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Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia

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ABSTRACT

Objectives: There is growing evidence that antihypertensive agents, particularly centrally acting ACE inhibitors (CACE-Is), which cross the blood–brain barrier, are associated with a reduced rate of cognitive decline. Given this, we compared the rates of cognitive decline in clinic patients with dementia receiving CACE-Is (CACE-I) with those not currently treated with CACE-Is (NoCACE-I), and with those who started CACE-Is, during their first 6 months of treatment (NewCACE-I).

Design: Observational case–control study.

Setting: 2 university hospital memory clinics.

Participants: 817 patients diagnosed with Alzheimer's disease, vascular or mixed dementia. Of these, 361 with valid cognitive scores were included for analysis, 85 CACE-I and 276 NoCACE-I.

Measurements: Patients were included if the baseline and end-point (standardised at 6 months apart) Standardised Mini-Mental State Examination (SMMSE) or Quick Mild Cognitive Impairment (Qmci) scores were available. Patients with comorbid depression or other dementia subtypes were excluded. The average 6-month rates of change in scores were compared between CACE-I, NoCACE-I and NewCACE-I patients.

Results: When the rate of decline was compared between groups, there was a significant difference in the median, 6-month rate of decline in Qmci scores between CACE-I (1.8 points) and NoCACE-I (2.1 points) patients ($p=0.049$), with similar, non-significant changes in SMMSE. Median SMMSE scores improved by 1.2 points in the first 6 months of CACE treatment (NewCACE-I), compared to a 0.8 point decline for the CACE-I ($p=0.003$) group and a 1 point decline for the NoCACE-I ($p=0.001$) group over the same period. Multivariate analysis, controlling for baseline characteristics, showed significant differences in the rates of decline, in SMMSE, between the three groups, $p=0.002$.

Conclusions: Cognitive scores may improve in the first 6 months after CACE-I treatment and use of CACE-Is is associated with a reduced rate of cognitive decline in patients with dementia.

ARTICLE SUMMARY

Article focus

- Treatment options for dementia, including Alzheimer's disease, remain limited. The purpose of this study was to examine the effect of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive decline in patients with dementia.
- This study also examined the acute effect of CACE-Is on cognition, during the first 6 months of treatment.

Key messages

- Reduced rates of cognitive decline were seen in an unselected outpatient sample, prescribed CACE-Is, irrespective of the blood pressure readings or diagnosis of hypertension.
- The rate of decline was reduced in patients in the 6 months after starting CACE-Is, compared to those already established on them.

Strengths and limitations of this study

- This study used observational data collected in a 'real world' setting, where treatments, including antihypertensive agents, were administered on the basis of clinical judgement.
- The study investigated the effects of CACE-Is in an unselected clinic sample of older adults with different dementia subtypes, whose mean age approached 80 years.
- Although most patients in the database had Qmci or SMMSE recorded, large numbers lacked results at the baseline or end point, limiting the numbers that could be included in the analysis.
- Change over 6 months of treatment was analysed. Different effects may have been demonstrated over a longer period.

INTRODUCTION

As populations age worldwide, the incidence of dementia will increase. By 2040, approximately 81 million people worldwide will be affected.[1] Until now, no agents have been identified that prevent, modify or reverse dementia, and available treatments for dementia are predominantly symptomatic.[2] There is growing recognition of the role of cardiovascular risk factors, especially in midlife, in the conversion and progression of mild cognitive impairment (MCI) and dementia.[3–5] Blood pressure (BP) control, in particular, is associated with both a reduced incidence of cognitive impairment (CI) and rate of cognitive decline.[6–9] Several antihypertensive agents are associated with a lower risk of developing dementia, including calcium channel blockers (CCBs),[10 11] diuretics,[8] angiotensin receptor blockers (ARBs)[12–14] and ACE inhibitors (ACE-Is).[15 16] ACE-Is and ARBs affect the renin angiotensin system and may lower dementia risk, independent of their BP lowering properties.[17] Results of clinical trials investigating the potential role of antihypertensives are limited and conflicting.[18] The Perindopril Protection against Recurrent Stroke Study (PROGRESS) demonstrated that a combination of perindopril (ACE-I) and indapamide (diuretic) was associated with a significant reduction in the incidence of stroke and in cognitive decline, compared to placebo.[8] The Systolic Hypertension in Europe (Syst-Eur) study found that the combination of enalapril (ACE-I), nitrendipine (CCB) and/or hydrochlorothiazide (diuretic) reduced the incidence of dementia by 55%, compared to placebo.[19 20] Monotherapy with the ARB, candesartan, in the Study on Cognition and Prognosis in the Elderly (SCOPE) also showed modest effects.[14] Not all studies have shown cognitive benefits with antihypertensive agents; some implicate them in the worsening of cognition.[21] The ONTARGET and TRANSCEND trials, two parallel studies involving more than 25 000 patients, found that ACE-Is did not have any measurable effects on cognition.[22] Although the evidence is limited, treatment with antihypertensives has been associated with reduced rates of cognitive[23 24] and functional decline[25] in those with established Alzheimer's disease (AD).

ACE-Is were one of the first antihypertensives to be studied, particularly in AD, the most prevalent form of dementia.[26] Patients with AD have abnormal cleavage of amyloid precursor protein resulting in a pathological accumulation of amyloid β (Aβ).[27] The relationship between ACE and the accumulation of Aβ is complex and different polymorphisms have been postulated to either increase,[28] or decrease,[29] the risk of developing AD. ACE activity is increased in AD, proportional to the Aβ load.[30] Centrally acting ACE-Is (CACE-Is) that cross the blood–brain barrier may have a greater impact than those that do not. The CACE-I perindopril, administered to mouse models, showed a significant protective effect[31] and reversed CI more than did the non-centrally acting imidapril and enalapril.[32] Patients receiving CACE-Is have a reduced rate of cognitive decline compared to both non-centrally acting ACE-Is and CCBs.[15] The Cardiovascular Health Study demonstrated no reduced risk in the incidence of dementia in those taking CACE-Is compared to other classes of antihypertensives.[33] Those prescribed CACE-Is had a reduced rate of cognitive decline and less impairment in instrumental activities of daily living compared to those taking non-centrally acting agents.[34] Prescription of ARBs and ACE-Is is also associated with reduced incidence of both vascular dementia and mixed dementia subtypes.[35 36]

Outside of clinical trials, there are few data on the effects of CACE-Is on the rate of cognitive decline in patients with dementia. Given this, and the growing evidence for antihypertensive agents, particularly CACE-Is, in reducing the incidence and rate of cognitive decline, we compared the rates of decline in patients taking CACE-Is (called CACE-I) with those not currently prescribed CACE-Is (called NoCACE-I), in those with established dementia, attending a memory clinic. We also examined whether patients started on CACE-Is while attending clinic (called NewCACE-I), behaved differently during their first 6 months of treatment, compared to the NoCACE-I group and those already established on CACE-Is.

METHODS

Data collection

Data were analysed from the Geriatric Assessment Tool (GAT) database, a customised software application that automates physicians' clinic assessments. Data were collected in memory clinics in two university hospitals in Ontario, Canada. The database contains over 8000 individual assessments from 1749 people aged 41–104 years. GAT data, collected between 1999 and 2010, includes age, gender, education, medical diagnosis, BP, laboratory findings, medications, etc and the scores of two cognitive screening tests, the Standardised Mini-Mental State Examination (SMMSE)[37 38] and the Quick Mild Cognitive Impairment (Qmci) screen,[39 40] a new cognitive screen, more sensitive and specific for differencing MCI from normal cognition and dementia than the SMMSE.[39] Both tests were administered to patients by trained raters (clinic nurses) blind to the diagnosis, prior to each assessment, to monitor progression.

The Qmci has six subtests covering five cognitive domains: orientation, working memory, semantic memory (verbal fluency for animals), visual spatial (clock drawing) and two tests of episodic memory (delayed recall and immediate recall logical memory). It is scored out of 100 points.

Subjects

Patients with dementia were diagnosed by a consultant geriatrician using NINCDS[41] and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.[42] Only patients with AD, vascular or mixed dementias (Alzheimer's/vascular) were included in this analysis. As there is little evidence that antihypertensive medications affect other dementia subtypes, patients with Parkinson's disease dementia,[43 44] frontotemporal dementia,[45] Lewy body dementia,[46] alcohol-related dementia, post-trauma and post-anaesthetic dementia were excluded. Patients with MCI, n=235, defined as those with subjective and corroborated memory loss, without obvious loss of function,[47] were excluded. Patients with MCI were excluded because few, n=12, had baseline and end-point Qmci scores available. Although the SMMSE was available, it is insensitive to MCI,[39] and rates of cognitive decline vary, depending on the cognitive measures used.[48] Patients with normal cognition, n=181 and depression, n=397 were also excluded. Participants were screened for depression using the 15-point Geriatric Depression Scale.[49] As there is limited evidence that ACE-Is affect comorbid depression,[50] while depression negatively affects the results of cognitive testing,[51] 397 participants with depression were excluded: 260 with CI and comorbid depression and 137 with normal cognition and depression. Patients with depression were predominantly (63%) women and were significantly younger than patients without depression, mean age 72.7 (SD 10.7), p<0.001. Patients were also excluded if they did not have the results of either the Qmci or SMMSE available at both the baseline and end point. Changes between the baseline and end-point (last visit) scores were standardised at 6 months to facilitate comparison between all groups. In total, 56% (n=456) of patients with dementia did not have the same cognitive test recorded at two visits and were therefore excluded. Regression analysis, adjusting for baseline characteristics (age, gender, education and BP) between participants without follow-up and those included, showed no significant difference in baseline SMMSE (p=0.06) or Qmci scores (p=0.51). Patient selection is presented graphically in figure 1. The CACE-I group included patients currently prescribed the following CACE-Is: perindopril, ramipril, trandolapril, captopril, fosinopril, lisinopril, prinivil and monopril.[34 52]

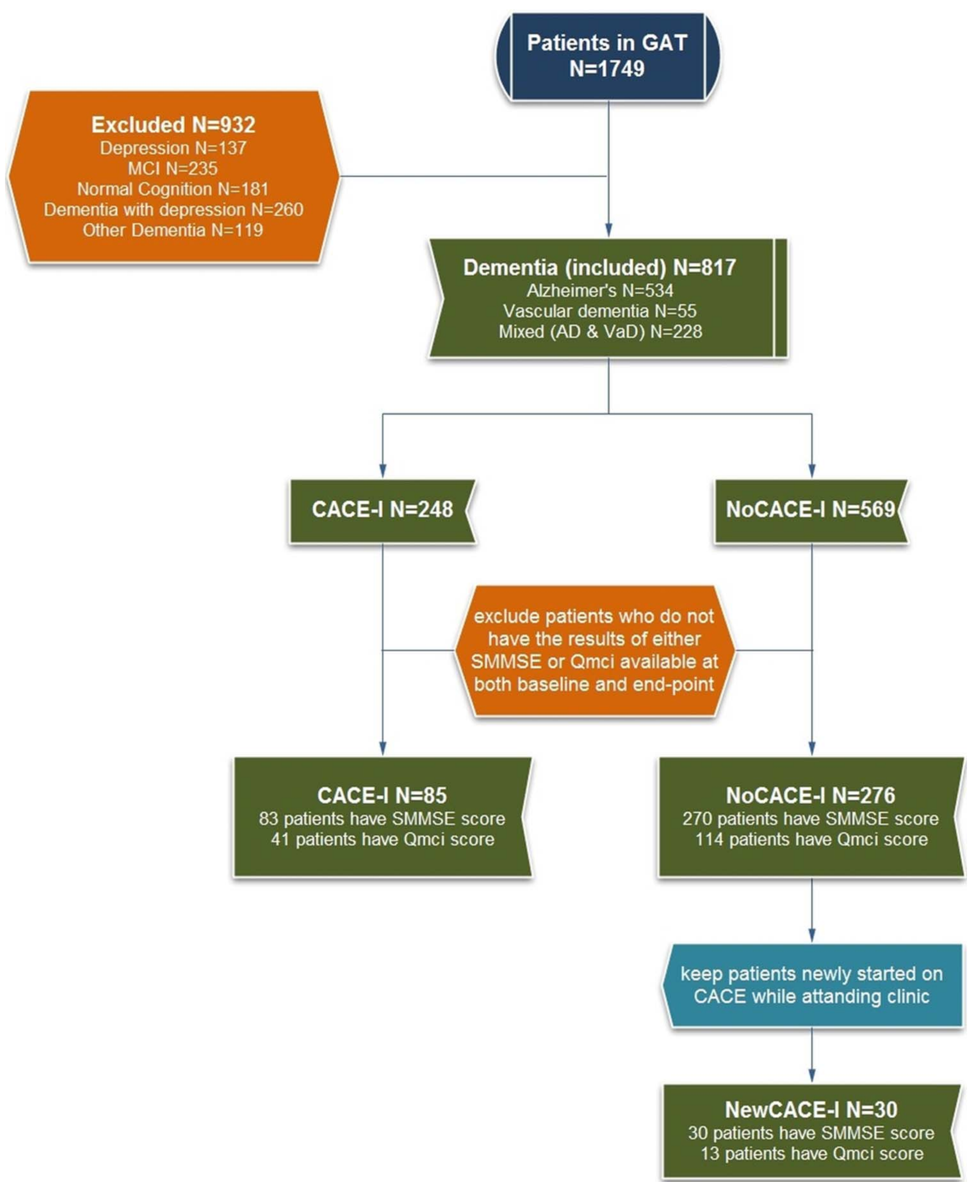

Figure 1 Flow chart demonstrating the breakdown of the patients included in the Geriatric Assessment Tool (GAT) database.

NoCACE-I included patients who were not currently receiving CACE-Is, irrespective of the BP readings, diagnosis of hypertension or whether they were receiving other antihypertensive medications.

Analysis

Our goal was to determine whether there were differences in rates of change, from the baseline to the end point (the time point when cognitive scores were last available), in Qmci and SMMSE scores between patients in the NoCACE-I, NoCACE-I and NewCACE-I groups while attending clinic. Given that regulatory authorities like the US Food and Drug Administration require evidence of change in cognitive tests over 6 months[41 53] to confirm benefit from new medications, we used change scores from the baseline, on a six-monthly basis, according to the formula:

$$\text{Rate of decline} = (\text{Baseline score} - \text{end - point score}) \times 6/\text{duration in months}$$

We also used multivariate regression to compare end-point cognitive scores (SMMSE and Qmci), adjusted for the baseline cognitive scores and characteristics (age, years of education, duration of follow-up and BP), between the three groups (CACE-I, NoCACE-I and NewCACE-I). Data were analysed using SPSS V.18.0. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality. Non-normally distributed data were compared with the Mann-Whitney U test. Categorical data were analysed with χ^2 tests.

RESULTS

Baseline characteristics

In total, there were 817 patients with dementia. Of these, 361 with SMMSE and Qmci scores recorded at two or more visits were included for analysis, 85 receiving CACE-Is and 276 receiving NoCACE-Is. The mean age of those included was 77.9 years with an SD of 8.1 years. Half (50.3%) were men and the mean time spent in education was 11.2 years. The mean age of patients taking CACE-Is was 77.2 years compared to 77 years for the NoCACE-Is group. Men represented 51.8% of the CACE-I group compared to 49.6% of the NoCACE-I group. Within the NoCACE-I group, 30 participants had been started on ACE-Is while attending clinic (NewCACE-I). Table 1 shows the baseline characteristics, including demographics and medication use, for the CACE-I, NoCACE-I or NewCACE-I groups.

Both SMMSE and Qmci scores were available for 147 participants at the baseline and end point, while 206 participants had SMMSE scores only and 8 had Qmci scores alone. For the participants included, the mean SMMSE scores at the baseline and end point were 21.6 (SD±5.6) and 18.1 (SD±8.0), respectively. Mean Qmci scores were 36.8 (SD±13.6) and 31.3 (SD±18.3), respectively. Table 2 presents the baseline and end-point Qmci and SMMSE scores for the CACE-I, NoCACE-I or NewCACE-I groups. After adjusting for the baseline characteristics (age, education, duration of follow-up and BP), there were no significant differences in the baseline cognitive scores (SMMSE and Qmci) between the three groups (CACE-I, NoCACE-I and NewCACE-I).

In relation to medications, 88.2% of the CACE-I group, 82.6% of the NoCACE-I group and 80% of those in the NewCACE-I group were receiving cholinesterase inhibitors (CholEIs). A smaller percentage was currently prescribed memantine. There was no difference in the distribution of CholEIs (p=0.40) or memantine (p=0.98) between the CACE-I, NoCACE-I and NewCACE-I groups.

Rate of decline

The median change in SMMSE scores between the baseline and end point for those included was 0.69 points per 6 months (IQR of 2). The median SMMSE score differences for the CACE-I, NoCACE-I and NewCACE-I groups were 0.8, 1.0 and −1.2, respectively, per 6 months. For the Qmci, the median change was 2 points per 6 months, with median Qmci score differences for the CACE-I and NoCACE-I groups of 1.8 and 2.1, respectively, per 6 months.

There was a small but non-significant difference in the SMMSE median rate of decline over 6 months for patients taking CACE-Is, compared to NoCACE-I patients, p=0.77. The difference in the median rates of

Table 1 Baseline characteristics of CACE-I, NoCACE-I or NewCACE-I patients

Groups	CACE-I	NoCACE-I	NewCACE-I
Number	85	276	30
Age (mean±SD)	77.2±6.4	77.0±7.6	77.3±8.2
Male (%)	44 (51.8)	137 (49.6)	15 (50)
Education (mean±SD)	10.6±3.8	11.4±4.0	12.1±3.9
Systolic BP in mm Hg (mean±SD)	133.4±21.2	135.5±16.9	141.1±16.2
Diastolic BP in mm Hg (mean±SD)	70.1±12.6	72.5±11.5	78.1±17.0
Cholinesterase inhibitor use (%)	75 (88.2)	228 (82.6)	24 (80)
Memantine use (%)	23 (27.1)	72 (26.1)	8 (26.7)

BP, blood pressure; CACE-I, patients currently receiving ACE inhibitors; NewCACE-I, patients who were newly started on CACE-Is; NoCACE-I, patients who are not currently prescribed CACE-Is.

Table 2 Baseline and end-point (last visit) SMMSE and Qmci scores

		N	Baseline age, mean (±SD)	Gender (male, %)	Duration of follow-up in months, median (Q3–Q1)	Baseline score, median (Q3−Q1)	End-point score, median (Q3–Q1)
SMMSE	CACE-I	83	77.3 (±6.6)	53	17 (34–7)	22 (25–19)	20 (25–14)
	NoCACE-I	270	77.1 (±7.6)	49.3	18 (31–9)	23 (26–19)	20 (25–13)
	NewCACE-I	30	77.3 (±8.2)	50	6 (7–4)	23 (27–18)	24 (27–19)
Qmci	CACE-I	41	78.9 (±6.1)	56.1	16 (31–7)	36 (44–23)	29 (49–15)
	NoCACE-I	114	78.0 (±7.6)	49.1	11 (24–6)	38 (47–27)	32 (45–17)

CACE-I, patients currently receiving ACE inhibitors; NewCACE-I, patients who were newly started on CACE-Is; NoCACE-I, patients who are not currently prescribed CACE-Is; Qmci, Quick Mild Cognitive Impairment; SMMSE, Standardised Mini-Mental State Examination.

decline in Qmci scores reached borderline significance, p=0.049. The median decline in scores (rate per 6 months) for the NewCACE-I group, on the SMMSE, was −1.2 points for the NewCACE-I group, significantly less than for the CACE-I group (median 0.8); p=0.003 and NoCACE-I group (median 1.0), p=0.001. The Qmci could not be compared for the NewCACE-I group, as the numbers were too small. These results are presented in table 3. Multivariate regression analysis was used to compare the end-point cognitive scores (SMMSE and Qmci), adjusting for baseline cognitive scores (SMMSE and Qmci) and patient characteristics (age, education, duration of follow-up and BP). There were significant differences in end-point scores for the SMMSE (p=0.002) between all three groups (CACE-I, NoCACE-I and NewCACE-I). No significant difference was seen, for the Qmci, comparing the CACE-I and NoCACE-I groups, (p=0.172).

CONCLUSION

This study demonstrates a small reduction in the rate of cognitive decline, measured with the SMMSE and Qmci, in patients taking CACE-Is compared to the NoCACE-I group. The changes in Qmci scores over 6 months were small but statistically significant. The SMMSE scores, while non-significant, suggested a possible slower progression among those currently receiving CACE-Is. NewCACE-I patients, started on CACE-Is while attending clinic, showed a median improvement rather than a decline in SMMSE scores, over the first 6 months of treatment, compared to those already taking CACE-Is and those not currently treated with CACE-Is. These results confirm an association between the use of CACE-Is, particularly during the first 6 months of treatment, and a reduced rate of cognitive decline. This is the first study to demonstrate that cognitive scores improve in patients starting on CACE-Is, compared to those already established on maintenance treatment. This may have been related to better medication compliance, the effects of improved BP control or increased cerebrovascular perfusion after initial treatment.[54 55]

The strength of the study lies in its large numbers and inclusion of different (AD, vascular and mixed) dementia subtypes. The study also investigates the effects of CACE-Is in an unselected clinic sample of older adults, whose mean age approached 80 years. It has a number of limitations. This study is an analysis of observational data collected in a 'real world' setting, where treatments, including antihypertensive agents, were administered on the basis of clinical judgement. Observational studies like this are subject to bias in that those who receive treatment may be systematically different from those

Table 3 Comparison of differences in Qmci and SMMSE scores between baseline and end point

	Groups	Mann-Whitney U test (p Values)
Changes in Qmci	CACE-I (53) vs NoCACE-I (102) median = 1.8* vs median = 2.1*	0.049
Changes in SMMSE	CACE-I (113) vs NoCACE-I (240) median = 0.8* vs median = 1.0*	0.77
	NewCACE-I (30) vs NoCACE-I (240) median = −1.2* vs median = 1.0*	0.001
	NewCACE-I (30) vs CACE-I† (83) median = −1.2* vs median = 0.8*	0.003

*Median score shows the change in six months for CACE-I, NoCACE-I and NewCACE-I
†CACE-I group excluding NewCACE-I patients.
CACE-I, patients currently receiving ACE inhibitors; NewCACE-I, patients who were newly started on CACE-Is; NoCACE-I, patients who are not currently prescribed CACE-Is; Qmci, Quick Mild Cognitive Impairment; SMMSE, Standardised Mini-Mental State Examination.

who do not. That said, the baseline demographic characteristics of the groups were similar and few participants, in the NewCACE-I group, received other medications that could have accounted for the differences observed. Compliance with antihypertensive treatment, which has been shown to reduce with time,[56 57] could also have been a confounding factor and may have accounted for the improvement in the NewCACE-I group. Similarly, duration of treatment with antihypertensive medications, prior to attending clinic, could not be established for the CACE-I and NoCACE-I groups in this retrospective analysis.

Although most patients in the database had a Qmci or SMMSE recorded, large numbers lacked results at the baseline or end point, limiting the numbers that could be included in the analysis. It is possible that the results would have differed with more complete data on all patients. However, the baseline cognitive scores were similar between those included and excluded because of missing data. In the comparison of the subgroup scores, change over the first 6 months of treatment was analysed as this is the accepted time scale to show evidence of benefit in clinical drug trials.[53] Although a small percentage (9%) had a shorter interval between the baseline and end-point scores, the duration of follow-up was standardised at 6 months to facilitate comparison. The accepted standard for measuring cognitive change is the ADAS-cog.[58] As this was an observational study in a clinic setting, only the Qmci and the commonly used SMMSE were available. The ADAS-cog is not an ideal test[59] and the Qmci has been shown to be as sensitive to change as its standardised version, the SADAS-cog.[60] Significant differences, between NewCACE-I and the other groups' scores, using the SMMSE, could not be replicated with the Qmci, as the numbers were too small to analyse.

In summary, this study demonstrates an association between the use of CACE-Is and reduced rates of cognitive decline, in an unselected sample of clinic patients with dementia, particularly in the first 6 months of treatment. This supports the growing body of evidence for the use of ACE-Is and other antihypertensive agents in the management of dementia.[18] Although the differences were small and of uncertain clinical significance, if sustained over years, the compounding effects may well have significant clinical benefits. However, this may be tempered by recent evidence suggesting that ACE-Is, by interfering with degradation of Aβ, could contribute to increased amyloid burden,[61–63] potentially accelerating dementia severity and rates of cognitive decline.[34] Indeed, ACE-Is may even increase mortality in patients with CI, suggesting that if ACE-Is are proven to be beneficial in dementia, not all patients will benefit.[64] Further study with an appropriately powered randomised trial is needed to confirm these findings and determine if and for how long these effects are sustained.[65] If these data can be reproduced in a randomised trial of sufficient length incorporating appropriate outcome measures, such as an amyloid positron emission tomography, then these agents are likely to have significant benefits in delaying or even preventing dementia.

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