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Can Angiotensin-Converting Enzyme Inhibitors Slow the Progression of Cognitive Decline In Elderly Patients With Dementia?

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Abstract

Background: Dementia is a slow progressing neurodegenerative disease characterized by loss of executive functioning, communication ability, and activities of daily living. With few treatment options currently approved for dementia, angiotensin-converting enzyme inhibitors (ACE-I) have been implicated as a new potential treatment to slow cognitive decline. ACE-I use in dementia, however, is controversial due to conflicting research and new discoveries into the pathophysiology of the brain and ACE. This systematic review aims to evaluate the current research on ACE-I use in cognitive decline.

Methods: Exhaustive search of available medical literature databases including Medline (Ovid/PubMed), Google Scholar, Clinical Key, and Web of Science was conducted. Keywords used in the search included: *Alzheimer's disease, dementia, ACE inhibitors, angiotensin converting enzyme inhibitors, cognitive decline, renin-angiotensin system,* and *RAS.* Alzheimer's disease (AD) and vascular dementia (VaD) was the focus of this review based on the proposed pathophysiology. Studies were included if cognitive assessment tools such as the mini mental status exam, mini-cog or Qmci, were assessed at baseline and an end-point with a minimum of 6 months. Articles were assessed for quality using the GRADE criteria.

Results: Five studies met inclusion criteria and were evaluated. Three of the studies found were observational, one study was a randomized controlled trial, and one was a cohort study. With the exception of one very low quality study, the results were consistent that ACE-I may provide slowing of the progression of cognitive decline in dementia patients.

Conclusion: Current research on dementia progression and ACE inhibitors, as measured by cognitive assessment tools, have been shown to slow cognitive decline in elderly patients. Further research, preferably multiple, large randomized controlled human trials are necessary to determine the risk versus benefit of ACE inhibitor use.

Keywords: Alzheimer's disease, dementia, ACE inhibitors, angiotensin converting enzyme inhibitors, cognitive decline, renin-angiotensin system, RAS.

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[Redacted for privacy]

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List of Abbreviations

Aβ	Amyloid-Beta
ACE-I	Angiotensin-Converting Enzyme Inhibitor
AD	Alzheimer's Disease
ADL	Activities of Daily Living
ARBs	Angiotensin II Receptor Blockers
BP	Blood Pressure
CACE-I	Centrally Acting ACE Inhibitors
CDR-SB	Clinical Dementia Rating scale – Sum of the boxes
CCB	Calcium Channel Blocker
DSM	Diagnostic and Statistical Manual
SMMSE	Standardized Mini-Mental State Examination
RAS	Renin-Angiotensin System
Qmci	Quick Mild Cognitive Impairment Screen
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association
NINCDS	National Institute of Neurological Clinical Disorders and Stroke
VaD	Vascular dementia

Can Angiotensin-Converting Enzyme Inhibitors Slow the Progression of Cognitive Decline In Elderly Patients With Dementia?

BACKGROUND

One in nine patients in the United States over the age of sixty-five have been diagnosed with dementia, a disease defined by an insidious, progressive, and significant decline in higher cognitive function.[1] Dementia types include Alzheimer's disease (AD), Lewy body dementia and Parkinson disease with dementia, frontotemporal dementia, and vascular (multi-infarct) dementia (VaD).[1] Despite these different sub-diagnoses, patients share difficulty with both executive functioning and activities of daily living (ADL). Deficits can include changes in learning, memory, language, attention, perceptual-motor function, and social cognition. In addition, these symptoms are associated with a high frequency of psychiatric changes such as depression.[11] These debilitating changes place a large emotional, physical, and financial burden on caregivers.

Unfortunately, treatment options are lacking and have been limited to N-methyl-D-aspartate (NMDA) receptor antagonists, cholinesterase inhibitors, as well as symptomatic care.[1] These medications are only marginally successful and a cure for dementia

has yet to be found. Current avenues of research have been focused on risk reduction, namely with genetic and cardiovascular risk factors. Angiotensin converting enzyme inhibitors (ACE-I) have been implicated as a potential new avenue of treatment, although their use in cognitive improvement is not without some controversy.

The renin-angiotensin system (RAS) has been thoroughly studied in the brain and is thought to be independent to that of the peripheral RAS system.[2] Traditionally, the RAS system includes renin acting on angiotensinogen to produce angiotensin I, which is then later cleaved by ACE to angiotensin II. Angiotensin II is associated with vasoconstriction and an increase in blood pressure (BP); one of the major risk factors for VaD and AD development. Angiotensin II is also associated with inhibition of acetylcholine release in the brain, an important avenue of the current drug therapy. It is hypothesized that inhibition of ACE may contribute to increases in acetylcholine and therefore improve cognitive function.[7]

It has now been observed that angiotensinogen cleaves into many different neuropeptides in the brain. These may mediate neuro-cognitive processes such as memory, processing sensory information, emotions, and learning.[2] Moreover, high levels of angiotensin receptors are found in areas of the brain associated with cognitive function and memory such as the cortex, hippocampus, and amygdala.

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The involvement of the role of ACE in relation to these various angiotensins and their receptors is still being investigated. The pathophysiology and role of ACE in the brain is further complicated by another proposed mechanism.

Alzheimer's disease, in particular, is marked by amyloid-beta (Aβ) protein aggregation and plaque formation. In animal models, ACE has been shown to degrade Aβ protein aggregation.[8] In addition, a study in 2014[6] examined the relationship between ACE inhibition, Aβ levels, and ACE in the CSF, further bolstering the current animal model research stating ACE has a helpful role in degradation of protein aggregates. In other words, inhibiting ACE via medication may increase plaque formation. The mechanism for which this occurs, is still being investigated. This finding, however, is inconsistent in the literature. Other animal model trials illustrated that despite injections of Aβ, cognitive outcomes were better with use of certain brain-penetrating ACE-Is.[7]

The extent of RAS involvement in the development of dementia is still unknown. The effect of ACE in relation to the pathophysiology of VaD and AD are also unresolved. This paper aims to review the current literature regarding ACE inhibitors and the progression of cognitive decline.

METHODS

An exhaustive systematic search of online databases including Medline (Ovid/PubMed), Google Scholar, Clinical Key, and Web of Science was conducted. Keywords used in the search included: *Alzheimer's disease, dementia, ACE inhibitors, angiotensin converting enzyme inhibitors, cognitive decline, renin-angiotensin system,* and *RAS.* In addition, the reference sections of relevant articles were also screened for pertinent studies.

Studies were included if patients involved were diagnosed with dementia according to National Institute of Neurological Clinical Disorders and Stroke (NINCDS) standards, National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), or the current Diagnostic and Statistical Manual (DSM-V). Based on the proposed mechanism of action of ACE inhibitors, only Alzheimer's dementia and/or vascular dementia types were included. All types of ACE inhibitors, both centrally acting and non-centrally acting were also included. Use of recognized cognitive diagnostic measures such as MMSE, MOCA, and Qmci, both before and after ACE inhibition, were necessary to track the progression of cognitive decline. A minimum total length of study for at least six months between baseline and subsequent cognitive testing was a requirement for inclusion.

The articles that were excluded did not take into account co-morbid factors such as years of education, history or current hypertension, cardiovascular disease, or depression that may have worsened dementia progression and outcomes. Studies that were based on specific diagnostic biomarkers or other objective measurable effects aside from cognitive assessment tools were also excluded. Non-English language articles or studies based on animal trials were excluded as well.

The quality of these articles was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.

RESULTS

The review of the literature yielded a total of five studies that matched the aforementioned inclusion criteria. Due to the nature of dementia and the cognitive assessment tools used, most studies are observational with the exception of one randomized control trial completed in 2004[3] and one cohort study.[11] After searching the reference sections of each article, no further studies were found to fit the criteria outlined in this review.

CAOIMH et al (2013)
This observational study is a secondary analysis of a previous randomized controlled trial (RCT) from the Doxycycline and Rifampin

for Alzheimer's Disease trial (DARAD). Participants were aged 50 years or more and were diagnosed with mild to moderate dementia based on the National Institute of Neurological Disorders and Stroke (NINCDS) criteria. Patients included in the study were from 14 geriatric outpatient clinics in Canada.

The study aimed to compare the rate of functional decline in patients using centrally acting angiotensin-converting enzyme inhibitors (CACE-I) compared to no CACE-I use. The CACE-I group was further divided into two groups, those using the specific CACE-I, Perindopril, and those who were using other CACE-Is. Perindopril has been shown to prevent cognitive impairment in mouse models, and therefore was analyzed more carefully in this study.[9] Out of a total sample of 406 participants, 41 were excluded. The excluded patients were reported as either lost to follow up, withdrawal from the trial, adverse events (unspecified), or other reasons such as moving or caregiver death. The CACE-I group was smaller (n=91) than the no CACE-I (n=274). The group taking CACE-I Perindopril was also smaller (n=21) compared to other CACE-I use (n=70).

Secondary outcomes for the DARAD trial included multiple cognitive assessment tools including the Qmci as well as other measures of ADL and cognition. Baseline and end-point scores were collected at an interval of 12 months. Background factors such as age,

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gender, years of education, blood pressure, cholinesterase inhibitor use and memantine use were taken into account and adjusted for in the analysis of data (multivariate regression analysis). The Qmci median interquartile range at baseline (4) versus at follow up 12 months later (5) showed a 20% slower rate of decline for the CACE-I group. In addition, perindopril was found to have slower rates of decline with Qmci. However, these finding were not statistically significant. The statistical significance in this study lies with the assessment of ADLs with the Lawton-Brody ADL scale, which showed a 25% reduction in the rate of decline over 12 months (p=0.034, adjusted for baseline factors).

Researchers in this study focused on the rate of functional decline, as compared to cognitive decline, however the results continue to support the use of CACE-I in the reduction of rate of disease progression in dementia.

GAO et al (2013)

Cognitive decline in dementia patients was observed in this study by comparing three groups; CACE-I, no CACE-I, and new CACE-I (patients who started CACE-Is during the first 6 months of treatment). Participants were sampled from two university hospital memory clinics in Canada via the Geriatric Assessment Tool database. All patients were diagnosed with dementia via the NINCDS guidelines. This study

included only AD, vascular, and mixed dementias (AD/vascular combinations). Participants were excluded if they had other types of dementia, normal or only mild cognitive impairment, or associated/co-morbid depression. Patients were also screened for depression with the Geriatric Depression Scale and were excluded if depression was found. This was done because it is shown that depression can negatively affect the results of cognitive testing. Characteristics such as age, gender, education, blood pressure, cholinesterase inhibitor use, and memantine use were also compared between groups. The participants ages were reported as 77.2 ± 6.4, with 50.3% of them being male, and with an average of 11.2 years of education. These demographics were similar across all groups. These characteristics were adjusted for in all analyses.

Baseline and end-point SMMSE and Qmci were used to measure cognitive decline. End-point testing was performed at 6 months by trained nurses who were blind to the diagnosis. Gao et al explain that a 6-month interval was chosen based on the fact that the US Food and Drug Administration requests this amount of time to pass before assessing the benefit from new medications for cognitive decline. Number of participants with SMMSE and Qmci scores differed significantly between groups; CACE-I (SMMSE 83, Qmci 41), No CACE-

I (SMMSE 270, Qmci 114), New CACE-I (SMMSE 30, No Qmci participants).

Nevertheless, the study found that there were statistically significant changes for Qmci scores within 6 months for CACE-I (p=0.049). In addition, the New CACE-I group showed a median improvement in SMMSE scores compared to the other groups, rather than a cognitive decline. Interestingly this study showed that the use of CACE-I may be most beneficial within the first 6 months, as compared to those on maintenance CACE-I. Gao et al attribute this to possible effects of medication compliance, improved BP control, or increased cerebrovascular perfusion.

HAJJAR et al (2008)

Hajjar et al is an observational, prospective, and longitudinal study that assessed both cognitive and functional decline in AD. Cognitive assessments included the MMSE, clock draw test, and working memory (digit ordering). For the purposes of comparison, MMSE will be the focus of the analysis of this paper. Participants with mild to moderate AD were recruited between July 2004 through June 2005 through a geriatric primary care practice and memory disorders clinic. The study included participants who were diagnosed with possible or probable AD according to the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's

Disease and Related Disorders Association (NINCDS-ADRDA).
Dementia types other than AD were excluded.

The participants also had to be older than 55 years of age, have a reliable caregiver, and perform cognitive and functional assessments at the study center. Exclusions were based on previous cardiovascular and neurological history (atrial fibrillation, myocardial infarct, stroke, delirium, seizures). Patients with depression were receiving antidepressants were allowed into the study if they had been on a stable dose for 6 months prior to the study start date. Recruitment for the study was done at geriatric primary care facilities, memory disorder clinics, as well as announcements at retirement homes, senior centers, and assisted living communities. A total of 62 participants were enrolled, however 10 were lost to follow up. Demographic information, family history, medication history, and history of alcohol or tobacco use was obtained. No change in use of ACE-I or acetylcholinesterase inhibitors was found during the study period.

Participants were categorized into ACE-I use and no ACE-I use. Cognitive and functional assessments were collected at baseline, 3 months, and 6 months. For the purposes of this review, measurements at 6 months were compared to those at baseline. At baseline no differences were found between groups at baseline in terms of age, gender, race, education, or cognitive or functional assessments. The

results of the study showed that for cognitive assessments (MMSE, clock draw test, and the digit ordering test) there was no statistical significance found, although there was a trend in slower decline. This study did demonstrate an improvement in ADLs in the ACE-I group versus the no ACE-I use group (P=0.005). Assessment of caregiver stress was also found to be significant (P=0.03 un-adjusted, P=0.04 adjusted). These results reveal that ACE-I have significant effects on functional decline.

OHRUI et al (2004)

Ohrui et al was the only randomized control trial found in the search of the literature. The study's goals were to determine the effect of ACE-I, specifically brain-penetrating inhibitors, on AD patients exposed to medications over a one-year period. Participants were chosen based on the NINCDS-ADRDA criteria from three long term care facilities in Sendai, Japan. These participants were 65 years of age and older with baseline MMSE scores putting them in the moderate dementia category (13 to 23). Patients were screened and eliminated from the study if they had a history of cardiovascular disease, renal failure, psychiatric disease, drug use or dependency. Although patients with co-morbid conditions such as cardiac arrhythmias, hypercholesterolemia, or osteoporosis were not excluded from the research criteria, they were represented in equal proportion throughout the three research groups.

In addition, the patients all underwent brain MRI studies to exclude patients with possible vascular or other types of dementia in order to focus as closely as possible to the effect of these medications on Alzheimer's disease. Other medications such as anticholinergics, anticonvulsants, antipsychotics or antidepressants were removed from the study. However, if the participant was on a stable cholinesterase inhibitor dose, statin, or low-dose aspirin, these were allowed. The number of participants on each of these medications was similar in all groups as well.

Patients (n=182) were randomly assigned into three groups of medication treatment; Group A: brain penetrating ACE-I (n=51), Group B: non-brain penetrating ACE-I (n=53), or Group C: calcium channel blocker (n=58). MMSE scores were used to measure cognitive status at baseline and at one-year. During the course of treatment, only one participant was lost to follow up due to hypotension.

Results indicated that there was a slower cognitive decline for patients taking brain penetrating ACE-I (group A) compared to both groups B and C (p=0.0023 and p<0.001, respectively). This indicates that brain penetrating ACE-I could slow the rate of cognitive decline in AD. Ohrui et al[10] state that the rate of decline for groups B and C were more severe than in previous studies, and therefore those that had significant decline (MMSE score decline of 6 points or greater) were re-

evaluated and were shown to have more impairment with ADL. Once these outliers were removed and the data was re-analyzed, groups B and C rates of MMSE decline were comparable to prior studies. Therefore, the researchers propose that the most benefit may be found with those patients started on a brain-penetrating ACE-I with mild ADLs to prevent rapid decline in MMSE scores.

SOTO et al (2013)

This cohort study had the longest baseline to endpoint time of four years, with biannual assessment of the MMSE by a memory expert physician. It also had the largest starting sample size of any study reviewed (n=686). Participants met dementia criteria according to the DSM and NINCDS-ADRDA standards. Only mild to moderate dementia patients were included, as defined by MMSE scores. Participants were acquired in 16 specialized memory clinics in France from April 2000 to October 2002. Caregiver support was also a requirement of this study. Brain CT scans were obtained at baseline to rule out any vascular lesions.

The participants were then grouped into four categories based on their use of hypertensive medications: continuous/intermittent other drug users, continuous ACE inhibitors users, intermittent ACE inhibitors users, and never drug users. Trained nurses obtained drug use information at each of the biannual visits. Continuous users were defined as patients who reported using the same medication at both

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visits. Intermittent users were defined as patients that discontinued or started an ACE-I during the study. Participants who were taking angiotensin II receptor blockers (ARBs) were excluded to assess the sole effect of ACE-I use.

Confounding factors such as sociodemographic characteristics, ADLs, behavioral and psychiatric conditions, and cardiovascular disease and risk factors were taken into account and adjusted for in the analysis of the data. Both unadjusted and adjusted data were presented without loss of significance in data. There were no significant changes in baseline MMSE scores between groups.

Unfortunately, there was a substantial loss of patients during follow-up, some of which dropped out of the study, died, were institutionalized, had caregiver health problems, or were unable to be contacted. At the 6-month assessment there were 513 completers. By the end of the 48-month assessment, there were a total of 179 completers. In total, for the continuous users of ACE-I group 70.5% of patients dropped out, in the intermittent users of ACE-I 59.6% dropped out, 66.1% of continuous or intermittent users of other antihypertensive drugs dropped out, and lastly, 68.1% of never users dropped out. [11]

Results showed a significant difference in MMSE scores between the groups as the study progressed. In comparing the continuous ACE-

I group to the never used antihypertensive drugs group, the MMSE for continuous ACE-I users showed significantly less decline (MMSE decline difference of -4.9 $\pm$ 1.8, p=0.01). However, when comparing the continuous versus intermittent ACE-I users, no significant difference was found (MMSE decline difference -3.1 $\pm$ 1.8, p=0.06). Continuous ACE-I users were also compared to the users of other antihypertensive drugs group. This comparison also revealed no significant difference in decline (MMSE decline difference -2.6 $\pm$ 1.9, p=0.20). The researchers state that in restricted analysis, however, participants that used ACE-I continuously or intermittently did show slower rates of cognitive decline compared to the two control groups. The significance in the data began in the second, third and fourth years (p=0.05, p=0.04, p=0.03 respectively). Due to the loss of follow up, Soto et al also calculated differences between the groups with slope analysis to represent the trend of the data. MMSE decline in both unadjusted (p<0.04) and adjusted (p<0.02) were significant.

The data presented in this study suggests that both continuous and intermittent use of ACE-I help to slow the progression of cognitive decline in MMSE scores compared to other hypertensive users or those that take no hypertensive medications. A secondary analysis was then done to determine any significance with users of ARBs, of which no significance was found. The evidence presented by Soto et al also

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suggest that ACE-I may have a separate mechanism by which they have cognitive benefits due to the superior change in MMSE scores compared to participants taking other antihypertensive medications.

DISCUSSION

Current dementia treatment is limited, giving both healthcare providers and family members few options. No current treatment exists to halt the progression of the disease, however the ability to preserve or slow cognitive decline is the primary goal. Angiotensin converting enzyme inhibitors have shown evidence to slow the rate of cognitive decline in elderly patients with dementia.[3,5,10] As a secondary adjunct to this analysis, ACE inhibitors also have been demonstrated to improve functional decline in relation to activities of daily living and caregiver burden.[3,5,9] While ADLs and caregiver burden are difficult to objectify, the value of allowing elderly patients greater function is priceless. This research implies the potential benefit of ACE inhibitors for dementia treatment.

Three studies[3,9,10] in particular investigated the effect of centrally acting or brain penetrating ACE-I. Medications that are considered brain penetrating include enalapril, perindopril, captopril or Lisinopril. However, these medications may have different levels of brain penetration, which are unknown. In this regard, all ACE-I are not created equal and more research needs to be conducted on the

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differences of these prescriptions.[7] If certain brain penetrating ACE-I are found to be more neuro-protective than others, this could change potential recommendations for which type of ACE-I could be effective in the demented patient.

Despite the cognitive benefits outlined in this review, we still do not understand the mechanism for which ACE inhibition acts on the brain of the demented patient. However, the research presented has adjusted in its analyses for measurements of blood pressure, suggesting that the benefits of ACE-I are independent of hypertension. In addition, most of the controversy surrounding ACE-I use for dementia is dependent on animal research. Animal models may not completely mimic the multifactorial components involved in cognition in the adult human and therefore this review aimed to focus solely on human outcomes.

Research on ACE-Is and dementia as a whole are not without limitations. Areas for further research are vast. For instance, we do not yet know if these potential benefits are dose dependent. Furthermore, it is important to recognize that medication compliance can be un-reliable at times with the geriatric population. Polypharmacy is also common. While many of these studies tried to adjust for the use of other medications, specifically those that effect cognition such as memantine or cholinesterase use, it is sufficiently challenging to find a

patient population where the effects of other medications can be ignored. Moreover, four out of the five studies reviewed[3,5,9,11] cannot account for the length of treatment with ACE-I prior to the start of their study date.

Other limitations of the articles reviewed[5] may be in the study design. Changes in symptoms of dementia are often insidious and slow progressing. There is question as to whether a six-month interval from baseline to end-point is too short. In addition, practice effects in neuropsychological testing are confounders that may result from task familiarity in directions and context of the test. Familiarity with specific items on the test such as words on a list or other items of recall may also occur.[4] Study design with as many participants as possible is also needed. Gao et al[3] and Hajjar et al[5] were downgraded by GRADE criteria due to small sample size.

In total, many of the studies presented in this review are observational.[3,5,9] According to the GRADE assessment, these studies are rated as low in quality. However, these studies collectively do show a positive effect for the potential use of ACE-I in dementia treatment. For the Gao et al (2013) study[3], it is also important to recognize inherent bias in that treatment options were given based on provider clinical judgement, and therefore these clinical recommendations may change from clinician to clinician. Further large-volume randomized

controlled trials will be needed to continue to investigate ACE inhibition on cognition in the demented elderly. This research could also be further expanded to include different dementia subgroups such as younger onset dementia or ACE-I could be used to study early intervention treatments.

CONCLUSION

No recommendations currently exist for the use of ACE inhibitors for risk reduction of dementia in the clinical setting, however research is promising for further avenues of treatment. Investigations into the pathophysiology involved are needed. Further research, preferably multiple, large randomized controlled human trials are also necessary to determine the risk versus benefit of ACE inhibitor use. Hopefully with further research the controversy of whether or not ACE inhibitors are helpful or harmful to dementia patients will be resolved. The systematic review of this issue shows evidence for the potential future use of ACE-I as another avenue of treatment for dementia.

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Table 1: Quality Assessment of Reviewed Articles

Study	Design	Downgrade Criteria					Upgrade Criteria	Quality
		Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		
Gao et al	Observational	Not Serious	Not serious	Not serious	Serious[a]	Unlikely	None	Low
Hajjar et al	Observational	Not Serious	Not serious	Not serious	Serious[b]	Unlikely	None	Very Low
O-Caoimh et al	Observational, secondary analysis	Not Serious	Not serious	Not serious	Not serious	Unlikely	None	Low
Ohrui et al	RCT	Serious[c]	Not serious	Not serious	Not serious	Unlikely	None	Moderate
Soto et al	Cohort	Not serious	Not serious	Not serious	Not serious	Unlikely	None	Low

[a]Small sample size between groups in SMMSE and Qmci
[b]Small sample size
[c]Study does not report any evidence of allocation concealment or blinding