.1)	24 466 (5.5)
2015	31 841 (7.3)	19 228 (2.6)	18 113 (6.0)	22 030 (4.9)
2016	32 908 (7.6)	16 116 (2.2)	18 129 (6.0)	21 680 (4.9)
2017	33 229 (7.6)	14 267 (1.9)	18 700 (6.2)	21 756 (4.9)
2018	35 216 (8.1)	13 570 (1.8)	17 966 (5.9)	22 251 (5.0)
2019	34 496 (7.9)	13 532 (1.8)	19 132 (6.3)	21 968 (4.9)
2020	–	1432 (0.2)	18 577 (6.2)	22 859 (5.1)
2021	–	–	–	11 476 (2.6)

Abbreviations: SD, standard deviation; IQR, interquartile range; BP, blood pressure; BMI, body mass index. The en dash symbol (–) represents data that is not available or not applicable.

Table 2. Primary analysis: Cox proportional hazards models and pooled meta-analysis for antihypertensive drug classes and the risk of incident all-cause dementia

Class	IPTW, adjusted HR (95% CI) [a]				
	Hong Kong	UK	Sweden	Australia	**Pooled**
ACEI	Ref.	Ref.	Ref.	Ref.	Ref.
ARB	1.05 (0.79–1.39)	0.91 (0.86–0.97)	0.88 (0.82–0.95)	0.92 (0.90–0.95)	0.92 (0.89–0.94)
Beta-blockers	0.93 (0.86–1.02)	0.93 (0.89–0.97)	1.03 (0.98–1.08)	1.09 (1.05–1.13)	1.00 (0.92–1.08)
CCB	0.96 (0.90–1.03)	0.99 (0.96–1.03)	0.95 (0.90–1.00)	1.01 (0.97–1.05)	0.99 (0.96–1.01)
Diuretics	1.00 (0.91–1.10)	0.98 (0.95–1.02)	1.26 (1.20–1.33)	1.17 (1.12–1.23)	1.10 (0.97–1.25)
Combination	0.94 (0.83–1.07)	1.01 (0.91–1.11)	1.11 (1.02–1.21)	–	1.02 (0.93–1.12)

Abbreviations: IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; ACEI = angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CCB, calcium channel blocker. The en dash symbol (–) represents data that is not available or not applicable. [a]IPTW and model adjustment variables are listed in Appendix 5.

the complexity of giving a dementia diagnosis, it is likely that clinicians have done an adequate clinical workup to arrive at a diagnosis of a specific dementia subtype to be recorded as such in electronic health databases. This leads to more stringent outcome definitions in these analyses, which reassures the validity of the observed associations. Nonetheless, this finding of reduced risk in secondary analyses should be interpreted with caution. Previous studies have reported mixed findings on the use of beta-blockers and the associated risk of AD and VaD [44, 45].

In the younger age subgroups of 40–49 and 50–59 years, the prescription of several antihypertensive drug classes was associated with a higher risk of all-cause dementia when compared with ACEI, including beta-blockers, CCBs and diuretics. This could potentially be due to better responsiveness with ACEI initiation in these age groups as younger people have higher plasma renin activity [46]. ACEI is also recommended as a first-line treatment in adults aged under 55 in hypertension management guidelines [37]. However, this warrants further studies due to the relatively

Table 3. Secondary outcomes: Cox proportional hazards models and pooled meta-analysis for antihypertensive drug classes and the risk of incident AD and VaD

Class	IPTW, adjusted HR (95% CI) [a]			
	Hong Kong	UK	Sweden	**Pooled**
Outcome: AD				
ACEI	Ref.	Ref.	Ref.	Ref.
ARB	0.47 (0.15–1.45)	0.95 (0.86–1.05)	0.88 (0.78–0.99)	0.92 (0.84–1.00)
Beta-blockers	0.98 (0.76–1.25)	0.93 (0.87–0.99)	0.96 (0.89–1.04)	0.94 (0.90–0.99)
CCB	1.06 (0.87–1.29)	0.90 (0.83–0.98)	0.99 (0.93–1.05)	0.96 (0.89–1.04)
Diuretics	1.06 (0.80–1.41)	1.01 (0.95–1.07)	1.04 (0.95–1.15)	1.02 (0.97–1.07)
Combination	0.81 (0.54–1.22)	1.05 (0.90–1.24)	0.79 (0.66–0.94)	0.90 (0.72–1.12)
Outcome: VaD				
ACEI	Ref.	Ref.	Ref.	Ref.
ARB	1.32 (0.66–2.64)	0.89 (0.80–0.99)	0.81 (0.69–0.95)	0.87 (0.78–0.96)
Beta-blockers	1.04 (0.83–1.30)	0.90 (0.83–0.97)	0.92 (0.83–1.02)	0.91 (0.86–0.97)
CCB	1.07 (0.91–1.26)	1.02 (0.95–1.08)	0.89 (0.79–1.01)	0.99 (0.90–1.08)
Diuretics	1.02 (0.77–1.34)	0.93 (0.87–0.99)	1.10 (0.97–1.24)	1.00 (0.88–1.13)
Combination	1.35 (0.97–1.88)	0.94 (0.78–1.13)	1.07 (0.88–1.29)	1.06 (0.89–1.26)

Abbreviations: AD, Alzheimer's disease; VaD, vascular dementia; IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CCB, calcium channel blocker. [a]IPTW and model adjustment variables are listed in Appendix 5.

low numbers of younger antihypertensive new users in these comparisons.

Strengths and limitations

This was one of the largest population-based cohort studies comparing different classes of antihypertensives and the risk of dementia, pooling almost 2 million new users of antihypertensives across the four countries/regions. As the first multicountry study across three continents including individuals with predominantly Chinese and Caucasian ethnicities and people with European ancestry, our study is an improvement on the generalisability of results compared to that of previous studies. This is an important addition to the literature given the different risks for adverse drug reactions of cardiovascular drugs [47]. First-line antihypertensive treatment can be determined by ethnicity, and, although the results could not be stratified by ethnicity due to data limitations, each database has a predominant ethnicity (Appendix 2) and the database-specific findings may impact treatment guideline recommendations [37].

One of the disadvantages of multidatabase studies is data heterogeneity and innate differences in how the data were collected, resulting in some analyses that could not be performed in all four datasets. However, a standardised methodology and protocol were used to ensure consistent study design and analysis across the study sites. One of the common limitations of conducting studies with dementia as the outcome of interest is the follow-up time needed to capture the event. Dementia is usually diagnosed in older-aged adults, while antihypertensive use is commenced during mid-life. A previous study demonstrated that 1.6–5.3 years of antihypertensive use will result in a significantly reduced risk of all-cause dementia and AD [48]. The median follow-up across datasets in this study ranged from 6 to 8 years. Therefore, we believe that we were able to capture adequate incident dementia events after exposure to antihypertensive drugs to achieve a statistically meaningful conclusion. There may be a degree of misclassification amongst the outcome of interest as diagnostic or drug codes were used to determine the outcome. Nevertheless, a previous study showed that the diagnoses of dementia in primary care, including AD, have a specificity of 83% in UK general practitioner data [49]. Furthermore, the positive predictive value of dementia diagnosis was 81% in the Swedish data [50]. Validation of dementia diagnoses was not performed in the Hong Kong Hospital Authority data, but other diagnoses, such as stroke [30] and myocardial infarction [51], have positive predictive values close to 90% that suggest a general high validity of the data. Any misclassification of the outcome is likely to have been nondifferential with respect to antihypertensive drug exposure and would be expected to bias results towards the null. Finally, although most major confounders were considered in propensity score weighting and regression adjustment, unmeasured confounding remains as a limitation in observational studies.

Conclusion

This population-based cohort study using databases from four countries/regions across three continents compared the use of different classes of antihypertensive drugs and the risk of incident dementia. Our findings suggest that ARB initiation may be associated with a lower risk of incident all-cause dementia and VaD but not AD compared with ACEI. No statistically significant association was observed for the risk of all-cause dementia with the other antihypertensive classes compared with ACEI. The results of this study can inform evidence-based guidelines for antihypertensive treatment in

generalisable clinical settings and will be of relevance in the decision-making process of both clinicians and patients.

Supplementary Data: Supplementary data are available at *Age and Ageing* online.

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