PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of Centrally Acting Angiotensin Converting Enzyme Inhibitors on the Rate of Cognitive Decline in Dementia
AUTHORS	Gao, Yang; O Caoimh, Ronan; Healy, Liam; Kerins, David; Eustace, Joseph; Guyatt, Gordon; Sammon, David; Molloy, D. William

VERSION 1 - REVIEW

REVIEWER	Dr Shaun O'Keeffe Consultant Physician and Geriatrician Galway university Hospitals Ireland
REVIEW RETURNED	02-Apr-2013

THE STUDY	It is not clear in the text (but is in the abstract) that only those subjects with a second Qmci or SMMSE at least 6 months after the baseline are included in this report. It is reported (page 10 line 10) that both Qmci and SMMSE were 'administered to patients by trained raters (clinic nurses), blind to the diagnosis, prior to each assessment to monitor progression'. However, more than 50% of possible subjects did not have baseline and 6 month assessments recorded. Since this is a major weakness of the study, as the authors acknowledge, some explanation of this finding should be provided, including reporting whether the baseline or the follow up readings were missing and whether subjects excluded because of missing values differed from those included. In Figure 1, newCACE patients appear as a subset of CACE rather than, as would be more logical, a subset of those with noCACE at initial presentation. Comment It would seem preferable to include NewCACE patients in the NoCACE for analysis of baseline values and for a primary outcome of comparing rates of decline in the two groups and to look at (the very small number of) NewCACE only as a secondary measure.
RESULTS & CONCLUSIONS	The presentation of the results is hard to follow. Baseline Characteristics The first sentence (page 12, line 3) refers to Tables 1 and 2, both of which include only subjects with baseline and follow-up assessments. Then lines 4-9 refer to all potential subjects (i.e. including those excluded for missing values), divided into CACE and noCACE with comparisons between these groups. I don't see why this division is made and these comparisons reported. Not having two assessments is an exclusion factor. As noted above, the only

	point of interest is whether those excluded differ significantly from those included not whether CACE and noCACE differ in the whole potential population. Line 9-12 reads: 'After adjusting for baseline characteristics (age, education, duration of follow-up and BP), there were no significant differences in baseline cognitive scores (SMMSE and Qmci) between the three groups (CACE, NoCACE, and NewCACE)'. Does this refer to all 817 patients, and has this group now been split into three? If so, (1) the number of NewCACE has not been given and (2) surely some have been excluded because baseline scores were missing. The next sentence (line 12) reads: 'The mean number of years spent in education for the total sample was 11.2 years'. Does this refer to the 817 patients? Should it not come before the previous sentence? Lines 21-23 report that 'In the NewCACE, eight subjects were co-administered other medications that are associated with improvement in cognitive scores: CholEI (n=5), a diuretic (n=1), CCB (n=1) and L-thyroxine (n=1), while three had such medications discontinued: CholEI (n=1) and diuretic (n=2). Firstly, there is no mention of other groups. Does this mean that no such co-administration or discontinuation occurred in the other groups? Secondly, this states that 5 NewCACE subjects were given cholinesterase inhibitor, yet in Table 1 24 NewCACE patients (80%) are recorded as receiving these medications! Table 1: Mean and SD should be reported. I presume BP is also a mean reading. Table 2. Is duration of follow up a mean or median? Either way how can the average duration of follow-up for NewCACE patients be only 5.6 months if a minimum 6 months is required for inclusion?

REVIEWER	Dr Patrick Kehoe Joint Lead of Dementia Research Group, University of Bristol, UK I have no competing interests in relation to this study or the drugs discussed. I have undertaken minor advisory work for Novartis regarding unrelated compounds in another condition.
REVIEW RETURNED	09-Apr-2013

THE STUDY	There were some headings for which I had some queries which mostly are minor but which may equally arise for other readers. Are the patients representative of actual patients the evidence might affect? No was selected, not because the selection of AD patients wasn't appropriate but because it was not clear exactly why people with MCI, which appeared to be an appreciable number of subjects, were excluded? Indeed, the authors cited some studies that investigated how these drugs reduce the rate of progression of amnestic MCI

	(Rozzini et al, 2006) and the same groups other study in relation to conversion rates of MCI to AD by anti-hypertensive drugs (Rozzini et al, 2008). Thus in many respects, I thought there was an opportunity for the authors to explore some of these reported associations and the authors appear to have this data covered through the use of the Qmci tool? A similar query arose for me in terms of the exclusion of 'co-morbid' depression as it is stated in the Abstract, yet in the description of subjects, it appears the authors refer to the exclusion of all patients with depression (N=397) and it is only in Figure 1 is it made clear that this number includes both those with co-morbid and singular depression. It would be helpful for the numbers in the text to reconcile with those in the figure, but also it would be helpful to more explicitly state the rationale for the exclusion of co-morbid depression (which again is an appreciable number). There is admittedly mixed evidence (see Rogers and Spies, 2008) regarding the link between ACE-Is and ARBs in relation to depression and this may be the rationale but it should be clarified. Overall, I did wonder whether it might have been more useful to retain both the MCI and the co-morbid depressed patients for an initial larger analysis of patients with cognitive impairment in general (which is valid since a relatively modest proportion of people with MCI convert to AD, and co-morbidity of AD and depression is relatively common in a clinical setting) which is of course representative of the wider spectrum of patients in a clinical setting. One could then have focussed on the individual sub-groups that although have the disadvantage of requiring more statistical tests all remain valid test because of prior reports in the literature. Are the methods adequately described? Overall the methods seem to be very appropriate but the authors have not cited any papers to support how they allocated various drugs to either the CACE and NoCACE groups. There is in fact some debate as to how ACE-Is are often incorrectly treated as a 'class' and also how there are debates as to how best sub-group ACE-Is. Indeed there is also some debate in the literature as to which of the ACE-Is cross the blood brain barrier and to what extent. The authors refer to the Ohrui et al, 2004 and Sink et al, 2009 that are studies that also include some sub-division of drugs but another recent paper that may also be of interest and which is relevance to this study is that by Solfrizzi and colleagues (2013) (PMID:22203459) who also discuss some of the issues around ACE-I classification. Is the standard of written English acceptable for publication? Overall, the paper is very well written, there is one very minor point that I felt needed addressing. The authors referred to their exposure groups as CACE, NoCACE and NewCACE. To some readers this may be slightly confusing because ACE usually refers to the target of these drugs (i.e. angiotensin converting enzyme) and not the drugs themselves, thus I think it might help some readers if the authors used abbreviations that were more aligned to those more commonly e.g. CACE-Is and NoCACE-Is might be more appropriate? Are the references up to date and relevant? (If not, please provide

	details of significant omissions below.) A few references already mentioned and some below related to the results and discussion would ensure a better and broader representation of the some of the literature that this interesting study will sit within.
RESULTS & CONCLUSIONS	Are they discussed in the light of previous evidence? Is the message clear? On these two points I refer the authors to their statement "..if sustained over years, the compounding effect may well have significant clinical benefits." Overall I do not have any issues with this statement because it is based on an extrapolation of their current observations and it also echoes with similar studies eg. Ohrui et al, 2004 and others the authors cite. However, the authors have omitted to qualify that there is also another interesting question, of equal, if not more important clinical interest, that was first prompted in 2001 by Hu and colleagues and has been supported by a number of pre-clinical studies which we and others have referred to in some recent reviews (Fournier et al, 2009; Kehoe and Passmore, 2012). In short, there is also emerging data that ACE, the enzyme which is inhibited by these enzymes, may have a role in the degradation of Abeta. Therefore, this poses an interesting question. ACE-Inhibitors may indeed have short term cognitive benefits (e.g. from improved cerebral blood flow etc) as demonstrated here and in other studies by Ohrui et al, 2004; Rozzini et al and Hajjar et al cited by the authors, however, in the longer term, if ACE does degrade Abeta in vivo (which has yet to be proven in humans) then they equally could contribute to increased amyloid burden in the same people, potentially contributing to a more severe and accelerated rate of dementia which admittedly has yet to be shown. Yet there are some studies that suggest that some ACE-Is can contribute to worse rates of progression (Sink et al, 2009); higher incidence of dementia (Khachaturian et al, 2006) and most recently our own findings that there was a higher rate of mortality amongst people with AD and who were previously exposed to ACE-Is (Kehoe et al, 2013). Yet, what may be evident is support yet again for the lack of correlation between amyloid related pathology and cognitive decline which has often been cited. So in summary, the authors extrapolations are valid but they need to be expressed against a wider field of evidence that certainly highlights that there is certainly a very complicated picture starting to emerge in relation to whether ACE-Is are likely to have a therapeutic role in AD, or whether in fact they may have some adverse effects for people with AD. I agree with the authors that randomised controlled trials would bring more rigorous evidence to identify what might be the role of ACE-Is in AD. However, were such trials to be designed in a typical shorter-term symptomatic treatment period, as the authors current study design is intended to approximate to, it would not necessarily detect any potential amyloid related changes. Thus any such trials would need to be of longer duration (e.g. a number of years) and would also require appropriate outcome measures of amyloid-PET, or CSF amyloid measures to assess this. Within this then are are two issues. The first is almost another debate in its own right, that is whether it is appropriate to attempt such a trial, on ethical grounds, if there is any concern, that the ACE-Is could have an exacerbating effect on the disease. Second, since most if not all ACE-Is are now available in generic form, the funding would likely have to arise from public or charitable funding

	sources, which would be a large investment. Yet, when balanced against the ongoing healthcare costs of AD, it might be a risk worth taking. I would humbly suggest that some further discussion of these issues is warranted to provide readers a better view of the current broader context that relates to their study.
GENERAL COMMENTS	This is a very welcome and worthwhile study and is very timely given the increased interest in the potential therapeutic benefit of angiotensin II targetting drugs (both Angiotensin Converting Enzyme Inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs)) in Alzheimer's disease. The comments provided are intended to hopefully be of assistance to the authors on a few points where I felt that clarification was needed to improve the overall readability and contextualisation of what I thought was otherwise a very worthwhile and interesting study.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.
Dr Shaun O'Keeffe
Consultant Physician and Geriatrician
Galway university Hospitals
Ireland

1. It is not clear in the text (but is in the abstract) that only those subjects with a second Qmci or SMMSE at least 6 months after the baseline are included in this report.

The authors agree with the reviewer, that this is unclear. This was stated in the abstract and was incorrect. Instead, the duration of follow up was standardised as six months to facilitate comparisons. Some patients had less than six months follow up. A minimum of six months was not an inclusion/exclusion criterion. The text, (abstract) has been amended to reflect this. The abstract now reads “Patients were included if baseline and end-point (standardized at six months apart) SMMSE or Qmci scores were available”.
See pages 5 Line 18-19.

2. It is reported (page 10 line 10) that both Qmci and SMMSE were ‘administered to patients by trained raters (clinic nurses), blind to the diagnosis, prior to each vnot have baseline and 6 month assessments recorded. Since this is a major weakness of the study, as the authors acknowledge, some explanation of this finding should be provided, including reporting whether the baseline or the follow up readings were missing and whether subjects excluded because of missing values differed from those included.

This study was a retrospective analysis of data collected in an outpatient clinic setting. Subjects were excluded when follow-up cognitive scores were not available. Overall, 438 patients with dementia had only one visit and did not return for a follow up visit, while 456 did not have the same cognitive test recorded on two visits. In many cases patients came for a diagnosis, treatment was commenced and they were followed by their family doctors. Explanations for this, seen in studies of patients attending GPs or memory clinics include: loss to follow-up because of death or missed appointments and/or

poor tolerance of cognitive testing [Meeuwsen et al, BMJ 2012]. Return visits, if they occurred, were for a variety of reasons and the same cognitive scores were not always recorded routinely. Another confounding problem was that the cognitive tests, used in this analysis evolved over time. For example, for a period of time, we used the ABCS 135 [Molloy 2005, Standish 2007], and then this was changed to the Qmci test. This affected the ability to measure change in cognition over time with the same test. Unfortunately, due to time constraints, in busy clinics, even if recorded, not all data were collated for each visit, resulting in additional missing data. As this was a retrospective analysis of an existing database, exact reasons for loss to follow-up could not be ascertained. A regression analysis was run to compare the baseline cognitive scores (SMMSE and Qmci), adjusting for baseline characteristics (age, gender, education and blood pressure), between subjects who did not have follow-up data and those who had. There was no significant difference in cognitive scores between those two groups (p=0.512 for SMMSE and p=0.06 for Qmci). This has been added to the methods, see Page 10, lines 8-11. The authors acknowledge that the extent of missing data is a weakness, although the baseline characteristics of excluded subjects did not differ significantly from those included. The conclusion has been amended accordingly, see Page 16, Lines 1-4.

Ref:
Meeuwsen EJ, Melis RJ, Van Der Aa GC, Golüke-Willemse GA, De Leest BJ, Van Raak FH, Schölzel-Dorenbos CJ, Verheijen DC, Verhey FR, Visser MC, Wolfs CA, Adang EM, Olde Rikkert MG.Effectiveness of dementia follow-up care by memory clinics or general practitioners: randomised controlled trial. BMJ. 2012 May 15;344:e3086. doi: 10.1136/bmj.e3086.

Molloy D W, Standish TIM, Lewis D L. Screening for Mild Cognitive Impairment: Comparing the SMMSE and the ABCS. Can J Psychiatry 2005;50:52–58.

Standish T I M, Molloy D W, Cunje A, Lewis D L. Do the ABCS 135 short cognitive screen and its subtests discriminate between normal cognition, mild cognitive impairment and dementia? Int J Geriatr Psychiatry 2007;22(3):189-94.

3. In Figure 1, newCACE patients appear as a subset of CACE rather than, as would be more logical, a subset of those with noCACE at initial presentation.

The authors acknowledge and agree with this and have corrected Figure 1, to show NewCACE-I subjects as a subset of NoCACE-I rather than CACE-I.

Comment
4. It would seem preferable to include NewCACE patients in the NoCACE for analysis of baseline values and for a primary outcome of comparing rates of decline in the two groups and to look at (the very small number of) NewCACE only as a secondary measure.

The authors agree and have included NewCACE-I as a subset of NoCACE-I in Figure 1 and in the comparison of baseline characteristics between the CACE-I and NoCACE-I groups, See Page 11, lines 4-7. After removing NewCACE-I patients from the established CACE-I group at baseline, we re-analysed rates of decline between the two groups amending Table 3 and changing the results, see Page 14, Line 3. Doing this made no appreciable difference to the rates of decline, median change in SMMSE of 0.8 points per six months, although the p value changed from p=0.002 to p =0.003.

5. The first sentence (page 12, line 3) refers to Tables 1 and 2, both of which include only subjects with baseline and follow-up assessments. Correct.

The authors acknowledge this and have corrected the text to clarify, see Page 12, Line 9-10. It now reads “Table I shows the baseline characteristics, including demographics and medication use, for the

CACE-I, NoCACE-I and NewCACE-I groups. Table II presents their baseline and end-point Qmci and SMMSE scores."
Table 2 has also been relabeled, "Baseline and end-point (last visit) SMMSE and Qmci scores".

6. Then lines 4-9 refer to all potential subjects (i.e. including those excluded for missing values), divided into CACE and NoCACE with comparisons between these groups. I don't see why this division is made and these comparisons reported. Not having two assessments is an exclusion factor. As noted above, the only point of interest is whether those excluded differ significantly from those included not whether CACE and noCACE differ in the whole potential population.

The authors agree and have altered the text. Data referring to the total sample of patients has been removed and changed to reflect only those included in the study, see Page 12, Lines 5-14.

7. Line 9-12 reads: 'After adjusting for baseline characteristics (age, education, duration of follow-up and BP), there were no significant differences in baseline cognitive scores (SMMSE and Qmci) between the three groups (CACE, NoCACE, and NewCACE)'. Does this refer to all 817 patients, and has this group now been split into three? If so, (1) the number of NewCACE has not been given and (2) surely some have been excluded because baseline scores were missing.

The authors acknowledge that this was not presented clearly. The results in lines 9-12 refer to those included (115 receiving CACE-Is and the 246 receiving NoCACE-Is i.e. 361 finally included), rather than the total sample. The number of NewCACE-I was provided in Table I but not mentioned in the text. Those with missing data were excluded initially. After adjusting for baseline characteristics (age, education, duration of follow-up and BP), there were no significant differences in baseline cognitive scores (either SMMSE and Qmci) between the three groups (CACE-I, NoCACE-I, and NewCACE-I). The text has been amended to clarify, see Page 12, Line 8-9 and 15-19. It now reads: "Within the NoCACE-I group, 30 subjects had been started on an ACE-I while attending clinic (NewCACE-I)….. After adjusting for baseline characteristics (age, education, duration of follow-up and BP), there were no significant differences in baseline cognitive scores (SMMSE and Qmci) between the three groups (CACE-I, NoCACE-I, and NewCACE-I)".

8. The next sentence (line 12) reads: 'The mean number of years spent in education for the total sample was 11.2 years'. Does this refer to the 817 patients? Should it not come before the previous sentence?

The authors acknowledge that this was misleading. "Total sample" here referred to the total sample included (n=361) rather than the initial sample of 817. The authors also agree that it was incorrectly placed in the text. Line 12 has been amended to refer only to the 361 subjects finally included and has been repositioned alongside the results of the baseline characteristics; see Page 12, Lines 5-6.

9. There is no mention of medications for the other groups. Does this mean that no such co-administration or discontinuation occurred in the other groups?

Details of medications co-administered (or discontinued) to NewCACE-I subjects were provided to demonstrate that reduced rates of decline in cognitive scores were attributable to the initiation of the CACE-I rather than any other medication. The distribution of medications prescribed for memory loss (cholinesterase inhibitors, ChEI or memantine) were similar for subjects in the CACE-I, NoCACE-I or NewCACE-I groups, ChEI p=0.40 and memantine, p=0.98. The text (results) has been amended to clarify; see Page 12, Lines 19-22. It now reads "In relation to medications, 88.2% of the CACE-I, 82.6% of the NoCACE-I and 80% of those in the NewCACE-I group, were receiving cholinesterase inhibitors (CholEI). A smaller percentage was currently prescribed memantine. There was no

difference in the distribution of ChEIs (p=0.40) or memantine (p=0.98) between CACE-I, NoCACE-I or NewCACE-I groups."

10. Secondly, this states that 5 NewCACE subjects were given cholinesterase inhibitor, yet in Table 1 24 NewCACE patients (80%) are recorded as receiving these medications!

The total number of NewCACE-I subjects (started on an CACE-Is while attending clinic) receiving cholinesterase inhibitors was 24 (80% of all NewCACE-I subjects). Of these, 5 (5/24), commenced cholinesterase inhibitors at the same time as the CACE-I. The authors agree that this was not clear and the sentence has been deleted.

11. Mean and SD should be reported in Table 1: I presume BP is also a mean reading.

The authors agree and have amended Table I accordingly. We have now included the standard deviations with the mean values in tables I and II.

12. In Table 2, is duration of follow up a mean or median? Either way how can the average duration of follow-up for NewCACE patients be only 5.6 months if a minimum 6 months is required for inclusion?

The duration of follow-up is expressed as a median. The authors acknowledge this and have corrected Table 2 accordingly, including the interquartile range. The authors acknowledge that the duration of follow-up was not clear. The median duration of follow-up for the NewCACE-I was 6 months (mean 5.6 months) with an interquartile range of 4 to 7 months because, as described above, we did not require a "minimum" of six months. This was stated in the abstract and was incorrect. Instead, the duration of follow-up was standardised as six months to facilitate comparisons. Some patients had less than six months follow up. A minimum of six months was not an inclusion/exclusion criterion. The text has been amended to clarify this. The conclusion has been amended to acknowledge this, see Page 16, Lines 6-8, which now reads "Although, a percentage (9%) had a shorter interval between baseline and end-point scores, the duration of follow-up was standardised as six months to facilitate comparisons".

Reviewer: Dr Patrick Kehoe
Joint Lead of Dementia Research Group,
University of Bristol, UK

1. Are the patients representative of actual patients the evidence might affect? Clarify why people with MCI, which appeared to be an appreciable number of subjects, were excluded?

The authors thank the referee for his comments. We excluded patients with MCI for a number of reasons. Firstly their rate of change is slower than dementia [Wilson et al Arch Neurol 2011; 68(3): 351–356.], and would in this respect, have affected and possibly biased the effects on the dementia group. Given that the rate of cognitive decline was the primary outcome, the large discrepancy between dementia and MCI would preclude putting these groups together. It would skew the data. In addition, the SMMSE, given its ceiling effects, is poor at measuring rate of cognitive change in MCI. The number of subjects with MCI who had a Qmci recorded at baseline and follow-up was too small to analyse in this study, n=13. The authors agree that this requires further assessment but believe that rate of change in subjects with MCI should be evaluated separately. We are currently looking at the rate of change of cognition, in a separate study, using the Qmci tool. The text (methods) have been amended to reflect this, see page 9, Line 23-25, which now reads " Subjects with MCI were

excluded because few, n=13, had baseline and end-point Qmci scores available, the SMMSE is insensitive to MCI [O'Caoimh Age and ageing 2012], and rates of cognitive decline vary depending on cognitive measures used [Monsell et al, Psychogeriatr 2012;24(10):1553-60.]".

Ref:
Wilson R S, Leurgans S E, Boyle P A, Bennett D A Cognitive Decline in Prodromal Alzheimer's Disease and Mild Cognitive Impairment. Arch Neurol 2011; 68(3): 351–356.

O'Caoimh R, Gao Y, McGlade C, Healy L, Gallagher P, Timmons S, et al. Comparison of the quick mild cognitive impairment (Qmci) screen and the SMMSE in screening for mild cognitive impairment. Age and ageing. 2012;41(5):624-9.

Monsell SE, Liu D, Weintraub S, Kukull WA. Comparing measures of decline to dementia in amnestic MCI subjects in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set. Psychogeriatr 2012;24(10):1553-60.

2. In relation to subjects with depression, it would be helpful for the numbers in the text to reconcile with those in the figure.

In the analysis presented in this paper, all subjects screening positive for depression, on the geriatric depression scale (15 point), were excluded. This included 260 persons with dementia and comorbid depression, and 137 with isolated depression with normal cognition. The authors acknowledge this and have amended the text (methods) to clarify, see Page 10, Lines 1-3 which reads "397 subjects were excluded because of depression: 260 with CI and co-morbid depression and 137 with normal cognition and depression".

3. Explicitly state the rationale for the exclusion of subjects with co-morbid depression.

Co-morbid depression was selected as an excluding factor as there is limited evidence that ACE-Is affect co-morbid depression (Rogers and Pies, 2008), while depression is known to negatively affect the results of cognitive testing [Porter BJP 2003]. To support this, we analysed the SMMSE and Qmci subtests, comparing the pattern of deficits for different conditions. We found that the pattern of deficits was different for each. Patients with depression had marked language impairment compared to those with dementia without depression. The majority (63%) of subjects, presenting with subjective memory loss but evident depression, were female, which may also have biased results. In addition, their mean age, 72.7 (SD of 10.7) of suspend with dementia, was significantly younger than subjects with dementia (n=817), $p<0.001$. The methods section has been amended to provide a rationale for the exclusion of residents with depression, see Page 9-10, Lines 26-5 which reads "Subjects were screened for depression using the 15-point Geriatric Depression Scale. As there is limited evidence that ACE-Is affect co-morbid depression (Rogers and Spies, 2008), while depression is known to negatively affect the results of cognitive testing, 397 subjects with depression were excluded: 260 with CI and co-morbid depression and 137 with normal cognition and depression. Subjects with depression were predominantly (63%) female and were significantly younger than subjects without depression, mean age of 72.7 (SD of 10.7), $p<0.001$.

Ref:
Porter RJ, Gallagher P, Thompson JM, Young AH.Neurocognitive impairment in drug-free patients with major depressive disorder. Br J Psychiatry. 2003;182:214-20.

Rogers D, Pies R. General Medical Drugs Associated with Depression. Psychiatry 2008; 5(12): 28–41.

4. Would it have been more useful to retain both the MCI and the co-morbid depressed patients for an initial larger analysis of patients with cognitive impairment in general.

Dr Kehoe raises a very interesting point. The authors agree that this requires further assessment and that both patients presenting with MCI and co-morbid depression should be analysed separately as part of an evaluation of CACE-Is treatment on cognitive impairment, in general. We chose to exclude MCI and depression from the analysing to try to keep the sample as clean as homogenous as possible. We believe that depression and MCI should be studied separately, because of the qualitative differences in the cognitive sub-scores and rate of decline.

5. Are the methods adequately described?
The authors have not cited any papers to support how they allocated various drugs to either the CACE and NoCACE groups. Clarify.

The authors thank and acknowledge the reviewer for this observation. The CACE-Is included in this study were perindopril, ramipril, trandolapril, captopril, fosinopril, lisinopril, prinivil and monopril. This list was obtained from the paper by Sink et al, 2009, see reference below. The authors have added the reference by Solfrizzi and colleagues (2013) (PMID:22203459). The methods section has now been amended to reference both papers, see Page 10, Line 13.

Ref:
Sink KM, Leng X, Williamson J, Kritchevsky SB, Yaffe K, Kuller L, Yasar S, Atkinson H, Robbins M, Psaty B, Goff DC Jr. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. Arch Intern Med. 2009 Jul 13;169(13):1195-202.

Solfrizzi V , Scafato E, Frisardi V, Seripa D, Logroscino G, Kehoe P G, Imbimbo B P, Baldereschi M, Crepaldi G, Di Carlo A, Galluzzo L, Gandin C, Inzitari D, Maggi S, Pilotto A, Panza F. Angiotensin-converting enzyme inhibitors and incidence of mild cognitive impairment. the italian longitudinal study on aging. Age 2013;35(2):441-453.

6. Is the standard of written English acceptable for publication?
There is one very minor point that I felt needed addressing. Please address the nomenclature.

The authors complete agree with the reviewer and have changed CACE to CACE-I, NoCACE to NoCACE-I and NewCACE to NewCACE-I throughout.

7. A few references already mentioned and some below related to the results and discussion would ensure a better and broader representation of the some of the literature that this interesting study will sit within.

The authors thank and acknowledge the reviewers suggestions. The references mentioned have been included. See references 49, 51, 59, 60, 61, 62.

8. Are the results discussed in the light of previous evidence? Is the message clear? The authors have omitted to qualify that ACE, may have a role in the degradation of Abeta, which could contribute to increased amyloid burden, potentially contributing to a more severe and accelerated rate of dementia.

The authors agree and have amended the discussion to incorporate this point, see Page 16, Lines 18-23, the line now reads: “if sustained over years, the compounding effects may have significant clinical benefit. However, this may be tempered by recent evidence suggesting that ACE-Is, by

interfering with degradation of Abeta, could contribute to increased amyloid burden (Hu et al 2001) (Kehoe, Passmore 2013) (Fournier et al 2009), potentially accelerating dementia severity and rates of cognitive decline (Sink et al, 2009). Indeed, ACE-I may increase mortality in subjects with CI, suggesting that even if ACE-I are proven to be beneficial in dementia, not all subjects will benefit (Kehoe et al, 2013).

Ref:

Hu J, Igarashi A, Kamata M, Nakagawa H. Angiotensin-converting enzyme degrades Alzheimer amyloid β-peptide (Aβ); retards Aβ aggregation, deposition, fibril formation; and inhibits cytotoxicity. Journal of Biological Chemistry. 2001;276(51):47863-8.

Kehoe PG, Passmore PA. The Renin-Angiotensin System and Antihypertensive Drugs in Alzheimer's Disease: Current Standing of the Angiotensin Hypothesis? Journal of Alzheimer's Disease. 2012;30:S251-S68.

Fournier A, Oprisiu-Fournier R, Serot J-M, Godefroy O, Achard J-M, Faure S, et al. Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. Expert review of neurotherapeutics. 2009;9(9):1413-31.

Sink KM, Leng X, Williamson J, Kritchevsky SB, Yaffe K, Kuller L, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. Archives of Internal Medicine. 2009;169(13):1195.

Kehoe PG, Davies NM, Martin RM, Ben-Shlomo Y. Associations of Angiotensin Targeting Antihypertensive Drugs with Mortality and Hospitalization in Primary Care Patients with Dementia. Journal of Alzheimer's Disease. 2013;33(4):999-1008.

9. I agree with the authors that randomised controlled trials would bring more rigorous evidence to identify what might be the role of ACE-Is in AD. However, such trials would need to be of a long duration and require appropriate outcome measure.

Thank you for your helpful comments. The authors agree and have included this in the discussion section, See page 16, lines 24-26. The line now reads: “If these data can be reproduced in a randomized trial, of sufficient length and incorporating appropriate outcome measures, such as amyloid-PET, then these agents are likely to have significant benefits, in delaying or even preventing dementia”.

VERSION 2 – REVIEW

REVIEWER	Dr Shaun O'Keeffe Consultant Physician and Geriatrician Galway university Hospitals
REVIEW RETURNED	13-May-2013

- The reviewer completed the checklist but made no further comments.