OPEN

Comparison of Antihypertensive Drug Classes for Dementia Prevention

Venexia M. Walker,[a,b,c] *Neil M. Davies,*[a,b,d] *Richard M. Martin,*[a,b] *and Patrick G. Kehoe*[e,f]

Background: Hypertension in midlife is associated with increased risk of Alzheimer disease and vascular dementia late in life. In addition, some antihypertensive drugs have been proposed to have cognitive benefits, independent of their effect on hypertension. Consequently, there is potential to repurpose antihypertensive drugs for the prevention of dementia. This study systematically compared seven antihypertensive drug classes for this purpose, using the Clinical Practice Research Datalink.

Methods: We assessed treatments for hypertension in an instrumental variable analysis to address potential confounding and reverse causation. We used physicians' prescribing preference as an ordinal instrument, defined by the physicians' last seven prescriptions. Participants considered were new antihypertensive users between 1996 and 2016, aged 40 and over.

Results: We analyzed 849,378 patients, with total follow up of 5,497,266 patient-years. We estimated that β-adrenoceptor blockers and vasodilator antihypertensives conferred small protective effects—for example, β-adrenoceptor blockers were associated with 13 (95% confidence interval = 6, 20) fewer cases of any dementia per 1000 treated compared with other antihypertensives.

Conclusions: We estimated small differences in the effects of antihypertensive drug classes on dementia outcomes. We also show that the magnitude of the differences between drug classes is smaller than that previously reported. Future research should look to implement other causal analysis methods to address biases in conventional observational research, with the ultimate aim of triangulating the evidence concerning this hypothesis.

Keywords: Alzheimer Disease; Antihypertensive Agents; Dementia; Drug Repositioning; Drug Repurposing

(*Epidemiology* 2020;31: 852–859)

There is a substantial unmet clinical need for treatments of dementia, where benefits to patients, society, and the public purse can be gained. Despite this, some drug companies have withdrawn from this therapy area due to failed and costly efforts to find new treatments.[1] Drug repurposing, the identification of existing compounds for other clinical conditions, offers substantial advantages over traditional drug-discovery approaches. This includes immediate access to human safety data from the original clinical development work, which can accelerate testing in clinical trials, saving both time and money.[2] Many antihypertensives have been proposed as drug-repurposing candidates for dementia prevention, in part because of research to better understand the observed associations between midlife hypertension and later-life risk of Alzheimer disease and vascular dementia.[3–6] Vascular dysregulation may also have a pathological role early in the development of Alzheimer disease.[7] Finally, there have been suggestions that some antihypertensives, specifically those that block angiotensin receptor and calcium-channel signaling, may have other neurological benefits.[7–9] Several observational studies have previously investigated repurposing antihypertensives for dementia prevention, but non-genetic instrumental variable analysis has not been applied in this setting.[10–17]

Submitted January 22, 2019; accepted July 22, 2020.

From the [a]MRC University of Bristol Integrative Epidemiology Unit, Bristol, United Kingdom; [b]Bristol Medical School: Population Health Sciences, University of Bristol, Bristol, United Kingdom; [c]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [d]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Norway; [e]Dementia Research Group, Bristol Medical School, University of Bristol, Bristol, United Kingdom; and [f] Bristol Medical School: Translational Health Sciences, University of Bristol, Bristol, United Kingdom.

This work was supported by the Perros Trust and the Integrative Epidemiology Unit. The Medical Research Council (MRC) and the University of Bristol support the MRC Integrative Epidemiology Unit [MC_UU_12013/1, MC_UU_12013/9, MC_UU_00011/1, MC_UU_00011/4]. N.M.D. is supported by a Norwegian Research Council (Grant number 295989).

N.M.D. has worked on an unrelated project funded by the Global Research Awards for Nicotine Dependence (GRAND), an independent grant-giving organization funded by Pfizer. The other authors have no conflicts of interest to declare.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

This study used data from the Clinical Practice Research Datalink (CPRD). We cannot directly share the data used, but interested parties should contact the CPRD's Independent Scientific Advisory Committee (ISAC) for access. The code related to this study has been made available via GitHub: https://github.com/venexia/repurposing-antihypertensives-dementia.

Correspondence: Venexia M. Walker, Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN, United Kingdom. E-mail: venexia.walker@bristol.ac.uk.

ISSN: 1044-3983/20/3106-0852
DOI: 10.1097/EDE.0000000000001245

Instrumental variable analysis, which estimates the causal effect of an exposure on an outcome by using a third variable (the instrument), can be robust to confounding and reverse causation if certain assumptions are met (Figure 1). That is, the instrument must (1) be associated with the exposure of interest; (2) affect the outcome only through its effect on the exposure; and (3) have no common causes with the outcome (i.e., no confounders of the instrument–outcome association).[18,19] Physicians' prescribing preference has been proposed as an instrumental variable in pharmacoepidemiology.[20–24] It meets the instrument conditions, as (1) it is associated with the prescription issued by the physician; (2) it is unlikely to relate to the patient's risk of dementia other than through the prescription issued; and (3) physicians' prescribing preference is unlikely to share a cause with the patient's outcome because patients have relatively little choice over which physician they see or knowledge of their physicians' preferences for antihypertensive drug classes.[22] The last condition is likely to hold in the UK setting used for this study because prior to 5 January 2015, patients were required to live within a practice's boundary area to register at that practice, which limited their choice of physician.[25] We therefore report a systematic assessment of antihypertensive drug classes as candidates for the prevention of dementia, using physicians' prescribing preference as an instrument in the Clinical Practice Research Datalink (CPRD).

METHODS

Study Design

We conducted a prospective new-user cohort study in the CPRD, a primary-care database with over 11.3 million people from more than 670 UK practices.[26,27] The data were extracted from the CPRD-GOLD primary-care dataset March 2016 snapshot. This snapshot included all patients, with data that met a minimum standard of quality set by the CPRD, who registered at a participating practice from 1 January 1987 to 29 February 2016.[28] The a priori protocol was published prior to study commencement (see eText 1; http://links.lww.com/EDE/B711 for amendments), and the study design diagram is included as eFigure 1; http://links.lww.com/EDE/B711.[29] The protocol for this study was approved by the CPRD's Independent Scientific Advisory Committee (ISAC 15_246R). This study did not directly involve patients; so further ethical approval was not required.

Participants

Patients were included in the analysis if they were aged 40 years or over and received a first prescription for an antihypertensive drug class of interest. We stopped follow-up at the earliest of a dementia outcome; death; end of registration at a CPRD practice; or the end of follow-up (29 February 2016). Patients were excluded if they were of unknown gender; had less than 12 months of good-quality data prior to their first prescription; or were initially prescribed multiple antihypertensive drug classes. We also excluded patients who were prescribed an antihypertensive before January 1996, as 1996 was the first complete year in which all of the drugs being considered were available.

Exposures

We considered seven antihypertensive drug classes based on the British National Formulary groupings.[30] These were α-adrenoceptor blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-adrenoceptor blockers, calcium-channel blockers, diuretics (either "thiazides and related diuretics" or "potassium-sparing diuretics and aldosterone antagonists"), and vasodilator antihypertensives. To mimic a randomized controlled trial (RCT), we analyzed exposure in an intention-to-treat framework, i.e., based on the first prescription irrespective of treatment discontinuation or subsequent switches to, or additions of, other drug classes.[31] The index date for each patient was the date of first prescription for an antihypertensive drug. We did not model treatment switching, as it was likely to be nonrandom and confounded by patients' unobservable characteristics.

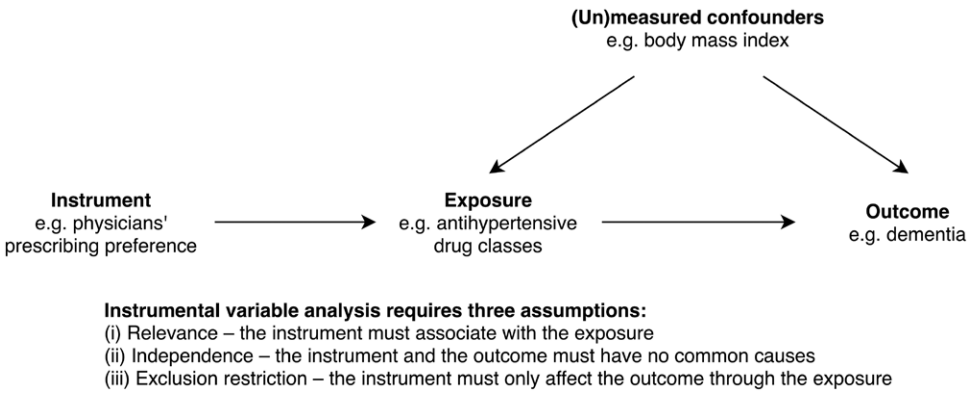

Figure 1. Directed acyclic graph for the instrumental variable analysis model.

Outcomes

Our primary outcome was dementia. We also defined four subtypes: probable Alzheimer disease, possible Alzheimer disease, vascular dementia, and other dementias (eFigure 2; http://links.lww.com/EDE/B711), which we considered as a sensitivity analysis.

Covariates

We adjusted the instrumental variable analysis for prescription year, as antihypertensive prescriptions have varied by year; so this may have influenced both the instrument–exposure and instrument–outcome associations. We assumed that other potential covariates influenced the exposure–outcome association but not the instrument–exposure or instrument–outcome associations, and so are expected to be balanced across levels of the instrument if the instrument assumptions are met. The instrumental variable analysis was compared with a multivariable logistic regression analysis to assess the extent of confounding. The multivariable logistic regression analysis was adjusted for prescription year; sex; age at index; previous history of coronary heart disease, coronary bypass surgery, or cerebrovascular disease; chronic disease; socioeconomic position; consultation rate; alcohol status; smoking status; and body mass index. All covariates were determined prior to index, and they are defined fully in eText 2; http://links.lww.com/EDE/B711. We imputed missing data in the covariates 20 times using the Imputation by Chained Equations package in Stata for each analysis dataset.[32]

Code Lists

We defined prescriptions using Product codes and diagnoses using Read codes. These codes are recorded at the time of the consultation and uniquely define prescriptions and clinical terms in the CPRD. The code lists for this study are provided on GitHub (https://github.com/venexia/repurposing-antihypertensives-dementia).

Assessment of Bias

We constructed scaled bias component plots using the subset of patients with complete covariate information.[33,34] Instrument–covariate associations were scaled by dividing the coefficient by the instrument–exposure association (i.e., the first stage regression result). To further assess bias, we repeated the analysis adjusting for each covariate, in turn to determine the effect on our results.

Statistical Methods

This study used instrumental variable analysis, with physicians-preferred antihypertensive drug class as an instrument to proxy for exposure. We compared each drug class against all other antihypertensives. We derived prescribing preference from the prescriptions issued by the physician to their seven most recent patients who received an antihypertensive.[35,36] This resulted in an ordinal instrument, with a minimum value of zero and a maximum value of seven, indicating how many of the previous prescriptions for antihypertensives the physician had chosen the drug class of interest. Seven previous prescriptions were selected, as this number has previously been used in the literature and is thought to balance instrument strength, which increases with additional prescriptions, and recent prescribing trends, which are lost with additional prescriptions.[20] We used the instrument in an ordinal form, rather than binary, to further improve instrument strength, as ordinal instruments capture more variation in the exposure. We calculated robust standard errors and statistics to address arbitrary heteroskedasticity and performed clustering by physician to address both arbitrary heteroskedasticity and intra-group correlations between physicians.[37] Obtaining a point estimate requires a fourth instrument assumption of monotonicity or no effect modification by values of the instrument.[38] Monotonicity assumes that if a patient saw a physician with a stronger preference for a given drug, they would be more likely to receive that drug. No effect modification requires that the physicians' preferences do not modify the effects of antihypertensives. Under monotonicity, the results were interpreted as the effect among patients whose prescription was affected by their physicians' preference (known as the local average treatment effect).[39] Under no effect modification, the estimates can be interpreted as the effects of treatment in those treated. For each analysis, we present the partial F statistic to quantify and test the strength of the instrument–exposure association and endogeneity test results. Finally, we present a corresponding multivariable logistic regression analysis. The instrumental variable analysis is presented in line with reporting guidelines (eText 3; http://links.lww.com/EDE/B711).[40] All analyses were conducted in Stata version 15MP (StataCorp, College Station, TX) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).[41,42] Code is available from GitHub (https://github.com/venexia/repurposing-antihypertensives-dementia).

Sensitivity Analyses

We performed seven sensitivity analyses to assess the stability of our results. First, we repeated the main analysis using the dementia subtype outcomes to ascertain whether the observed effects were being driven by a particular subtype.

Beta-adrenoceptor blockers can be prescribed in low doses for the treatment of anxiety.[43] To test the effect of removing these patients, the second sensitivity analysis removed individuals who both received a drug class of interest and had a Read code indicating anxiety, or other neurotic, stress-related, and somatoform disorders in the same consultation.[44] The third sensitivity analysis also tested this but instead removed individuals whose dose was in the bottom 25% for their index drug class.

Differential prescribing occurs in women of childbearing age due to risks associated with some antihypertensives during pregnancy.[45] This might affect the youngest members of the cohort; so the fourth sensitivity analysis restricted the patients to those aged 55 years and over at index, as in the Reducing pathology in Alzheimer's Disease through Angiotensin Targeting trial.[46]

The fifth sensitivity analysis repeated the main analysis, with adjustment for the average age and socioeconomic position of the past seven patients seen by the physician, i.e., the patients used to define the instrument. These factors, particularly age, are strong confounders of our outcome and so may have a large impact on our results if incorrectly accounted for.

Our sixth sensitivity analysis also repeated the main analysis but with control for prescribing physician fixed effects. This model removes time-invariant differences between physicians, focusing instead on variation present within physicians, but can lack precision.[47]

Using an ordinal instrument could potentially lead to over-identification. To test this, we performed a final sensitivity analysis that applied the Sargan–Hansen test to two dichotomized instruments. The first instrument took a value of one if the treatment of interest was prescribed four or more times and a value of zero otherwise. The second instrument took a value of one if the treatment of interest was prescribed six or more times and a value of zero otherwise.

RESULTS

Patient Characteristics

A total of 849,378 patients, with follow-up of 5,497,266 patient-years, met the criteria for our analysis. eFigure 3; http://links.lww.com/EDE/B711 outlines patient attrition. Most patients were excluded for being aged under 40 years at index (n = 93458), having less than 12 months' worth of data prior to index (n = 682465), or initially receiving multiple antihypertensives (n = 45777). Table presents patient characteristics of those remaining in the cohort.[48–50] Of the 849,378 patients, 410,805 (48%) had complete covariate information. Incomplete covariate information was mainly due to missing values for the Index of Multiple Deprivation, which was used to adjust for socioeconomic position, as this measure is only available for patients in English practices. One notable feature of the patient characteristics is that 97% of patients receiving α-adrenoceptor blockers and 99% of patients receiving vasodilator antihypertensives were men—this difference persists, regardless of the age at first prescription (eTable 1; http://links.lww.com/EDE/B710). We also observed that 32% of patients received a prescription for the antihypertensive they were initially prescribed 5 or more years after their initial exposure, with some variation in retention based on drug class.

Instrument Evaluation

We tested the independence assumption using the F statistic and mean instrument–exposure association. Our proposed instruments had a minimum F statistic of 4,702 in the main analyses, indicating that weak instrument bias is unlikely to have affected the results. Meanwhile, the mean instrument–exposure association was calculated to be 0.08 (SD, 0.03; eTable 2; http://links.lww.com/EDE/B710). We assessed whether we could falsify the independence and exclusion restriction assumptions using Bonet's instrumental variable inequality tests.[51–53] The inequalities held at each level of the instrument in our main analyses (eTable 3; http://links.lww.com/EDE/B710). The independence assumption was further assessed using bias component plots—see "Assessment of bias" for full details. We could not assess whether the monotonicity assumption held because there are no established methods for ordinal instruments used to proxy binary exposures that we could implement with the available data (e.g., we could not survey physicians included in this analysis).[54] Nor is it possible to directly test the no effect modification assumption. For the assumptions we did assess, estimates based on the instrument may suffer from bias even if they did not associate with measured confounders (i.e., unmeasured confounding). The distribution of the instrument varied by drug class (eFigure 4; http://links.lww.com/EDE/B711). Vasodilator antihypertensives and angiotensin II receptor blockers were not commonly prescribed; so the instruments used to study them tended to favor the comparator.

Primary Analyses

This analysis estimated that β-adrenoceptor blockers were protective, resulting in 13 (95% CI = 6, 20) fewer dementia cases when compared with other antihypertensives per 1000 people treated. Vasodilator antihypertensives also had a point estimate consistent with a protective effect; however, suffered from much uncertainty due to only 1% of participants being exposed to this drug class. Meanwhile, we estimated that diuretics were harmful, resulting in 14 (95% CI = 7, 20) additional dementia cases compared with other antihypertensives per 1000 people treated. Instrumental variable effect estimates for all drug classes are presented in Figure 2 and eTable 4; http://links.lww.com/EDE/B710. The results of the corresponding multivariable logistic regression using imputed data are presented in eFigure 5; http://links.lww.com/EDE/B711 and eTable 5; http://links.lww.com/EDE/B710. Endogeneity tests found little evidence to reject the null that the exposure was exogenous, i.e., there was a difference between the instrumental variable analysis and ordinary least squares results (eTable 4; http://links.lww.com/EDE/B710).

Assessment of Bias

Bias component plots were used to assess bias among patients using the imputed datasets to account for missing covariate information (eFigures 6; http://links.lww.com/EDE/B711 and 7; http://links.lww.com/EDE/B711). The bias component plots suggested that the instrumental variable analysis for certain drug classes may have been biased for several of the covariates tested. There was also substantial uncertainty surrounding some of the scaled instrument–covariate associations. Repeating the analysis with adjustment for each covariate produced consistent results with the main analysis (eFigure 8; http://links.lww.com/EDE/B711 and eTable 6; http://links.lww.com/EDE/B710). The exceptions to this were the results concerning α- and β-adrenoceptor blockers after adjustment for age. Patients taking these drug classes had among the oldest and youngest median ages at index, respectively

Table.Characteristics of Patients in the Main Analysis by Exposure and in the Whole Sample

	α-Adrenoceptor Blockers	Angiotensin II Receptor Blockers	Angiotensin-converting Enzyme Inhibitors	β-Adrenoceptor Blockers	Calcium-channel Blockers	Diuretics	Vasodilator Antihypertensives	Whole Sample
Sample size	67,360	14,717	195,891	240,864	139,730	180,946	9,870	849,378
Median year of first prescription	2008	2005	2007	2005	2008	2003	2008	2006
Male sex	97% (65,365)	55% (8,141)	58% (113.667)	43% (104,096)	49% (68,739)	36% (65,177)	99% (9,796)	51% (434,981)
Median age at first prescription	65	59	59	55	64	66	57	61
Previous history of coronary artery disease	0.2% (129)	0.6% (85)	0.8% (1536)	0.9% (2056)	0.4% (562)	0.1% (203)	0.1% (11)	0.5% (4582)
Previous history of coronary bypass surgery	0.3% (193)	0.3% (45)	0.5% (946)	0.5% (1,262)	0.3% (418)	0.1% (265)	0.1% (14)	0.4% (3,143)
Previous history of cerebrovascular disease	2.0% (1,319)	2.1% (311)	3.0% (5,813)	1.4% (3,387)	2.3% (3,194)	2.8% (5,090)	0.7% (73)	2.3% (19,187)
At least one comorbidity on the Charlson index[a]	37% (24,817)	42% (6,238)	51% (99,492)	26% (62,604)	39% (54,081)	36% (65,212)	43% (4,207)	37% (316,651)
Median Index of Multiple Deprivation 2010 score[b]	8	8	9	9	9	9	8	9
Mean annual consultation rate (SD)	5.6 (5.4)	6.1 (6.3)	6.1 (6.0)	5.8 (5.3)	5.9 (5.8)	6.0 (5.6)	5.5 (5.1)	5.9 (5.7)
Ever drinker[c]	89% (60,070)	85% (12,538)	86% (167,636)	86% (207,457)	85% (118,104)	84% (152,473)	92% (9,059)	86% (727,337)
Ever smoker[d]	55% (36,691)	53% (7,729)	54% (105,401)	54% (130,894)	53% (74,540)	55% (99,793)	58% (5,688)	54% (460,736)
Mean body mass index (standard deviation)[e]	26.5 (4.2)	28.6 (5.7)	29.0 (5.9)	26.6 (5.0)	27.5 (5.4)	27.5 (5.5)	27.3 (4.4)	27.5 (5.4)
Same antihypertensive after 5 y	24% (15,877)	45% (6,575)	34% (66,639)	28% (67,705)	29% (39,879)	39% (70,446)	13% (1,267)	32% (268,388)

[a]A classification of 17 chronic diseases that may alter mortality risk.
[b]A proxy for socioeconomic position that is measured as "twentiles" (1 = least deprived and 20 = most deprived). Index of Multiple Deprivation 2010 score was missing for 39% (328,233) of the whole sample.
[c]Missing for 16% (132,387) of the whole sample. For this table, it has been classified as "ever" (i.e., former or current) vs. "never".
[d]Missing for 6.4% (54,447) of the whole sample. For this table, it has been classified as "ever" (i.e., former or current) vs. "never".
[e]Either calculated from height and weight measurements or provided. Missing for 16% (128,830) of the whole sample.

(Table), which may explain why they were most affected by the adjustment.

Sensitivity Analyses

The dementia subtype analyses revealed some variation in the effect for some drug classes (eFigure 9; http://links.lww.com/EDE/B711 and eTable 7; http://links.lww.com/EDE/B710). For example, diuretics were estimated to result in 14 (95% CI = 7, 20) additional cases of dementia per 1000 individuals treated but had little effect on vascular and other dementias. However, other drug classes, such as α-adrenoceptor blockers, were very consistent in their estimated effect on all outcomes. This sensitivity analysis is limited by the fact that distinguishing dementia subtypes is difficult, and so there is the potential for outcome misclassification. The other sensitivity analyses also had mixed effects across drug classes (eFigure 10; http://links.lww.com/EDE/B711 and eTable 8; http://links.lww.com/EDE/B710). For instance, results of two of the five sensitivity analyses were concordant with the main analysis for α-adrenoceptor blockers. The remaining three sensitivity analyses were suggestive of bias by age, as restricting the analysis to those aged 55 years and older or including adjustment for age and socioeconomic position led the estimates to be discordant with the main analysis. Despite this, other drug classes, such as the angiotensin-converting enzyme inhibitors and diuretics, had consistent estimates, regardless of the sensitivity analyses performed. For the final sensitivity analysis, we performed the Sargan–Hansen test to assess whether over-identification was likely to have affected our results (eTable 9; http://links.lww.com/EDE/B710). The test found little evidence to suggest this was the case, increasing our confidence that the ordinal instrument used in this study was appropriate.

DISCUSSION

Principal Findings

We report a systematic assessment of antihypertensive drug classes as candidates for the prevention of dementia, using physicians' prescribing preference as an instrument in

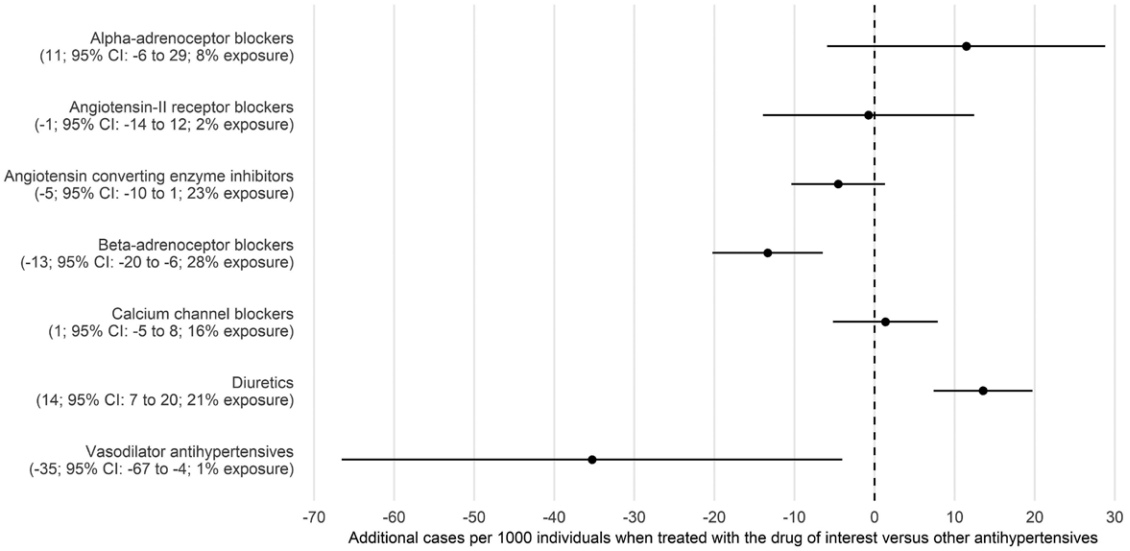

Figure 2. Instrumental variable estimates for the number of additional cases of dementia per 1000 individuals treated with each antihypertensive drug class versus all other antihypertensive drug classes.

the CPRD. In our study, β-adrenoceptor blockers and vasodilator antihypertensives showed negative associations with risk of dementia when compared with other antihypertensive drug classes in this study, while diuretics showed a positive association with risk. Diuretics work by increasing the amount of urine produced by the body. Differences in serum uric acid—a metabolite removed from the body in urine—have previously been observed between dementia patients and controls, though the evidence as a whole for dementia is mixed.[55] Vasodilator antihypertensives, which—unlike the diuretics—showed an imprecise negative association with the risk of dementia outcomes when compared with other antihypertensive drug classes, act on resistance vessels by relaxing their vascular smooth muscle.[56] Consequently, their effect on dementia may be related to increased blood flow and reduced vascular burden. An important consideration in the evaluation of these drugs, and other antihypertensives, is whether they cross the blood–brain barrier, as this is likely to be relevant to their utility in dementia prevention.

Comparison with Existing Literature

There have been no RCTs published to date that have directly compared antihypertensive drug classes with each other for the prevention or treatment of Alzheimer disease. However, the Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension trial compared the effect of intensive versus standard blood pressure control on probable dementia, mild cognitive impairment, and a composite outcome combining these outcomes. The trial, which combined antihypertensive medications, found intensive blood pressure control to be beneficial for the mild cognitive impairment and composite outcomes. It also reported a hazard ratio of 0.83 (95% CI = 0.67, 1.04) for the probable dementia outcome but suggested analysis of this outcome may have been underpowered due to the early termination of the trial.

A meta-analysis by Larsson et al.[10] identified seven prospective observational studies that have compared antihypertensives against each other.[10–17] Two of these studies also make use of the CPRD (eText 4; http://links.lww.com/EDE/B711).[13,16] Among the studies identified by Larsson et al.[10] Davies et al.[13] estimated angiotensin II receptor blockers to have a relative risk of 0.55 (95% CI = 0.49, 0.62), and Hwang et al.[17] estimated calcium-channel blockers to have a relative risk of 0.81 (95% CI = 0.75, 0.87) when compared with other antihypertensives for dementia prevention. These relative risks correspond to −13 (95% CI = −15, −11) additional cases per 1000 for angiotensin II receptor blockers and −6 (95% CI = −7, −4) for calcium-channel blockers (see eText 5; http://links.lww.com/EDE/B711 for estimate conversion).[57] In contrast to this, our analysis estimated that β-adrenoceptor blocker and vasodilator antihypertensives were among the most protective drug classes when compared with other antihypertensives. The major difference between our study and those previously conducted is the statistical methods used. When the analysis assumptions are met, instrumental variable analysis should not be subject to unmeasured confounding, which the other analyses may have been susceptible to.

Limitations

A limitation of this study is we cannot prove that the instrumental variable assumptions hold. The only assumption that can be empirically tested is relevance, i.e., the instrument is associated with the rates of prescribing. Our instruments had a minimum F statistic of 4,702 in the main analyses, demonstrating a strong association with the exposure. In addition, by defining our instrument using the past seven prescriptions as opposed to the last prescription issued, we are potentially

weakening our instrument, as older prescriptions may be less relevant to the present patient. Our study may also have been subject to bias amplification, where the use of a weak instrument amplifies bias caused by violation of the independence assumption.[33] We have tried to minimize the effect of this phenomenon in our bias assessment by accounting for the instrumental variable analysis scaling factor. Further to this, our study may have misclassified the exposure due to the use of the intention-to-treat framework, which defines exposure based on the first treatment prescribed. However, the benefits of this approach—such as preserving sample size and minimizing immortal time bias—outweigh the concerns. Related to misclassified exposures, there is also the potential for misclassified outcomes due to the difficulties associated with dementia diagnosis. This is less of a concern for the main analysis that considers all dementia subtypes together but should be considered when making inferences based on the dementia subtype analyses. Finally, this study does not make use of the time-to-event data available from the CPRD, which could be explored in the future using the instrumental variable estimation in a survival context models proposed by Tchetgen Tchetgen.[58]

CONCLUSIONS AND IMPLICATIONS

This study provides new evidence about the potential effects of antihypertensives on the risk of dementia through the novel application of non-genetic instrumental variable analysis to this research question. There were small differences in estimated effects on risk of dementia between drug classes. For example, we estimated that β-adrenoceptor blockers resulted in 13 (95% CI = 6, 20) fewer cases of any dementia compared with other antihypertensive drugs per 1000 people treated. However, we found that the magnitude of the differences between drug classes was smaller than many observational studies have previously reported. Future research should identify potential sources of unmeasured confounding that may have affected previous observational studies to understand this inconsistency. This may also provide a stimulus for more in-depth investigations of the related biological mechanisms, which will in turn inform the study of both the disease process and potential drug targets for dementia prevention.

ACKNOWLEDGMENTS

This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone.

REFERENCES

1. Jobke B, McBride T, Nevin L, et al; as the PLOS Medicine Editors. Setbacks in Alzheimer research demand new strategies, not surrender. *PLoS Med*. 2018;15:e1002518.
2. Appleby BS, Cummings JL. Discovering new treatments for Alzheimer's disease by repurposing approved medications. *Curr Top Med Chem*. 2013;13:2306–2327.
3. Corbett A, Pickett J, Burns A, et al. Drug repositioning for Alzheimer's disease. *Nat Rev Drug Discov*. 2012;11:833–846.
4. Abell JG, Kivimäki M, Dugravot A, et al. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. *Eur Heart J*. 2018;39:3119–3125.
5. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia: a double edged sword. *Ageing Res Rev*. 2009;8:61–70.
6. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005;4:487–499.
7. Kehoe PG, Miners S, Love S. Angiotensins in Alzheimer's disease—friend or foe? *Trends Neurosci*. 2009;32:619–628.
8. Kehoe PG, Passmore PA. The renin-angiotensin system and antihypertensive drugs in Alzheimer's disease: current standing of the angiotensin hypothesis? *J Alzheimers Dis*. 2012;30(suppl 2):S251–S268.
9. Wright AK, Kontopantelis E, Emsley R, et al. Life expectancy and cause-specific mortality in type 2 diabetes: a population-based cohort study quantifying relationships in ethnic subgroups. *Diabetes Care*. 2017;40:338–345.
10. Larsson SC, Markus HS. Does treating vascular risk factors prevent dementia and Alzheimer's disease? A systematic review and meta-analysis. *J Alzheimers Dis*. 2018;64:657–668.
11. Ohrui T, Matsui T, Yamaya M, et al. Angiotensin-converting enzyme inhibitors and incidence of Alzheimer's disease in Japan. *J Am Geriatr Soc*. 2004;52:649–650.
12. Sink KM, Leng X, Williamson J, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med*. 2009;169:1195–1202.
13. Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM. Associations of antihypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *J Alzheimers Dis*. 2011;26:699–708.
14. Li NC, Lee A, Whitmer RA, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ*. 2010;340:b5465.
15. Hsu CY, Huang CC, Chan WL, et al. Angiotensin-receptor blockers and risk of Alzheimer's disease in hypertension population—a nationwide cohort study. *Circ J*. 2013;77:405–410.
16. Goh KL, Bhaskaran K, Minassian C, Evans SJ, Smeeth L, Douglas IJ. Angiotensin receptor blockers and risk of dementia: cohort study in UK Clinical Practice Research Datalink. *Br J Clin Pharmacol*. 2015;79:337–350.
17. Hwang D, Kim S, Choi H, et al. Calcium-channel blockers and dementia risk in older adults—National Health Insurance Service—senior cohort (2002-2013). *Circ J*. 2016;80:2336–2342.
18. Hernán MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology*. 2006;17:360–372.
19. Hernán MA, Robins JM. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC. 2020.
20. Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ*. 2007;176:627–632.
21. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med*. 2005;353:2335–2341.
22. Davies NM, Gunnell D, Thomas KH, Metcalfe C, Windmeijer F, Martin RM. Physicians' prescribing preferences were a potential instrument for patients' actual prescriptions of antidepressants. *J Clin Epidemiol*. 2013;66:1386–1396.
23. Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med*. 2008;358:771–783.
24. Taylor GMJ, Taylor AE, Thomas KH, et al. The effectiveness of varenicline versus nicotine replacement therapy on long-term smoking cessation in primary care: a prospective cohort study of electronic medical records. *Int J Epidemiol*. 2017;46:1948–1957.

25. NHS. Patient Information—Choice of GP Practice. Available at: https://assets.nhs.uk/prod/documents/141230-patient-information-choice-of-gp-practice.pdf.
26. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep*. 2015;2:221–228.
27. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol*. 2015;44:827–836.
28. Walker V, Davies N, Kehoe P, Martin R. CPRD codes: neurodegenerative diseases and commonly prescribed drugs, University of Bristol. 2017. Available at: https://doi.org/10.5523/bris.1plm8il42rmlo2a2fqwslwckm2.
29. Walker VM, Davies NM, Jones T, Kehoe PG, Martin RM. Can commonly prescribed drugs be repurposed for the prevention or treatment of Alzheimer's and other neurodegenerative diseases? Protocol for an observational cohort study in the UK Clinical Practice Research Datalink. *BMJ Open*. 2016;6:e012044.
30. BNF Legacy. BNF July 2017: BNF Legacy. Available at: https://www.medicinescomplete.com/mc/bnflegacy/64/. Accessed 16 February 2018.
31. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183:758–764.
32. Royston P. *ICE: Stata Module for Multiple Imputation of Missing Values. Statistical Software Components*. Boston College Department of Economics. 2014.
33. Jackson JW, Swanson SA. Toward a clearer portrayal of confounding bias in instrumental variable applications. *Epidemiology*. 2015;26:498–504.
34. Davies NM, Thomas KH, Taylor AE, et al. How to compare instrumental variable and conventional regression analyses using negative controls and bias plots. *Int J Epidemiol*. 2017;46:2067–2077.
35. Brookhart MA, Wang PS, Solomon DH, Schneeweiss S. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. *Epidemiology*. 2006;17:268–275.
36. Brookhart MA, Schneeweiss S. Preference-based instrumental variable methods for the estimation of treatment effects: assessing validity and interpreting results. *Int J Biostat*. 2007;3:Article 14.
37. Baum CF, Schaffer ME, Stillman S. ivreg2: Stata module for extended instrumental variables/2SLS, GMM and AC/HAC, LIML and k-class regression. 2010. Available at: http://ideas.repec.org/c/boc/bocode/s425401.html. Accessed 9 November 2017.
38. Clarke PS, Windmeijer F. Instrumental variable estimators for binary outcomes. *J Am Stat Assoc*. 2012;107:1638–1652.
39. Imbens GW, Angrist JD. Identification and estimation of local average treatment effects. *Econometrica*. 1994;62:467–475.
40. Davies NM, Smith GD, Windmeijer F, Martin RM. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology*. 2013;24:363–369.
41. StataCorp. *Stata Statistical Software*. College Station, TX: StataCorp LP; 2015.
42. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing.
43. The National Institute for Health and Care Excellence. Beta-adrenoceptor blocking drugs. Available at: https://bnf.nice.org.uk/treatment-summary/beta-adrenoceptor-blocking-drugs.html. Accessed 19 March 2018.
44. CPRD @ Cambridge–Code Lists. Primary Care Unit. Available at: http://www.phpc.cam.ac.uk/pcu/cprd_cam/codelists/. Accessed 19 March 2018.
45. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. 2011. Available at: http://www.nice.org.uk/guidance/cg127/resources/hypertension-in-adults-diagnosis-and-management-35109454941637. Accessed 2 June 2017.
46. Kehoe PG, Blair PS, Howden B, et al. The rationale and design of the reducing pathology in Alzheimer's disease through Angiotensin targeting (RADAR) trial. *J Alzheimers Dis*. 2018;61:803–814.
47. Gunasekara FI, Richardson K, Carter K, Blakely T. Fixed effects analysis of repeated measures data. *Int J Epidemiol*. 2014;43:264–269.
48. Lad M. The English Indices of Deprivation 2010. 2011. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/6871/1871208.pdf. Accessed 22 January 2019.
49. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
50. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Fam Pract*. 2010;11:1.
51. Labrecque J, Swanson SA. Understanding the assumptions underlying instrumental variable analyses: a brief review of falsification strategies and related tools. *Curr Epidemiol Rep*. 2018;5:214–220.
52. Glymour MM, Tchetgen Tchetgen EJ, Robins JM. Credible Mendelian randomization studies: approaches for evaluating the instrumental variable assumptions. *Am J Epidemiol*. 2012;175:332–339.
53. Bonet B. Instrumentality tests revisited. In *Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence*. San Francisco, CA: Morgan Kaufmann Publishers; 2001, pp. 48–55.
54. Swanson SA, Miller M, Robins JM, Hernán MA. Definition and evaluation of the monotonicity condition for preference-based instruments. *Epidemiology*. 2015;26:414–420.
55. Mousavi M, Jonsson P, Antti H, et al. Serum metabolomic biomarkers of dementia. *Dement Geriatr Cogn Dis Extra*. 2014;4:252–262.
56. Jackson RE, Bellamy MC. Antihypertensive drugs. *Contin Educ Anaesth Crit Care Pain*. 2015;15:280–285.
57. BMJ Best Practice. How to calculate risk. Available at: https://bestpractice.bmj.com/info/toolkit/learn-ebm/how-to-calculate-risk/ Accessed 8 August 2019.
58. Tchetgen Tchetgen EJ, Walter S, Vansteelandt S, Martinussen T, Glymour M. Instrumental variable estimation in a survival context. *Epidemiology*. 2015;26:402–410.