Journal of Alzheimer's Disease 26 (2011) 699–708
DOI 10.3233/JAD-2011-110347
IOS Press

Associations of Anti-Hypertensive Treatments with Alzheimer's Disease, Vascular Dementia, and Other Dementias

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Handling Associate Editor: Francesco Panza

Accepted 9 May 2011

Abstract. We investigated whether angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACE-Is) are more strongly associated with Alzheimer's disease (AD), vascular dementia (VaD), and other dementias, than other anti-hypertensive drugs. We conducted a nested case-control analysis within the UK general practice research database, with prospectively recorded anti-hypertensive prescribing data. We sampled cases aged ≥60 years and diagnosed between 1997–2008 (5,797 with AD, 2,186 with VaD, 1,214 with unspecified/other dementia) which were matched to up to four controls by age, general practice and gender. We computed odds-ratios and dose response effects for AD, vascular and unspecified/other dementia, comparing those prescribed ARBs or ACE-Is for at least six months with patients prescribed other anti-hypertensives. We controlled for matching factors, co-morbidities, smoking status, an area measure of socioeconomic status, consultation rate and blood pressure and accounted for reverse causality by introducing time-lags of up to eight years prior to diagnosis/index date. Patients diagnosed with AD, vascular and unspecified/other dementia had fewer prescriptions for ARBs and ACE-Is. Inverse associations with AD were strongest for ARBs (odds-ratio; 0.47, 95%CI: 0.37–0.58) compared with ACE-Is (odds-ratio; 0.76, 95%CI: 0.69–0.84) ($p_{difference} < 0.001$). Associations of ARBs with AD were stronger than for vascular dementia ($p_{difference} = 0.01$) and unspecified/other dementia ($p_{difference} = 0.23$). There were inverse dose-response relationships between ARBs and ACE-Is with AD (both $p_{trend} < 0.01$). The inverse association of ACE-Is with AD diminished when using longer time lags but the ARB-AD association persisted. Patients with AD were around half as likely to be prescribed ARBs. Further randomized controlled trial evidence is required to rigorously test these findings.

Keywords: All cognitive disorders/dementia, Alzheimer's disease, case control studies, risk factors in epidemiology, vascular dementia

Supplementary data available online: http://www.j-alz.com/issues/26/vol26-4.html#supplementarydata04

INTRODUCTION

Alzheimer's disease (AD) and vascular dementia (VaD) are common forms of dementia. AD has characteristic neuropathological hallmarks of cortical and cerebrovascular deposits comprised mainly

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of amyloid-β (Aβ) peptides and intracellular neurofibrillary tangles comprised of hyperphosphorylated forms of microtubule-associated tau protein [1]. VaD pathology is more heterogeneous and results from various forms of cerebral ischemic disease and damage and diminished cerebral blood flow due to cardiac function abnormalities [2]. AD and VaD often coexist as a mixed dementia [3], thereby complicating diagnosis [2]. Hypertension is a risk factor for dementia. While anti-hypertensive drugs reduce VaD risk [4], the association between hypertension and AD appears more complicated [5, 6]. Observed reductions in cerebral blood flow [7, 8] may be secondary to AD [9], microvascular abnormalities may precede neuropathology [1, 10], and intra-arterial infusion of Aβ raises blood pressure in normotensive or naturally hypertensive rats [11]. Additionally, a number of reported Aβ-degrading enzymes, also important in vasoregulation, have altered behavior in postmortem brain tissue [5, 12].

Angiotensin-1 converting enzyme-inhibitors (ACE-Is) reduce blood pressure by reducing both the formation of the vasoconstrictor angiotensin II and the degradation of the vasodilator bradykinin. Reported associations with dementia has been inconsistent; some studies suggest modest cognitive benefits in mild cognitive impairment [5, 12] or AD [5] while others show an increased risk of dementia and disability [5]. The latter adverse associations are consistent with genetic, biochemical, and neuropathological evidence that ACE-Is may contribute to Aβ-related pathology in AD because ACE reputedly degrades Aβ [5]. In contrast, the newer angiotensin II receptor blockers (ARBs), which block angiotensin II signaling rather than its production, are therefore 'ACE sparing' and theoretically preserve ACE's proposed Aβ-degrading function while still being anti-hypertensive. ARBs protect against both cognitive deficits and Aβ related pathology in animal models of AD [5]. In one small trial, elderly hypertensive patients treated with losartan (an ARB) had better cognitive outcomes than atenolol-treated patients [13], while more recent observational data suggested ARBs were associated with lower rates of dementia incidence and slower progression of AD compared to lisinopril (an ACE-I) and other anti-hypertensive treatments [14].

We conducted a case-control study nested with UK primary care data to examine associations of ARBs and ACE-Is with AD and VaD. Our study improves on previous observational studies, by controlling for possible confounders including blood pressure, which may determine the type of anti-hypertensive prescribed, and protopathic bias [15]. We hypothesized *a priori* that AD would be more strongly associated with ARBs than ACE-Is, compared to other anti-hypertensives, and the associations would be strongest for diagnoses of AD compared to non-specific dementia or VaD.

METHODS

We conducted a case-control study nested within the United Kingdom (UK) General Practice Research Database (GPRD), an anonymized database holding longitudinal administrative, clinical and prescribing records of 10.6 million patients, from 593 general practices across the UK [16]. Data collected include demography, general practitioner consultations (GP), test results, diagnoses from primary and secondary care, prescriptions issued and outpatient clinic referrals. Participating GPs are required to meet specified quality criteria for research purposes. Diagnoses were recorded using the Oxford Medical Information System (OXMIS) or Read codes and prescriptions were coded using multilex product codes. Previous studies have confirmed the quality of GPRD data and recording of clinical [17], prescribing, and dementia diagnoses data [18].

Patient selection

Cases were defined as a patients aged over 60 years with a diagnosis of AD, VaD, or unspecified/other dementia based on OXMIS/Read codes in the referral or clinical files, first diagnosed between 01/01/1997–15/10/2008. We allocated cases to one of four categories of dementia: probable AD; possible AD; VaD; combined unspecified or other dementia. The OXMIS/Read codes defining dementia ranged from highly specific codes (e.g., AD) to uncertain codes (e.g., unspecified dementia) (see Supplementary Table 1 code lists; available online: http://www.j-alz.com/issues/26/vol26-4.html#supplementarydata04). Some patients had more than one dementia diagnosis, so we developed a decision hierarchy for allocating final diagnosis. Possible AD was allocated to patients with non-specific codes for AD and no records indicating either VaD or specific codes for AD or other specific dementia diagnosis. We assumed that letters between clinicians would provide more precise diagnoses; hence for patients with records indicating diagnoses of VaD and probable AD, we used referral diagnoses over the primary care diagnosis. If there were multiple inconsistent diagnoses, the most recent

Table 1
Characteristics of participants analyzed in study. Values are numbers (proportions) unless stated otherwise

	Probable Alzheimer's disease	Possible Alzheimer's disease	Probable vascular dementia	Unspecified or other dementia	Total with dementia	Controls
N	2,227	3,570	2,186	1,214	9,197	39,166
Mean age, years (SD)	81.5 (6.8)	83.3 (6.9)	81.4 (6.9)	82.1 (7.6)	82.2 (7.0)	82.2 (6.8)
Male	617 (0.28)	1,082 (0.30)	898 (0.41)	436 (0.36)	3,033 (0.33)	13,015 (0.33)
Number of consultations (SD)	256.1 (136)	246.7 (137)	284.1 (148)	277.1 (150)	261.9 (142)	240.3 (135)
Comorbidities						
Coronary heart disease	669 (0.30)	1,175 (0.33)	834 (0.38)	428 (0.35)	3,106 (0.34)	12,938 (0.33)
Diabetes	268 (0.12)	501 (0.14)	402 (0.18)	192 (0.16)	1,363 (0.15)	5,629 (0.14)
Stroke	315 (0.14)	918 (0.26)	882 (0.40)	300 (0.25)	2,415 (0.26)	7,091 (0.18)
Systolic blood pressure,[a] mmHg (SD)	149.3 (18.0)	150.8 (18.8)	149.4 (18.7)	147.5 (18.2)	149.7 (18.6)	150.9 (19.1)
Diastolic blood pressure,[b] mmHg (SD)	81.7 (9.4)	81.7 (10.3)	81.5 (9.8)	80.3 (10.2)	81.5 (10.0)	81.6 (10.4)
Ever on:						
ACE-I[c]	734 (0.33)	1,225 (0.34)	841 (0.38)	451 (0.37)	3,251 (0.35)	14,794 (0.38)
ARB[c]	89 (0.04)	143 (0.04)	123 (0.06)	60 (0.05)	415 (0.05)	2,741 (0.07)
CC-blocker	885 (0.40)	1,446 (0.41)	1,007 (0.46)	505 (0.42)	3,843 (0.42)	17,451 (0.45)
Beta-blocker	921 (0.41)	1,365 (0.38)	956 (0.44)	501 (0.41)	3,743 (0.41)	16,263 (0.42)
Thiazide diuretic	1,117 (0.50)	1,812 (0.51)	1,067 (0.49)	614 (0.51)	4,610 (0.50)	20,792 (0.53)
Other	219 (0.10)	350 (0.10)	256 (0.12)	134 (0.11)	959 (0.10)	4,660 (0.12)

[a]$n = 48{,}363$; [b]$n = 48{,}328$; [c]Exposures split into two groups: ever on ACE-Is or ever on ARBs. Patients exposed to both ACE-Is and ARBs were excluded; however it is possible for patients to also have been prescribed other anti-hypertensive medication. The other anti-hypertensive groups are not exclusive; hence it is possible, for example, for a patient to be both in the calcium channel (CC)-blocker group and the beta-blocker group, and the total numbers ever on antihypertensive drugs can exceed the total N in row 1.

diagnosis was used and diagnoses date was defined using the first record indicating any dementia.

We matched up to four controls aged over 60 years to each case by age (±5 years), practice, and gender. Each control was assigned an index date (equivalent to the diagnosis date for cases) matched to their respective case. All cases and controls must have registered with the practice at least five years before the diagnosis/index date.

Data analysis

We derived exposure to anti-hypertensive drugs from GPRD therapy files. These included data on the preparations prescribed, date of prescription, strength, daily dose, and the total quantity of tablets prescribed. We ascertained: i) whether patients were ever prescribed an anti-hypertensive drug; and ii) the total number of defined daily doses (DDD - as defined by the World Health Organization (WHO)) of each of these drugs prescribed prior to the index date [19]. We converted each prescription into DDDs according to WHO parameters: for example, atenolol's DDD is 75 mg; therefore a 30 day course of 75 mg has a total exposure of 30 DDDs; each patient's cumulative dose was then defined as their total DDDs/365.25. Only prescription records with over 80% treatment coverage in the following six months (to ensure patients had long-term exposure) were included in the analyses. We defined the exposure to be mutually exclusive: patients categorized as ever prescribed 'ACE-Is' must never have been prescribed ARBs; patients categorized as ever prescribed 'ARBs' patients must never have been prescribed ACE-Is; to be in the 'other anti-hypertensives' category, a patient could never have been prescribed an ARB or an ACE-I. Patients prescribed both ARBs and ACE-Is were excluded ($n = 2{,}022$) from all analyses.

We included the following confounding factors defined prior to the index date: matching factors (age at index date, gender, and geographical region); number of consultations; co-morbidities (diabetes, stroke and coronary heart disease); smoking (ever/never); and a time weighted average of all available systolic blood pressure measurements. A census-based measure of area deprivation (Index of Multiple Deprivation), as a proxy for individual socio-economic status or educational level, based on patients' addresses, was available for approximately 50% of GP practices.

We restricted all our analyses to the sub-group of cases and controls ever treated with an anti-hypertensive drug to confine the sample to patients with similar indications for treatment, which may also be risk factors for dementia [20, 21]. We examined associations of ever prescribed ACE-Is or ARBs versus other anti-hypertensives with probable AD, possible AD, VaD, and unspecified and other dementia using uncon-

ditional logistic regression. We used unconditional rather than conditional logistic regression to maximize the power of the study, as restricting our analysis to patients ever treated with an anti-hypertensive drug considerably reduced the number of matched sampled case-control pairs that could be included in a conditional analysis. However, as a sensitivity analysis we also investigated associations using conditional logistic regression. Our basic model controlled for the matching variables (age, gender, and region) and our fully-adjusted model also controlled for number of GP consultations, a weighted average of systolic blood pressure measurements and a history of diabetes, stroke or coronary heart disease. For each outcome we tested for differences in the odds-ratios for ACE-Is compared with ARBs [22]. We conducted a dose response analysis by categorizing patients who had ever received an ACE-I or ARB into quartiles of DDDs of exposure and used the lowest DDD quartile as the reference group. We tested for evidence of a linear dose response using the Wald test on the quartiles of exposure entered as a linear variable and tested the assumption of linearity using the likelihood ratio test (based on fully adjusted models, null hypothesis is no difference between linear trend and quartile of exposure entered as indicator variables).

The onset of neuropathology underling dementia occurs many years before diagnosis [3, 23]. These initial clinically undetectable changes may influence behavior, including treatment compliance and attendance at consultations, leading to differences in anti-hypertensive prescribing in cases versus controls (protopathic bias) [15, 21]. To address this possibility, we repeated our analyses introducing time lags of up to eight years prior to the index date. A time lag of one year ignored all prescriptions in the year prior to the diagnosis/index data; a lag of two years ignores those two years prior to the index date etc. Therefore, differences in exposure due to behavioral changes prior to diagnosis should be reduced.

We tested for an interaction with age (dichotomized as below or above 80 years as the median value) using likelihood ratio tests. We also repeated the analyses on patients only exposed to ARBs or ACE-Is as sole-therapy, excluding patients ever treated with any other anti-hypertensive drug. This post-hoc analysis tested the possibility that our results were due to patients with a reduced risk of developing AD being more likely to report side effects with other anti-hypertensive medication and hence being switched to ARBs or ACE-Is. We also repeated the analysis classifying exposure based on the first prescription received (ARBs or ACE-Is versus other antihypertensives as initial therapy regardless of future therapy) in order to investigate whether immortal time bias could explain our findings [24]. Analyzes were conducted using STATA SE10.1.

Standard protocol approvals, registrations, and patient consents.

The GPRD has obtained approval from the Trent Multi-Centre Research Ethics Committee for the provision of anonymized data for use in observational epidemiology. The study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research.

RESULTS

There were a total of 20,021 cases and 77,475 controls, of which 9,197 (46%) cases and 39,166 (51%) controls were on anti-hypertensive treatment. Amongst those on anti-hypertensive treatment, 2,227 patients were categorized as probable AD; 3,570 possible AD; 2,186 probable VaD; and 1,214 as unspecified or other dementia group (Table 1). Coronary heart disease, stroke, and diabetes co-morbidity were more common in patients with probable VaD compared to those with probable AD or controls (all p values < 0.001). There was little difference in mean blood pressure across the different groups. Treatment with ACE-Is was more common in patients with probable VaD (38%) and controls (38%) than probable AD (33%). Treatment with ARBs was more common in controls (7%) than those who developed probable AD (4%).

In fully-adjusted models, patients ever prescribed either ARBs or ACE-Is were less likely to develop probable AD, possible AD, VaD, and unspecified/other dementia than patients ever prescribed other anti-hypertensive drugs (Table 2). Fewer patients ever prescribed ARBs developed AD (fully adjusted odds ratio (OR); 0.47, 95%CI: 0.37–0.58) compared with other anti-hypertensive drugs. The association was weaker with ACE-Is (OR; 0.76, 95%CI: 0.69–0.84) (test for difference between ARB and ACE-I associations $p < 0.001$) [22]. Associations of ARBs with AD were stronger than for VaD ($p_{difference} = 0.01$) and unspecified/other dementia ($p_{difference} = 0.12$); in contrast there was little statistical evidence that associations of ACE-Is with AD were stronger than for unspecified/other dementia ($p_{difference} = 0.15$) and VaD ($p_{difference} = 0.22$). The fully adjusted model hardly differed from the basic adjusted associations for probable

Table 2
Association of ACE-Is and ARBs with dementia outcomes

	Exposed		Unexposed		Basic adjusted[a]		Fully adjusted[b]	
	Cases	Controls	Cases	Controls	OR (95% CI)	*P* value	OR (95% CI)	*P* value
ACE-Inhibitors versus other anti-hypertensives								
Probable Alzheimer's disease	734	14,794	1,404	21,631	0.77 (0.71–0.85)	<0.001	0.76 (0.69–0.84)	<0.001
Possible Alzheimer's disease	1,225	14,794	2,202	21,631	0.82 (0.77–0.89)	<0.001	0.80 (0.75–0.87)	<0.001
Probable vascular dementia	841	14,794	1,222	21,631	0.98 (0.89–1.07)	0.64	0.82 (0.75–0.91)	<0.001
Unspecified or other dementia	451	14,794	703	21,631	0.93 (0.82–1.05)	0.22	0.85 (0.75–0.96)	0.01
Any dementia	3,251	14,794	5,531	21,631	0.86 (0.82–0.90)	<0.001	0.80 (0.76–0.84)	<0.001
Angiotensin II receptor blockers versus other anti-hypertensives								
Probable Alzheimer's disease	89	2,741	1,404	21,631	0.49 (0.39–0.61)	<0.001	0.47 (0.37–0.58)	<0.001
Possible Alzheimer's disease	143	2,741	2,202	21,631	0.52 (0.44–0.62)	<0.001	0.51 (0.43–0.61)	<0.001
Probable vascular dementia	123	2,741	1,222	21,631	0.80 (0.66–0.97)	0.02	0.70 (0.57–0.85)	<0.001
Unspecified or other dementia	60	2,741	703	21,631	0.67 (0.51–0.88)	0.004	0.62 (0.47–0.81)	0.001
Any dementia	415	2,741	5,531	21,631	0.59 (0.53–0.66)	<0.001	0.55 (0.49–0.62)	<0.001

[a] Adjusted for age at index date, gender and region; [b] additionally adjusted for diabetes, stroke, coronary heart disease, number of consultations with GP prior to index date and blood pressure prior to index date. *Odds-ratio (OR).*

Table 3
Association between years of defined daily doses of ACE-Is and ARBs and dementia

	Years of DDD	Basic adjusted[a]		Fully adjusted[b]		*p*-value trend[c]
		ORs (95% CI)	*p*-value	ORs (95% CI)	*p*-value	
ACE-Is						
Probable or	0.003 to 0.85	1.00		1.00		
Possible	0.85 to 2.80	0.99 (0.87–1.13)	0.85	0.99 (0.87–1.13)	0.87	
Alzheimer's Disease	2.81 to 7.44	0.86 (0.75–0.98)	0.02	0.85 (0.74–0.97)	0.02	<0.001
(*n* = 16,753)	7.44 to 61.78	0.77 (0.68–0.89)	<0.001	0.75 (0.66–0.87)	<0.001	
Vascular	0.003 to 0.85	1.00		1.00		
Dementia	0.85 to 2.80	0.82 (0.67–1.00)	0.05	0.80 (0.66–0.98)	0.03	
(*n* = 15,635)	2.81 to 7.44	0.79 (0.65–0.97)	0.02	0.76 (0.62–0.92)	0.006	0.01
	7.44 to 61.78	0.85 (0.70–1.03)	0.10	0.76 (0.63–0.93)	0.008	
Unspecified	0.003 to 0.85	1.00		1.00		
or other	0.85 to 2.80	0.94 (0.72–1.23)	0.65	0.92 (0.70–1.21)	0.55	
dementia	2.81 to 7.44	1.04 (0.80–1.35)	0.77	1.00 (0.76–1.30)	0.98	0.26
(*n* = 15,245)	7.44 to 61.78	0.88 (0.67–1.15)	0.34	0.82 (0.62–1.08)	0.16	
Any	0.003 to 0.85	1.00		1.00		
dementia	0.85 to 2.80	0.94 (0.84–1.04)	0.24	0.93 (0.84–1.04)	0.20	
(*n* = 18,045)	2.81 to 7.44	0.86 (0.77–0.96)	0.007	0.84 (0.75–0.94)	0.002	<0.001
	7.44 to 61.78	0.81 (0.73–0.90)	<0.001	0.76 (0.68–0.85)	<0.001	
ARBs						
Probable or	0.009 to 0.73	1.00		1.00		
Possible	0.73 to 1.92	0.87 (0.60–1.24)	0.44	0.86 (0.60–1.23)	0.41	
Alzheimer's Disease	1.92 to 4.26	0.64 (0.43–0.93)	0.02	0.63 (0.43–0.93)	0.02	0.009
(*n* = 2,973)	4.26 to 23.00	0.67 (0.46–0.98)	0.04	0.64 (0.44–0.94)	0.02	
Vascular	0.009 to 0.73	1.00		1.00		
Dementia	0.73 to 1.92	1.03 (0.60–1.78)	0.92	1.03 (0.59–1.80)	0.93	
(*n* = 2,864)	1.92 to 4.26	1.37 (0.82–2.29)	0.23	1.45 (0.85–2.45)	0.17	0.63
	4.26 to 23.00	1.08 (0.63–1.85)	0.77	1.03 (0.59–1.78)	0.92	
Unspecified	0.009 to 0.73	1.00		1.00		
or other	0.73 to 1.92	0.88 (0.42–1.86)	0.74	0.93 (0.44–1.97)	0.85	
dementia	1.92 to 4.26	0.88 (0.42–1.85)	0.74	0.89 (0.42–1.88)	0.76	0.86
(*n* = 2,801)	4.26 to 23.00	0.97 (0.48–1.98)	0.94	0.94 (0.46–1.93)	0.87	
Any	0.009 to 0.73	1.00		1.00		
dementia	0.73 to 1.92	0.91 (0.68–1.22)	0.53	0.90 (0.67–1.21)	0.50	
(*n* = 3,156)	1.92 to 4.26	0.84 (0.63–1.13)	0.24	0.84 (0.63–1.13)	0.25	0.08
	4.26 to 23.00	0.81 (0.60–1.08)	0.16	0.76 (0.57–1.03)	0.08	

[a] Adjusted for age at index date, gender and region; [b] Adjusted additionally for diabetes, stroke, or coronary heart disease, and number of consultations with GP prior to index date and blood pressure prior to index date. [c] Wald test for linear trend in relation to exposure of quartiles of defined daily dose (DDD) years; analysis restricted to patients exposed to ACE-I or ARBs, respectively. Exposures were measured in DDD years. *Odds-ratio (OR).*

Table 4
Associations of ACE-Is with dementia after sequentially excluding all prescriptions between one to eight years prior to diagnosis (lags)

Lag years[a]	Exposed		Unexposed		ORs (95% CI)	*p*-value
	Cases	Controls	Cases	Controls		
Probable or possible Alzheimer's disease						
0	1,959	14,794	3,606	21,631	0.79 (0.74–0.83)	<0.001
1	1,826	13,229	3,614	21,781	0.83 (0.78–0.88)	<0.001
2	1,624	11,730	3,514	21,571	0.85 (0.79–0.91)	<0.001
3	1,428	10,265	3,437	21,080	0.86 (0.80–0.92)	<0.001
4	1,239	8,832	3,288	20,366	0.88 (0.82–0.94)	<0.001
5	1,068	7,392	3,105	19,530	0.92 (0.85–0.99)	0.03
6	883	6,071	2,897	18,114	0.92 (0.84–1.00)	0.04
7	723	4,881	2,638	16,585	0.94 (0.86–1.03)	0.17
8	586	3,942	2,360	14,791	0.94 (0.85–1.04)	0.22
Probable vascular dementia						
0	841	14,794	1,222	21,631	0.82 (0.75–0.91)	<0.001
1	800	13,229	1,227	21,781	0.89 (0.81–0.98)	0.02
2	711	11,730	1,215	21,571	0.90 (0.82–1.00)	0.05
3	619	10,265	1,198	21,080	0.90 (0.81–1.00)	0.05
4	536	8,832	1,183	20,366	0.90 (0.81–1.01)	0.06
5	445	7,392	1,145	19,530	0.89 (0.79–1.00)	0.06
6	373	6,071	1,055	18,114	0.92 (0.81–1.04)	0.20
7	312	4,881	974	16,585	0.95 (0.83–1.09)	0.50
8	254	3,942	897	14,791	0.94 (0.81–1.09)	0.45

[a]A time lag of one year ignores all prescriptions in the year prior to the diagnosis/index date; a lag of two years ignores prescriptions in the two years prior to the index date; and so on up to 8 years· All models are adjusted for age at index date, gender region, diabetes, stroke, or coronary heart disease, number of consultations with GP prior to index date and blood pressure prior to index date. *Odds-ratio (OR).*

and possible AD. However, after adjustment for confounders, inverse associations of ARBs and ACE-Is with VaD and unspecified/other dementia increased in magnitude beyond that observable by chance. Further adjustment for the index of multiple deprivation or smoking status had negligible impact on observed associations (Supplementary Tables 2 and 3). As there was little evidence of differences in associations for probable and possible AD outcomes ($p = 0.28$), we combined probable and possible AD into a single category in subsequent tables to enhance statistical power. We found evidence of a dose response relationship between DDDs of ACE-I and probable/possible AD ($p < 0.001$) (Table 3). Similarly, we found evidence of a dose response relationship between ARBs and probable/possible AD ($p = 0.009$) (Table 3); there was little evidence that these associations were non-linear (both $p > 0.26$). We also found evidence of a dose response relationship between DDDs of ACE-Is and VaD ($p = 0.01$), but this was not evident for ARBs ($p = 0.63$). We found no evidence of any interactions between exposure to either ARBs or ACE-Is and age and probable or possible AD (both LR-tests $p > 0.10$).

Tables 4 and 5 show the fully adjusted associations of ARBs and ACE-Is with probable or possible AD and VaD after the introduction of sequentially increasing time lag periods. The inverse association of ACE-Is with probable AD was increasingly attenuated with increased lags. In contrast, even after the introduction of lag times of eight years, the 50% reduction in risk of probable and possible AD associated with ARBs with remained (Table 5). There was little evidence of an association of ACE-Is or ARBs with VaD after the introduction of a lag time of at least two years.

Analyses using conditional logistic regression gave similar results. When we restricted the analyses to patients exposed either to ARBs or ACE-Is as sole-therapy (Supplementary Table 4), there was little evidence of an association of ACE-I sole-therapy (OR; 1.01, 95%CI, 0.91–1.12), but there was an inverse association of ARB sole-therapy (OR; 0.63, 95%CI, 0.45–0.88), with probable or possible AD. Results were similar when we classified exposure based on initial therapy received (OR for ACE-I as initial therapy = 1.04; 95%CI: 0.96–1.12; OR for ARB as initial therapy = 0.66; 95%CI: 0.50, 0.86).

DISCUSSION

This is the first large UK-based investigation of the association of anti-hypertensive medication expo-

Table 5
Associations of ARBs with dementia after sequentially excluding all prescriptions between one to eight years prior to diagnosis (lags)

Lag years[a]	Exposed		Unexposed		ORs (95% CI)	*p*-value
	Cases	Controls	Cases	Controls		
Probable or possible Alzheimer's disease						
0	232	2,741	3,606	21,631	0.49 (0.43–0.56)	<0.001
1	209	2,271	3,614	21,781	0.54 (0.47–0.63)	<0.001
2	176	1,789	3,514	21,571	0.59 (0.50–0.69)	<0.001
3	132	1,378	3,437	21,080	0.57 (0.48–0.69)	<0.001
4	90	979	3,288	20,366	0.56 (0.45–0.70)	<0.001
5	58	657	3,105	19,530	0.54 (0.41–0.71)	<0.001
6	34	418	2,897	18,114	0.50 (0.35–0.71)	<0.001
7	18	240	2,638	16,585	0.46 (0.28–0.75)	0.002
8	9	128	2,360	14,791	0.43 (0.22–0.84)	0.01
Probable vascular dementia						
0	123	2,741	1,222	21,631	0.70 (0.57–0.85)	<0.001
1	114	2,271	1,227	21,781	0.79 (0.65–0.97)	0.02
2	100	1,789	1,215	21,571	0.88 (0.71–1.09)	0.25
3	83	1,378	1,198	21,080	0.93 (0.74–1.18)	0.57
4	64	979	1,183	20,366	1.00 (0.77–1.31)	0.98
5	42	657	1,145	19,530	0.96 (0.69–1.33)	0.81
6	25	418	1,055	18,114	0.92 (0.61–1.39)	0.70
7	11	240	974	16,585	0.69 (0.37–1.27)	0.23
8	6	128	897	14,791	0.63 (0.28–1.46)	0.28

[a]A time lag of one year ignores all prescriptions in the year prior to the diagnosis/index data; a lag of two years ignores prescriptions in the two years prior to the index date; and so on up to 8 years. All models are adjusted for age at index date, gender region, diabetes, stroke, or coronary heart disease, number of consultations with GP prior to index date and blood pressure prior to index date. *Odds-ratio (OR).*

sure with risk of AD and other dementias in primary care. We tested whether ARBs had a stronger association with AD than ACE-Is or other anti-hypertensives and whether the association was specific to AD rather than VaD. This hypothesis was generated because of ARBs influence on two biological pathways. While both ARBs and ACE-Is reduce angiotensin II signaling, now believed to be involved in the pathobiology of AD [5], ARBs are unlikely to interrupt ACE-mediated Aβ degradation (unlike ACE-Is) [5]. These mechanisms of action suggest that ARBs may have benefits over ACE-Is in the etiology of AD [5].

We found that fewer patients prescribed ARBs and ACE-Is went on to develop probable AD. Patients taking ARBs and ACE-Is had 53% and 24% lower risks of AD respectively, compared to patients taking other anti-hypertensive medications in basic adjusted analyses. These associations did not differ by age, co-morbidities, and blood pressure, suggesting little confounding by observed co-morbidities. The inverse association was not specific, as those ever prescribed ACE-Is or ARBs were also less likely to develop VaD and adjustment for confounders strengthened these associations. However, associations of ARBs (but not ACE-Is) with AD were stronger than for VaD and unspecified/other dementia; this finding was supported by our time-lag models, where associations of ACE-Is with AD and VaD and ARBs with VaD, substantially reduced with longer lags while ARBs remained inversely associated with AD.

Our findings that ACE-Is are inversely associated with dementia are consistent with some but not all previous studies [5]. Some studies suggest that ACE-Is or specific types of ACE-Is may be positively associated with risk of dementia [5]. Very recently, in a largely male study population from the United States, patients prescribed ARBs were reported to have lower incidence and rate of progression of AD [14], and stronger associations were found for ARBs than either ACE-Is or other non-ACE-I/ARB anti-hypertensives, which is consistent with our results and other publications [4, 5, 13, 25–29]. Our results are consistent with some randomized controlled trial (RCT) evidence where patients treated with losartan for six months had better word recall than those prescribed the beta-blocker, atenolol [13]. Another RCT showed that valsartan improved word recall from baseline assessments, while there was no benefit for enalapril-treated patients [29].

That specific angiotensin II targeting drugs demonstrate protective effects on AD risk [13, 29] and general cognition supports the 'angiotensin II' hypothesis of AD [5] whereby ARBs and ACE-Is are protec-

tive by reducing angiotensin II-mediated inhibition of acetylcholine release [30–32]. However, recent publication of secondary outcome measures on cognitive impairment and cognitive decline in the much larger ONTARGET and TRANSCEND trials provide less convincing evidence [33]. For ONTARGET, there was weak evidence that the ARB telmisartan outperformed the ACE-I ramipril (OR of cognitive impairment 0.90, 95%CI: 0.80–1.01, $p = 0.06$). However, this was not replicated in the TRANSCEND study, a placebo-controlled RCT of telmisartan in ACE-I intolerant subjects (OR of cognitive impairment 0.97, 95%CI: 0.81–1.17, $p = 0.76$); a greater benefit might have been expected as the comparator was placebo. An accompanying commentary [34], highlighted that neither trial differentiated type of pathology; hence specific benefits for AD pathology would be attenuated, especially given that patient populations were selected for high cardiovascular disease risk which would increase the ratio of vascular to AD pathology. In addition, the mean age of patients in these trials was around 16 years younger than patients in our study, and the trials had a shorter follow-up period. AD pathology increases with age; hence our population should have lower cognitive reserve and greater AD pathology. Similar arguments apply to meta-analyses which suggest that ACEI/ARB regimes do not reduce dementia risk [35, 36]. Whether these methodological differences are sufficient to explain our discrepant findings and/or whether the results from the observational studies reflect uncontrolled confounding or other types of bias is uncertain (see below).

Our study has several strengths. It is the first large nationally representative study of primary care subjects with full prescribing histories and measurement of co-morbidities such as blood pressure for both males and females. We used patients' long-term prospective prescription histories, defining exposures using 5.92 million eligible prescriptions over 24 years. We included exposure time lags of up to eight years prior to diagnosis. We tested whether the associations between ACE-Is and ARBs were specific to AD, or whether fewer patients exposed to ARBs or ACE-Is also developed VaD. We were able to adjust for blood pressure prior to index date, which may be a strong determinant of prescribing decisions for type of anti-hypertensive. We estimated dose response associations between exposures and outcomes and assessed the specificity of the dose-response association with AD. Validation exercises have shown 80–90% agreement between a diagnosis of dementia in the GPRD database and diagnoses confirmed by correspondence with the GPs [37] or blinded medical record review [18].

There are several possible alternative explanations for our observed associations. Chance can be excluded given the precision of the results and the consistency with previous studies [14]. The prospective nature of exposure recording excludes recall bias. Confounding may explain discrepant findings between our observational results and the trial results. We controlled for several potential confounding factors. Critically, we adjusted for blood pressure history, but this adjustment did not meaningfully change the associations for AD. The sample was restricted to patients treated with anti-hypertensives; hence all patients should have similar indications for anti-hypertensive treatment. Adjusting for IMD (a proxy measure of individual level education and socioeconomic characteristics) and smoking behavior made little difference to the results. However, while GPRD has been shown to be relatively good in the recording of current smoking behavior, past smoking is less well recorded and so our results may be subject to some residual confounding due to smoking [38].

Our results may suffer from protopathic bias, in which pre-clinical manifestation of disease may determine exposure. We used two strategies to address this. First, examining time lags between exposure and disease assumed that persistent associations with incrementally larger lags were less likely to reflect pre-morbid disease. Our lagged sensitivity analyses suggested that the inverse association of ARBs with AD was robust, in contrast to the associations with VaD and between ACE-Is and AD. Second, we calculated associations for patients exposed to ARB or ACE-I sole-therapy to avoid any confounding due to drug tolerance and switching. There was evidence of an inverse association of ARB sole-therapy, but not ACE-I sole-therapy. Prescribing habits may have changed over time. If these changes are related to the likelihood of diagnosis or type of dementia diagnosis then this could bias the results. However, the robustness of the time lag associations between ARBs and AD makes this less likely.

Similarly, our other sensitivity analyses confirmed the consistency of association for ARBs even when we reclassified exposure based on sole or initial therapy only suggesting that immortal-time bias is unlikely to explain our findings. We are uncertain why associations between ACE-I and AD diminish with latency period though one potential explanation could be different prescribing patterns as regards centrally or peripherally acting ACE-Is. One previous study failed

to find association between ACE-Is (as a 'class') with incidence of AD but on sub-group analyses revealed lower risk of cognitive decline for centrally-acting ACE-Is while peripherally-acting ACE-Is were associated with increased risk of dementia and higher levels of disability [39]. We did not conduct a similar post-hoc analysis as we regard the classification of ACE-Is into centrally and peripherally-acting compounds as controversial. This is exemplified by current conflicting evidence around the central action of lisinopril [40–42] and ramipril [40, 43].

It is likely that there will be some under-diagnosis and/or under-recording of AD and VaD in the GPRD [44]. While the validity of a GPRD diagnosis of AD and dementia is relatively good, we are unaware of comparative data for a VaD diagnosis [37]. We believe that these potential misclassifications of the dementia outcomes would be non-differential in relation to the type of antihypertensive prescribed and therefore more likely to attenuate, rather than generate, observed associations.

The observational and biological evidence in favor of ARBs protecting against dementia, presented here and by others [14], strengthens the need for them to be studied more rigorously in the future. We show that ARBs are associated with a reduced risk of AD which could provide significant patient and socio-economic benefits if these data reflect a true causal effect. Further evidence from randomized trials with detailed phenotypic assessment of dementia type are required to verify whether these associations are causal or reflect some form of bias. Such studies should examine both secondary prevention of mild cognitive impairment to dementia as well as tertiary prevention for patients with newly diagnosed AD.

ACKNOWLEDGMENTS

We are grateful to patients and general practitioners participating in the General Practice Research Database and to General Practice Research Database staff for help and advice, particularly Tarita Murray-Thomas for preparing the data extract.

This study is based on data from the Full Feature General Practice Research Database obtained under licence from the UK Medicines and Healthcare Products Regulatory Agency (MHRS). However, the interpretation and conclusions contained in this study are those of the author/s alone. Access to the GPRD database was funded through the Medical Research Council's licence agreement with MHRA.

This study was undertaken with support from a small Flexibility and Sustainability Funding grant from North Bristol NHS Trust. Mr Davies is a recipient of a 4-year PhD studentship from the MRC Centre for Causal Analyses in Translational Epidemiology.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=875).

REFERENCES

[1] Miners J, Baig S, Palmer J, Palmer L, Kehoe P, Love S (2008) Abeta-degrading enzymes in Alzheimer's disease. *Brain Pathol* **18**, 240-252.

[2] Grinberg LT, Heinsen H (2010) Toward a pathological definition of vascular dementia. *J Neurol Sci* **299**, 136-138.

[3] Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study(MRC CFAS) (2001) Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet* **357**, 169-175.

[4] Hanon O, Seux M, Lenoir H, Rigaud A, Forette F (2004) Prevention of dementia and cerebroprotection with antihypertensive drugs. *Curr Hypertens Rep* **6**, 201-207.

[5] Kehoe P, Miners S, Love S (2009) Angiotensins in Alzheimer's disease-friend or foe? *Trends Neurosci* **32**, 619-628.

[6] Skoog I, Gustafson D (2006) Update on hypertension and Alzheimer's disease. *Neurol Res* **28**, 605-611.

[7] Jagust W (2000) Neuroimaging in dementia. *Neurol Clin* **18**, 885-902.

[8] Kalaria R (2009) Linking cerebrovascular defense mechanisms in brain ageing and Alzheimer's disease. *Neurobiol Aging* **30**, 1512-1514.

[9] Shiraishi H, Chang C, Kanno H, Yamamoto I (2004) The relationship between cerebral blood flow and cognitive function in patients with brain insult of various etiology. *J Clin Neurosci* **11**, 138-141.

[10] Buée L, Hof P, Bouras C, Delacourte A, Perl D, Morrison J, Fillit H (1994) Pathological alterations of the cerebral microvasculature in Alzheimer's disease and related dementing disorders. *Acta Neuropathol* **87**, 469-480.

[11] Arendash G, Su G, Crawford F, Bjugstad K, Mullan M (1999) Intravascular [beta]-amyloid infusion increases blood pressure: implications for a vasoactive role of [beta]-amyloid in the pathogenesis of Alzheimer's disease. *Neurosci Lett* **268**, 17-20.

[12] Palmer J, Baig S, Kehoe P, Love S (2009) Endothelin-Converting enzyme-2 is increased in Alzheimer's disease and up-regulated by A beta. *Am J Pathol* **175**, 262-270.

[13] Fogari R, Mugellini A, Zoppi A, Derosa G, Pasotti C, Fogari E, Preti P (2003) Influence of losartan and atenolol on memory function in very elderly hypertensive patients. *J Hum Hypertens* **17**, 781-785.

[14] Li N, Lee A, Whitmer R, Kivipelto M, Lawler E, Kazis L, Wolozin B (2010) Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ* **340**, b5465.

[15] Walker A (1996) Confounding by indication. *Epidemiology* **7**, 335-336.

[16] General Practice Research Database (GPRD) (2010) The database. http://www.gprd.com/products/database.asp.
[17] Khan N, Harrison S, Rose P (2010) Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* **60**, e128-e136.
[18] Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA (2000) Statins and the risk of dementia. *Lancet* **356**, 1627-1631.
[19] World Health Organization. The anatomical therapeutic chemical classification system with defined daily doses, http://www.who.int/classifications/atcddd/en/.
[20] Salas M, Hotman A, Stricker B (1999) Confounding by indication: an example of variation in the use of epidemiologic terminology. *Am J Epidemiol* **149**, 981-983.
[21] McMahon AD (2003) Approaches to combat with confounding by indication in observational studies of intended drug effects. *Pharmacoepidemiol Drug Saf* **12**, 551-558.
[22] Altman DG, Bland JM (2003) Statistics Notes: Interaction revisited: the difference between two estimates. *BMJ* **326**, 219.
[23] den Heijer T, van der Lijn F, Koudstaal PJ, Hofman A, van der Lugt A, Krestin GP, Niessen WJ, Breteler MMB (2010) A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. *Brain* **133**, 1163-1172.
[24] Suissa S (2008) Immortal time bias in pharmacoepidemiology. *Am J Epidemiol* **167**, 492-499.
[25] Zou K, Yamaguchi H, Akatsu H, Sakamoto T, Ko M, Mizoguchi K, Gong J, Yu W, Yamamoto T, Kosaka K (2007) Angiotensin-converting enzyme converts amyloid β-protein 1-42 (Aβ 1-42) to Aβ 1-40, and its inhibition enhances brain Aβ deposition. *J Neurosci* **27**, 8628-8635.
[26] Rozzini L, Chilovi V (2008) Antihypertensive medications influence the rate of conversion from mild cognitive impairment to Alzheimer disease. *Arch Neurol* **65**, 993-995.
[27] Rosenberg P, Mielke M, Tschanz J, Cook L, Stat M, Corcoran C, Hayden K, Norton M, Rabins P, Green R (2008) Effects of cardiovascular medications on rate of functional decline in Alzheimer disease. *Am J Geriatr Psychiatry* **16**, 883-892.
[28] Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S (2008) Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol* **7**, 683-689.
[29] Fogari R, Mugellini A, Zoppi A, Marasi G, Pasotti C, Poletti L, Rinaldi A, Preti P (2004) Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension. *Eur J Clin Pharmacol* **59**, 863-868.
[30] Barnes J, Barnes N, Costall B, Horovitz Z, Naylor R (1989) Angiotensin II inhibits the release of [3H] acetylcholine from rat entorhinal cortex in vitro. *Brain Res* **491**, 136-143.
[31] Barnes J, Barnes N, Costall B, Horovitz Z, Ironside J, Naylor R, Williams T (1990) Angiotensin II inhibits cortical cholinergic function: implications for cognition. *J Cardiovasc Pharmacol* **16**, 234-238.
[32] Barnes J, Barnes N, Costall B, Horovitz Z, Ironside J, Naylor R, Williams T (1990) Angiotensin II inhibits acetylcholine release from human temporal cortex: implications for cognition. *Brain Res* **507**, 341-343.
[33] Anderson C, Teo K, Gao P, Arima H, Dans A, Unger T, Commerford P, Dyal L, Schumacher H, Pogue J (2011) Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. *Lancet Neurol* **10**, 43-53.
[34] Odili AN, Richart T, Staessen JA (2011) Methodological issues in the assessment of cognitive decline in ONTARGET and TRANSCEND. *Lancet Neurol* **10**, 22-24.
[35] Staessen JA, Thijs L, Richart T, Odili AN, Birkenhager WH (2011) Placebo-controlled trials of blood pressure-lowering therapies for primary prevention of Dementia. *Hypertension* **57**, e6-e7.
[36] Staessen JA, Richart T, Birkenhager WH (2007) Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. *Hypertension* **49**, 389-400.
[37] Dunn N, Mullee M, Perry VH, Holmes C (2005) Association between dementia and infectious disease: evidence from a case-control study. *Alzheimer Dis Assoc Disord* **19**, 91-94.
[38] Lewis JD, Brensinger C (2004) Agreement between GPRD smoking data: a survey of general practitioners and a population based survey. *Pharmacoepidemiol Drug Saf* **13**, 437-441.
[39] Sink K, Leng X, Williamson J, Kritchevsky S, Yaffe K, Kuller L, Yasar S, Atkinson H, Robbins M, Psaty B (2009) Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med* **169**, 1195-1202.
[40] Furberg C, Pitt B (2001) Are all angiotensin-converting enzyme inhibitors interchangeable? *J Am Coll Cardiol* **37**, 1456-1460.
[41] Jouquey S, Mathieu MN, Hamon G, Chevillard C (1995) Effect of chronic treatment with trandolapril or enalapril on brain ACE activity in spontaneously hypertensive rats. *Neuropharmacology* **34**, 1689-1692.
[42] Sakaguchi K, Chai S, Jackson B, Johnston C, Mendelsohn F (1987) Blockade of angiotensin converting enzyme in circumventricular organs of the brain after oral lisinopril administration demonstrated by quantitative in vitro autoradiography. *Clin Exp Pharmacol Physiol* **14**, 155-158.
[43] Duron E, Hanon O (2010) Antihypertensive treatments, cognitive decline, and dementia. *J Alzheimers Dis* **20**, 903-914.
[44] Jordan K, Porcheret M, Croft P (2004) Quality of morbidity coding in general practice computerized medical records: a systematic review. *Fam Pract* **21**, 396-412.