

# Effects of Centrally Acting Angiotensin Converting Enzyme Inhibitors on Functional Decline in Patients with Alzheimer's Disease

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## Abstract.

**Background:** Centrally acting angiotensin converting enzyme inhibitors (CACE-Is) are associated with reduced rates of cognitive decline in patients with dementia. CACE-Is may also improve exercise tolerance in functionally impaired older adults with normal cognition, suggesting that CACE-Is may positively influence activities of daily living (ADL) in dementia.

**Objective:** To compare rates of decline in patients with mild to moderate Alzheimer's disease (AD) receiving CACE-Is to those not currently treated with CACE-Is (NoCACE-I), included in the Doxycycline and Rifampicin for Alzheimer's Disease study ( $n = 406$ ).

**Methods:** Patients were included if baseline and end-point (twelve months apart) scores were available for measures including the Standardized Alzheimer's Disease Assessment Scale – Cognitive Subscale; Quick Mild Cognitive Impairment screen; Clinical Dementia Rating Scale (CDR-SB), and Lawton-Brody ADL Scale.

**Results:** There was a significant, 25% difference (median one-point) in the 12-month rate of decline in ADL scores in patients taking CACE-Is ( $n = 91$ ), compared to the NoCACE-I group ( $n = 274$ ),  $p = 0.024$ . This remained significant after adjusting for age, gender, education, and blood pressure,  $p = 0.034$ . When individual CACE-Is were compared to the NoCACE-I group, a significant reduction in the rate of decline in ADLs (median one versus four points), were only observed for perindopril,  $p = 0.01$ . The CDR-SB was also reduced (median one-point) for the perindopril compared to the NoCACE-I group,  $p = 0.04$ .

**Conclusion:** This observational study suggests that CACE-Is, and potentially perindopril in particular, are associated with a reduced rate of functional decline in patients with AD, without an association with mood or behavior. This suggests that CACE-Is may slow disease progression in AD.

Keywords: ACE inhibitors, Alzheimer's disease, cognitive, dementia, function, psychological decline

## INTRODUCTION

Although higher midlife blood pressure (BP) is associated with increased risk of dementia [1], it is not a simple association [2]. Authors have suggested that a variety of anti-hypertensives improve cognition in

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older adults with elevated BP [3, 4] and have potential as therapeutic agents in dementia [5–11]. Results are however, inconsistent [12–14] with some observational studies even suggesting harm [15, 16].

#### *Dementia and angiotensin converting enzyme*

Angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) may lower dementia risk or slow progression independent of their BP lowering properties [9, 10, 17, 18]. Centrally acting ACE-Is (CACE-Is), which cross the blood-brain barrier, are associated in observational studies with a reduced incidence of mild cognitive impairment (MCI) [19, 20] and dementia [14], and slower rates of cognitive decline in Alzheimer's disease (AD), relative to non-centrally acting ACE-Is [21, 22]. In patients with AD, CACE-Is may modulate the pathological accumulation of amyloid- $\beta$  ( $A\beta$ ), a key neuropathological hallmark of AD [23]. ACE gene polymorphisms are associated with increased risk of AD [24, 25]: alleles putatively associated with AD are also associated with low levels of plasma ACE [26, 27]. Pre-clinical studies suggest that ACE degrades  $A\beta$  [28–30], and marked increases in ACE activity have been reported in the frontal cortex of patients with AD [31–33]. More recently, lack of evidence from large scale genetic studies [5, 16] has diminished interest in ACE [24] while interest in Angiotensin II, the potent vasoconstrictor formed by ACE action in AD pathology, has increased [35, 36].

#### *Centrally-acting ACE-Is and cognition*

The strongest pre-clinical evidence to date for the utility of ACE-Is in affecting cognitive decline is for the CACE-I perindopril. Perindopril reversed  $A\beta$ -induced cognitive impairment [37], inhibited brain ACE activity, elevating extracellular acetylcholine levels in mice [38], while two non-centrally acting ACE-Is did not. Perindopril, but not other ACE-Is, significantly inhibited hippocampal ACE and prevented cognitive impairment in mouse models of AD [39, 40, 41]. Clinically, the Cardiovascular Health Study reported observational data that perindopril, rather than non-centrally acting ACE-Is or calcium channel blockers, decreased the rate of decline in patients with mild to moderate AD [14]. Results, however, are inconsistent. Secondary analysis of randomized trials have failed to detect an effect of ACE-Is [42] or ARBs on cognition [12, 43]. Furthermore, a small placebo controlled

clinical trial in non-demented offspring of AD patients showed no effect on cognition [44].

#### *Effects of CACE-Is on ADLs and the behavioral and psychological symptoms of dementia (BPSD)*

Observational studies suggest that beta-blockers are associated with reduced rates of functional decline in patients with established AD [45]. Although, there is no association for ACE-Is [14, 45], they are associated with increased exercise tolerance, muscle strength [46], and lower falls risk [46, 47], suggesting effects independent of their BP lowering properties. Furthermore, the discontinuation of ACE-Is in those with AD is associated with increased rates of functional decline [48]. Studies investigating ACE genotypes in functional decline suggest both increased [49] and decreased disability [50]. There is also evidence that ACE-Is modulate mood, including anxiety [51] and depression in hypertensive patients with normal cognition [52]. Again, evidence is inconsistent [53, 54].

#### *Objective*

The aim of this paper was to compare rates of cognitive, functional, and neuropsychological decline in patients with AD receiving CACE-Is (called CACE-Is) to those not currently treated with CACE-Is (NoCACE-I) by conducting a secondary analysis of data from a randomized control trial.

## **METHODS**

#### *Data collection*

We performed a secondary analysis of data from the Doxycycline and Rifampin for Alzheimer's Disease (DARAD) trial [55], a multi-center, blinded, randomized  $2 \times 2$  factorial controlled trial, conducted between 2006 and 2010, comparing two antibiotics (doxycycline and rifampicin) to placebo, to investigate if these can delay progression of AD [55]. The co-primary outcomes were the Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale (SADAS-cog) [56] and the Clinical Dementia Rating scale–Sum of the Boxes (CDR-SB) [57]. Secondary outcomes included the Standardized Mini-Mental State Examination (SMMSE) [58, 59], Quick Mild Cognitive Impairment screen (*Qmci*) [60–62], the Geriatric Depression Scale (GDS) [63], Cornell Scale for Depression in Dementia (CSDD) [64], Lawton-Brody ADL Scale [65], and the Dysfunctional Behaviour Rating Instrument (DBRI),

frequency (DBRIF) and reaction (DBRIR), subscales [66, 67]. The SADAS-cog, CDR-SB, *Qmci*, Lawton-Brody ADL Scale, and DBRI were available at one, three, six, nine, and twelve months (end-point). The SMMSE was recorded at screening and end-point, the GDS at baseline and end-point and the CSDD at baseline, six-months and end-point only.

The SADAS-cog is a standardized version of the ADAS-cog [68], the existing, accepted standard for measuring cognitive function in clinical trials [69]. Consisting of 11 domains (including word recall, object naming, command following, construction, orientation, word recognition, language, speech comprehension, word finding and recall), the SADAS-cog improved inter-rater reliability using explicit administration and scoring guidelines. Scored from 0–70, scores  $\geq 13$  indicate increasing cognitive impairment [56]. The CDR-SB, a measure of global function, is scored from 0–18 with a score of 0 indicating no impairment, 0.5–4.0 possible impairment, and 4.5–9.0, 9.5–15.5, and 16.0–18.0 suggesting mild, moderate, and severe impairment, respectively [57]. The *Qmci* screen is a short (3–5 min), cognitive screening instrument composed of six subtests, covering five domains: orientation, registration, clock drawing, delayed recall, verbal fluency (naming animals) and logical memory (immediate verbal recall of a short story), scored out of 100 points. It has superior accuracy for detecting MCI compared to the SMMSE [60] and similar accuracy as the Montreal Cognitive Assessment (O’Caoimh 2013 unpublished work). The Lawton-Brody ADL Scale, combining both basic (Physical Self-Maintenance Scale) and instrumental ADLs, covering 14 categories, is scored out of 64 points, with higher scores suggesting greater independence [65]. The GDS short-form is scored from 0–15 with a score  $\geq 5$  suggesting depression [63, 70]. The CSDD is a 19-item scale, range of 0–39: normal  $< 6$ , probable depression 10–17, definite depression  $\geq 18$ . The DBRI, completed by caregivers, scores the frequency of (from ‘never’ to ‘greater than five times per day’) and reaction to (impact from ‘no problem’ to ‘great deal of a problem’) 25 behaviors [66].

### Participants

In total, 406 patients with mild to moderate AD (SMMSE scores between 14 and 26) were included from 14 geriatric outpatient clinics in Canada [55]. All patients were aged 50 years or more and met the National Institute of Neurological Disorders and Stroke (NINCDS) criteria for AD [71]. In this study,

patients were subdivided into a CACE-I group, including patients currently prescribed centrally acting ACE-Is: ramipril ( $n = 57$ ), perindopril ( $n = 21$ ), lisinopril ( $n = 9$ ), trandolapril ( $n = 3$ ), and fosinopril ( $n = 1$ ) [14, 19], and a NoCACE-I group not currently receiving CACE-Is, irrespective of BP readings, diagnosis of hypertension, or receipt of other anti-hypertensives.

### Analysis

The average 12-month rate of change in outcomes, measured as the difference between baseline and 12-month scores, were compared between patients receiving CACE-Is and the NoCACE-I group. For the *Qmci*, CSDD, GDS, and Lawton-Brody ADL Scale, change was calculated as the baseline minus the 12-month score. The SADAS-cog, CDR-SB, DBRIF, and DBRIR scales were calculated as the score at month 12 minus the baseline. In this way, irrespective of the scoring instructions, positive change denoted improvement. The SMMSE, used as an inclusion criterion, was not used in the analysis. Data were analyzed using SPSS 20.0. Non-normally distributed numerical data were compared using the independent samples median test, while chi-square tests were used for categorical data. Multivariate regression analysis was used to compare baseline measurement scores, adjusted for baseline characteristics; age, years of education, and BP (systolic and diastolic), between the CACE-I and NoCACE-I groups and CACE-I subgroups: perindopril and other CACE-Is. Multivariate regression was also used to compare the rate of decline, in each measure, between the subgroups.

## RESULTS

### Baseline demographics

Co-primary outcome measures were available for 365 patients at 12 months; for most, secondary outcomes were also available. The remaining 41 patients were lost to follow-up because of death ( $n = 13$ ), refusal ( $n = 14$ ), adverse events ( $n = 6$ ), withdrawal from the trial ( $n = 5$ ), and other reasons (moved, caregiver death,  $n = 3$ ). Table 1 presents patients’ baseline characteristics. Of the 365 patients included, 91 were taking CACE-Is during the course of the trial: 21 receiving perindopril and 70 other CACE-Is (Figure 1). Although no difference in baseline outcome measure scores were present between the CACE-I and NoCACE-I groups, when the CACE-I subgroups (perindopril and other CACE-Is) were compared to the NoCACE-I group,

Table 1  
Differences in baseline demographic characteristics and outcome measures of patients receiving centrally acting ACE inhibitors (CACE-I) to those not currently treated with CACE-Is (NoCACE-I)

	CACE (n=91) Median (IQR)	NoCACE (n=274) Median (IQR)	Perindopril (n=21) Median (IQR)	Other CACE-Is (n=70) Median (IQR)	p-value <sup>1</sup>	p-value <sup>2</sup>
Age	79 (8)	78 (10)	78 (9)	79 (10)	0.90	0.72
Gender (male %)	45.1%	51.1%	23.8%	51.4%	0.46	0.05
Education (years)	12 (4)	12 (5)	12 (5)	12 (3.5)	0.06	0.15
Blood pressure systolic	138 (19)	134 (22.5)	140 (19)	135.5 (17.25)	0.41	0.45
Blood pressure diastolic	70 (14)	72 (14)	70 (11)	70 (12.5)	0.41	0.66
Cholinesterase inhibitor use (%)	89.0%	92.3%	76.2%	92.9%	0.32	0.03
Memantine use (%)	15.4%	15.3%	14.2%	15.7%	0.64	0.99
SMMSE	23 (4.5)	22.5 (5)	24 (2)	23 (5)	0.14	0.22
Qmci	39.5 (18)	39 (19)	40 (12)	39 (20)	0.74	0.90
SADAS-cog	18 (12)	21 (11)	16 (9)	19 (12)	0.05	0.04
Lawton-Brody ADL	51 (10)	52 (10)	52 (9)	51 (11)	0.34	0.57
CDR-SB	5 (4)	5 (4)	4.5 (4)	6 (4)	0.74	0.23
CSDD	3 (5)	3 (4)	4 (8)	3 (5)	0.09	0.23
GDS	1 (2)	1 (3)	2 (2)	1 (2)	0.74	0.82
DBRIF	4 (13)	5 (10)	3 (11)	4 (13)	0.61	0.88
DBRIR	11 (12)	13 (11)	12 (16)	11 (12)	0.45	0.75

<sup>1</sup>p-values are provided for independent samples median test (numerical data) or Chi-square test (categorical data) for comparison between CACE-I and NoCACE-I groups; <sup>2</sup>p-values are provided for independent samples median test (numerical data) or Chi-square test (categorical data) for comparison between perindopril, other CACE-Is and NoCACE-I groups; ADL, activities of daily living; CDR-SB, Clinical Dementia Rating scale-Sum of the Boxes; CSDD, Cornell Scale for Depression in Dementia; DBRIF, Dysfunctional Behaviour Rating Instrument-frequency; DBRIR, Dysfunctional Behaviour Rating Instrument-reaction; GDS, Geriatric Depression Scale; IQR, interquartile range; Qmci, Quick Mild Cognitive Impairment screen; SADAS-cog, Standardized Alzheimer's Disease Assessment Scale-Cognitive Subscale; SMMSE, Standardized Mini-Mental State Examination.

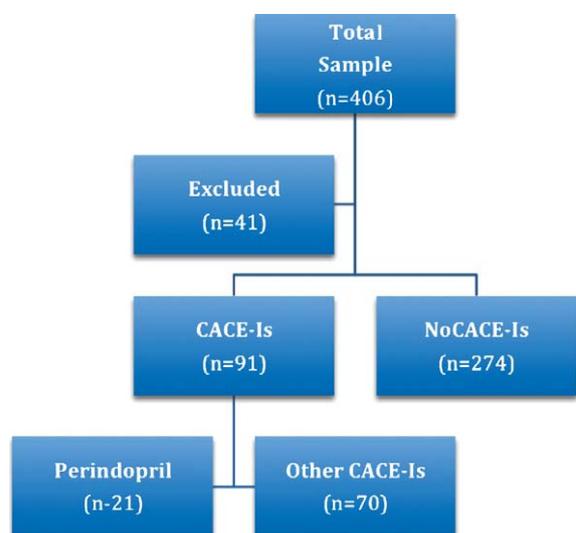


Fig. 1. Flow diagram demonstrating the breakdown of the patients included from the Doxycycline and Rifampin for Alzheimer's Disease (DARAD) trial database receiving centrally acting ACE inhibitors (CACE-Is: perindopril and others) and those not currently treated with CACE-Is (NoCACE-I).

there was a marginal statistically significant difference in baseline characteristics for gender ( $p=0.05$ ), cholinesterase inhibitor use ( $p=0.03$ ), and SADAS-cog scores ( $p=0.04$ ) (Table 2).

Table 2  
Comparison of the rate of decline, from baseline to one year, between patients receiving centrally acting ACE inhibitors (CACE-I) and those not currently treated with CACE-Is (NoCACE-I)

Variable	CACE-I Median (IQR)	NoCACE-I Median (IQR)	p-value <sup>1</sup>	p-value <sup>2</sup>
Blood pressure systolic	0 (30)	1.5 (24)	0.38	0.69*
Blood pressure diastolic	0 (20)	0 (18)	0.69	0.71*
SADAS-cog	2 (9)	4 (8)	0.41	0.86
CDR-SB	2 (4)	1.5 (3.5)	0.83	0.84
Qmci	4 (12)	5 (13)	0.15	0.49
Lawton-Brody (ADL)	3 (6)	4 (7)	0.024	0.034
CSDD	0 (3)	1 (4)	0.13	0.001
GDS	0 (2)	0 (2)	0.95	0.94
DBRIF	0 (9)	0 (8)	0.50	0.24
DBRIR	4 (13)	2 (11)	0.50	0.44

<sup>1</sup>p-values are provided for unadjusted comparisons between CACE-I and NoCACE-I groups; <sup>2</sup>p-values are provided for multivariate regression (adjusted for age, gender, education, and blood pressure) for comparison between the CACE-I and NoCACE-I groups; \*Adjusted for age, gender, and education; ADL, activities of daily living; CDR-SB, Clinical Dementia Rating scale-Sum of the Boxes; CSDD, Cornell Scale for Depression in Dementia; DBRIF, Dysfunctional Behaviour Rating Instrument-frequency; DBRIR, Dysfunctional Behaviour Rating Instrument-reaction; GDS, Geriatric Depression Scale; IQR, interquartile range; Qmci, Quick Mild Cognitive Impairment screen; SADAS-cog, Standardized Alzheimer's Disease Assessment Scale-Cognitive Subscale.

### Rate of decline

Patients receiving CACE-Is had a median decline of three points (IQR six) in ADL scores between baseline and 12 months, in comparison to a decline of four points (IQR seven) in the NoCACE-I group ( $p=0.024$ ). No statistically significant differences in decline were evident for the other outcome measures in the unadjusted analysis. However, patients taking CACE-Is demonstrated a median decline in *Qmci* screen scores of four (IQR 12) versus five (IQR 13) points in the NoCACE-I group ( $p=0.15$ ). The deterioration in CDR-SB and CSDD scores was also less marked in the CACE-I group relative to the NoCACE-I group, although again differences were not statistically significant (Table 2). Adjusting for age, education, gender, and BP confirmed a significant difference in ADL scores ( $p=0.034$ ). The adjusted analysis also showed a significant one point difference in the rate of decline between groups in the CSDD scores ( $p=0.001$ , Table 2): 57% ( $n=52$ ) of CACE-I improved or remained the same, compared to 47% ( $n=128$ ) in the NoCACE-I group.

When individual CACE-Is were compared to the NoCACE-I group, a significant median reduction in the rate of decline in ADLs, one point compared to four points, was observed for those receiving perindopril ( $p=0.01$ ). The CDR-SB was also reduced by a median of one point ( $p=0.04$ ) for the perindopril compared to the NoCACE-I group. Median decline in CDR-SB scores was 0.5 (IQR 3) in patients receiving perindopril versus 2.5 (IQR 4) in those receiving other CACE-Is ( $p=0.05$ ). Patients receiving other CACE-Is showed a median decline in ADL scores of three points (IQR seven), compared to one point (IQR six) for perindopril ( $p=0.09$ ). Patients reported few adverse events that could possibly be related to ACE-I treatment. Of those taking CACE-Is, six noted a fall, while none reported cough or orthostatic symptoms.

## DISCUSSION

This study found a small (25%, three versus four points) reduction in the rate of decline in ADL scores, measured with the Lawton-Brody ADL Scale, over a 12-month period, in patients taking CACE-Is compared to those not currently receiving CACE-Is. Other outcomes measures were also associated with a decreased progression for the CACE-I compared to the NoCACE-I group, although only changes in ADL and CSDD scores were statistically significant. In

particular, the *Qmci* screen scores declined 20% less (four versus five points respectively), for the CACE-I group over one year, not inconsistent with other studies demonstrating a slower rate of cognitive decline in persons with dementia receiving CACE-Is [21, 22, 72].

Investigators have not previously reported a reduced rate of decline in ADLs in patients with established dementia receiving CACE-Is, although the effect has been shown with beta-blockers [45]. Since we found no significant changes in BP over the 12-month follow-up period, these benefits are likely to be independent of an anti-hypertensive effect. There are a number of possible mechanisms by which CACE-Is could impact upon ADLs. Perindopril improves exercise tolerance in older adults with normal cognition, with [73] and without heart failure [46]. This might be explained by the reported ability of ACE-Is to reduce inflammation and to improve endothelial function, increasing muscle blood flow and glucose delivery [74] to both skeletal and cardiac muscle, thereby improving exercise tolerance and capacity. Previous trials have demonstrated benefits, equivalent to six months of training, with four weeks exposure to ACE-Is [46]. These effects appear to be unique to ACE-Is, when compared to other classes of anti-hypertensives [75], further supporting that the benefits are independent of the drugs BP lowering properties. In addition, individuals with polymorphisms, resulting in low ACE activity, have an enhanced response to training [76] although this contrasts with the observations of increased ADL disability for the same gene variants in older populations [49]. The association between treatment with either ACE-Is and/or ARBs, with a lower incidence of falls also supports the theory that these medications may produce global effects on physical function [47]. Therefore, one year of ACE-I treatment could, theoretically, result in improvements in muscle strength and function, sufficient to alter the rate of decline in ADLs.

Other studies, however, contradict these findings. Results from the Cardiovascular Health Study, investigating incidence of dementia, suggest that exposure to ACE-Is and non-CACE-Is in particular, are associated with an increased dependency in ADLs [14]. Although these reductions may have been relative to smaller disimprovements with other anti-hypertensives, such as calcium channel blockers, which are also associated with reduced incidence of dementia [77, 78] and possibly reduced progression that is currently being tested in clinical trials [Nilvad registered trial EudraCT Number: 2012-002764-27]. The TRAIN study demonstrated no benefit in muscle strength or

exercise performance for fosinopril over placebo in patients with high cardiovascular risk but normal cognition [79].

In this study, the use of perindopril was associated with a slower rate of decline in measures of cognition (SADAS-cog and *Qmci*), global function (CDR-SB), and ADLs compared to other CACE-Is, although only the CDR-SB reached statistical significance. The potential benefits of perindopril on exercise tolerance over other ACE-Is has been commented upon previously [79], with most studies reporting positive findings using perindopril [46, 73, 79] and negative findings using other agents such as fosinopril [79] or quinapril [81].

The results presented here also suggest that depressive symptoms (measured using the CSDD) were more likely to improve or remain unchanged in patients receiving CACE-Is. Although reductions in the adjusted one-year rate of decline were statistically significant for the CSDD, between the CACE-I and NoCACE-I groups, the effects were small (both had a median three-point change over the year, see Table 2). The frequency of the BPSD, as measured by the DBRIF and DBRIR, reduced for both CACE-I and NoCACE-I groups, although this did not achieve statistical significance. Thus, minimal or no effects of CACE-Is on mood or the BPSD were demonstrated in this study. Both the CACE-I and NoCACE-I groups appeared to demonstrate little difference in rates of decline in their GDS, CSDD, and DBRI scores over the year of follow-up. Although more patients in the CACE-I group compared to the NoCACE-I group showed a significant improvement in CSDD scores (57% versus 47%) over one year, CSDD scores were significantly higher in the CACE-I group at baseline. These data support the current evidence that ACE-Is, in general, have little effect on mood and depression [53, 54].

Strengths of our study include that the data were collected as part of a clinical trial, with rigorous interviewer training and quality checks. Furthermore, the DARAD trial had a relatively low loss to follow-up and good compliance with measurements throughout [55]. Other strengths include the large numbers, regular assessment, and measurement of a wide variety of outcomes over one year [55]. Limitations to this study included the fact that patients had established dementia, median SMMSE of 23, and may have been taking CACE-Is for many years. Another limitation is that as this was an observational study, derived from the secondary analyses of data from a randomized control trial; it was not possible to identify duration or previous history of anti-hypertensive treatment. Furthermore,

compliance with anti-hypertensive medications, which has been shown to reduce with time, may also have been a confounder [82, 83]. A percentage of patients in the NoCACE-I group (41%) were not receiving any anti-hypertensive treatment. By lowering BP, which is associated with progression of cognitive and functional impairment [45], these medications may have caused bias from confounding by indication favoring those currently receiving them. However, baseline characteristics including BP were similar between the CACE-I and NoCACE-I groups and were not associated with rates of decline. Likewise, most anti-hypertensive drugs have been linked with reduced rates of cognitive and or functional decline [9, 10, 14, 17, 18, 45]. There were marginal differences of borderline significance between the three groups (CACE-I, NoCACE-I, and perindopril) in gender, cholinesterase inhibitor use, and SADAS-cog scores. However, the difference in deterioration in ADLs remained after adjustment for these variables. The marker of ADLs used, the Lawton-Brody ADL Scale score, is not a gold standard outcome measure, but it is still a widely used instrument that incorporates both instrumental and basic activities of daily living [14, 65, 84]. Indeed, like most instruments measuring ADLs, it is subject to potential bias arising from self or informant reporting rather than a demonstration of ability, and insensitivity to small changes in function. Another limitation and perhaps most important, is that inferences regarding treatment effects are limited by the small effects, the borderline significance of the findings, and the multiple comparisons increasing the likelihood of chance findings. Small effects may however also reflect that this analysis was conducted in patients with more advanced disease. Therefore greater effects may be gained from longer treatment periods in patients with less advanced pathology or people with early stages of cognitive impairment (e.g., MCI), where cognitive benefits have previously been reported [19, 20].

Overall, this study suggests the possibility of benefit for patients with established AD taking CACE-Is compared to a group not currently treated with CACE-Is, across a range of outcome measures, particularly ADLs. The finding of a reduced rate of progression in ADL disability is small and if real of uncertain significance and with an unclear mechanism. Nevertheless, if such an effect were sustained over years, patient-important benefit may result. Our data provide modest support for the hypothesis that CACE-Is, and perhaps perindopril in particular, may slow disease progression in patients with dementia. At present no anti-hypertensive agents have been licensed for the

treatment of AD. These data support the need for further study.

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