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Research paper

Renin–angiotensin system-targeting antihypertensive drugs and risk of vascular cognitive impairment: A meta-analysis

Shan Zhuang, Jun Li, Xin Wang, Hai-feng Wang, Wei-jie Zhang, Hong-yan Wang, Cheng-ming Xing*

Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, Qingdao, China

HIGHLIGHTS

- RAS-targeting drugs treatment may prevent the incidence of VCI and VD, whereas, neither ACEI nor ARB produced remarkable efficacy on VaCI.
- Our meta-analysis found that ACEI use, rather than ARB use, significantly protected against VCI and VD incidence.
- We found that RAS-targeting drugs use could decrease the incidence of VCI and VD in case-control studies; however, RCTs alone showed no effect on VCI or VD.
- Further more RCTs are required to reliably establish whether RAS-targeting drugs use and its classes drugs affect the risk of VCI (VD and VaCI).

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ABSTRACT

Objectives: To evaluate the effects of renin–angiotensin system (RAS)-targeting antihypertensive drugs and its classes on the incidence of vascular cognitive impairment (VCI).
Methods: Pubmed, Embase, and Cochrane Library database of selected articles, and previous systematic reviews through May 2015 were searched. Studies that evaluated the association between use of RAS-targeting drugs and VCI were included. Relative risks (RRs) with 95% confidence intervals (CIs) were pooled using fixed effects models or random effects models.
Results: In all studies as a whole, the use of RAS-targeting drugs was significantly associated with a reduced risk of VCI (RR, 0.87; 95% CI, 0.75–0.98) and vascular dementia (VD) (RR, 0.78; 95% CI, 0.64–0.93), compared no use of RAS-targeting drugs. Subgroup analysis showed that subjects with Angiotensin-Converting Enzyme Inhibitors (ACEI) use significantly associated with a reduced incidence of VCI (RR, 0.81; 95% CI 0.70–0.91) and VD (RR, 0.75; 95% CI, 0.57–0.93); however, subjects with Angiotensin Receptor Blockers (ARB) use had not this effect on VCI (RR, 0.94; 95% CI 0.76–1.13) or VD (RR, 0.94; 95% CI, 0.45–1.44). In an analysis of subgroups, case-control studies found that the use of RAS-targeting drugs could effectively decrease the incidence of VCI (RR, 0.77; 95% CI 0.66–0.87) and VD (RR, 0.77; 95% CI, 0.66–0.88); however, the randomized trials alone showed no significant effect on the incidence of VCI (RR, 0.94; 95% CI 0.82–1.07) or VD (RR, 0.94; 95% CI, 0.35–1.53). Meanwhile, in an analysis of cognitive impairment of vascular origin (VaCI), no significant association was found between RAS-targeting drugs, ACEI, or ARB and the incidence of VaCI.
Conclusion: RAS-targeting drugs treatment may produce remarkable efficacy on reducing the incidence of VCI and VD. Meanwhile, ACEI use, rather than ARB use, significantly protects against VCI and VD incidence. However, among the classes of RAS-targeting drugs, neither ACEI nor ARB plays protective role in VaCI incidence. Further more RCTs are required to reliably establish whether RAS-targeting drugs use decreases the risk of VCI (VD and VaCI).

* Corresponding author at: Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, No. 5 Donghai Middle Road, Qingdao, Shandong Province 266071, China.
E-mail address: xingchengming@medmail.com.cn (C.-m. Xing).

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1. Introduction

'Vascular cognitive impairment' (VCI) was introduced to explain all cognitive disorders associated with vascular disease, including forms that range from mild cognitive impairment of vascular origin (VaMCI) to overt vascular dementia (VD) [11]. As a leading cause of dementia, VD is second only to Alzheimer disease [17]. Meanwhile, cognitive impairment of vascular origin (VaCI) is not severe enough to interfere with autonomy in activities of daily living (ADLs) on behalf of an 'at risk' state for developing into VD, which may be preventable or delayed by regulating vascular risk factors [12].

Substantial evidence showed that deteriorating cognitive function could increase the risk of dementia. Cognitive dysfunction contributes to increase in the rate of decline and predicts the risk for the development of dementia [14]. Hypertension could contribute to cognitive decline [21] and is the major player in the pathogenesis of VD by promoting of lacunar and cortical infarcts [22]. Therefore, early identification of VaCI in the setting of hypertension may provide a unique opportunity to institute preventive therapy before the development of overt VD. Recent clinical trials have demonstrated that taking renin–angiotensin system (RAS) targeting antihypertensive drug has a reduced incidence of VD [23] and VaCI [2,23]. This meta-analysis was conducted to establish the exact association between RAS-targeting drugs used (e.g., all RAS-targeting drugs, Angiotensin-Converting Enzyme Inhibitors (ACEI), and Angiotensin Receptor Blockers (ARB) and the incidence of VCI (VD and VaCI).

2. Methods

2.1. Search strategy

Pubmed, the Embase database, and the Cochrane library were searched from their commencement to May 2015 with the terms (cogniti* or vascular cognitive impairment or vascular dementia or cognitive impairment of vascular origin) and (antihypertensi* or renin–angiotensin system or Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers or *sartan or *pril) in title/abstract/keywords. We also retrieved the reference lists of the identified articles to find additional potential relevant studies.

2.2. Eligibility criteria

The studies eligible had to strictly meet the following criteria: (1) a randomized controlled trial (RCT) or observational study; (2) VCI (VD and VaCI) with internationally valid criteria or diagnostic codes with additional confirmation; (3) explicitly described exposure to ACEI or ARB; (4) presented data on hazard ratios (HRs) or relative risks (RRs) or odds ratios (ORs) with confidence intervals (CIs) or offered data to calculate these.

2.3. Quality assessment

The quality of observational studies was assessed with the Newcastle-Ottawa Scale (NOS) criteria. The detail of the NOS grading standard was as follows: (1) selection, total score: 4; (2) comparability, total score: 2; (3) exposure (case-control studies)/outcome (cohort studies), total score: 3. A high score out of a total of 9 points, and a score greater than or equal to 5 indicates high methodological quality. For RCTs, we assessed the methodological quality according to the guidelines of the Cochrane Collaboration's tool for assessing the risk of bias [15]. The detail of the Cochrane Collaboration's tool was listed as follows: random sequence generation, allocation concealment, blind, incomplete outcome data, selective reporting, and other possible sources of bias.

2.4. Data abstraction

Two authors independently extracted data from the studies, in particular, regarding: first author, year of publication, study design, study location, number of participants, age at baseline, sex (male), outcome definition, exposure definition, number of years of follow-up, effect estimates and 95% CIs (or information required to compute these), and information required to complete the NOS questionnaire. When multiple effect estimates were reported, maximally adjusted estimates were extracted. The estimates based on the longest time between exposure and disease onset were chosen, if results were presented with and without lag periods, with multiple lag periods, or with multiple periods of exposure ascertainment. When more than one studies used the same study population during the same time period, only one study with the highest quality score was included.

2.5. Statistical analysis

Primary analyses compared exposed with unexposed for each of the three RAS-targeting drugs exposures of interest: all RAS-targeting drugs, ACEI, and ARB. Moreover, subgroup analyses were conducted to examine the differences by study design and RAS-targeting drugs classes. For all analyses, the random-effects or fixed-effects model with an inverse variance method was used, and the pooled RRs and 95% CIs were calculated according to the heterogeneity between studies [5]. The HRs and ORs were considered to be approximations of the RRs. We used the Cochrane Q test and the I^2 test to assess the heterogeneity across all of the eligible comparisons and to quantify the heterogeneity [16]. An error $p \leq 0.10$ and an $I^2 > 50\%$ were considered as significant heterogeneity of the outcomes. If the heterogeneity was insignificant, the RR from a fixed-effect model was chosen. But if heterogeneity was present, subgroup analysis was chosen to explore the potential sources of heterogeneity for the classified variable. Meanwhile, a random-effect meta-regression was performed for continuous variables with more than 10 studies. Sensitivity analysis was conducted to assess the robustness of the primary analyses for each exposure type and to exclude studies of poor quality or those with the greatest weight. The RR from a random-effect method was chosen, if the heterogeneity is still significant after subgroup analysis, meta-regression or sensitivity analysis. Publication bias was assessed via visual inspection of the Begg's funnel plot. Except for heterogeneity, a two-tailed p-value <0.05 was considered significant. All analyses were performed with STATA12.0 software.

3. Results

3.1. Literature search findings and characteristics of the included trails

The search strategy identified 1304 citations. After screening according to titles and abstracts, 86 publications were included in the full-text and 81 were excluded for the reasons that are shown in Fig. 1. Eventually, 5 studies, including 3 RCTs, and 2 case-control studies met our inclusion criteria. The characteristics of the 5 included studies in the meta-analysis are shown in Table 1. Furthermore, the quality of all of the included studies was assessed. All of the observational studies met 5 NOS criteria. The quality scores are listed in Table 1. The RCTs were also of good quality.

3.2. RAS-targeting drugs use and VaCI risk

Three studies (three RCTs [1,7,23]) compared the incidence of VaCI between subjects with and without RAS- targeting drugs use. There was no significant difference in the incidence of VaCI between