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Pre-stroke use of angiotensin receptor blockers and stroke outcomes: systematic review

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ABSTRACT

Hypertension is the major risk factor and the most important modifiable risk factor for stroke. Angiotensin receptor blockers (ARB) are widely used in patient at high risk of cardiocerebrovascular events. The objective of this literature review was to determine the efficacy of pre-stroke use of ARB on stroke outcomes. Major medical databases (PubMed, MEDLINE, Clinical Key, Cochrane Library, EMBASE) were systematically searched using keyword: "hypertension", "ARB", "stroke", and "outcome". The search were limited to clinical trials published within the last 10 years, written in English, with full-text availability. We used GRADE Working Group to measure the quality of evidence. Four clinical studies, 3 retrospective studies and 1 nationwide population-based cohort study met our inclusion criteria with total of 102.644 patients for analysis. The scientific quality of the studies varied from poor (1 study), moderate (1 study), and high quality (2 studies). Generally, the subjects of the studies were acute ischemic stroke patients. Three studies showed pre-stroke use of ARB were significantly associated with better stroke outcomes. Only one study found different result whereas pre-stroke use of ARB did not appear to affect stroke outcomes. Outcome of the studies was explored according to morbidity (severity and functional status upon discharge) and mortality (30-days mortality or in-hospital mortality). Several limitations were present, including non-random treatment assignment, retrospective study design, and lack of data for longitudinal medication exposure in observational studies. In conclusion, this systematic review shows evidence that there is possible benefit of pre-stroke ARB treatment in relation to better ischemic stroke outcomes. However, further studies with better research method quality are still needed. The efficacy of ARB treatment in relation to other type of stroke outcomes also needs to be furtherly examined.

ABSTRAK

Hipertensi adalah faktor risiko utama dan faktor risiko paling penting yang dapat dimodifikasi untuk stroke. *Angiotensin Receptor Blockers* (ARB) banyak digunakan pada pasien yang berisiko tinggi kejadian kardioserebrovaskular. Tujuan dari tinjauan literatur ini adalah untuk menentukan efikasi hasil luaran penggunaan ARB pada pasien pre-stroke. Pencarian secara sistematis pada *database* literatur kesehatan (PubMed, MEDLINE, Key klinis, Cochrane Library, EMBASE) dengan kata kunci: "hipertensi", "ARB", "stroke", dan "outcome". Pencarian terbatas pada uji klinis yang diterbitkan dalam 10 tahun terakhir, ditulis dalam bahasa Inggris, dan tersedia dalam teks lengkap. Kami menggunakan penilaian

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GRADE Working Group untuk mengukur kualitas literatur yang didapatkan. Empat studi klinis, 3 studi retrospektif dan 1 penelitian kohort berbasis populasi nasional memenuhi kriteria inklusi dengan total subyek 102,644 pasien. Kualitas ilmiah dari penelitian bervariasi dari buruk (1 studi), sedang (1 studi), dan kualitas baik (2 studi). Secara umum, subyek penelitian adalah pasien stroke iskemik akut. Tiga studi menunjukkan penggunaan ARB pre-stroke secara signifikan terkait dengan outcome stroke yang lebih baik. Hanya satu studi menemukan hasil yang berbeda dimana penggunaan ARB pre-stroke tidak menunjukan pengaruh luaran stroke. Luaran stroke dari dari literatur dapat dikelompokan menjadi morbiditas (keparahan dan status fungsional saat pulang dari rumah sakit) dan mortalitas (30-hari kematian atau mortalitas di rumah sakit). Beberapa keterbatasan yang ada, termasuk *study* yang tidak random, desain penelitian retrospektif, dan kurangnya data untuk paparan obat longitudinal pada studi observasional. Dapat disimpulkan, review sistematis ini menunjukkan bukti bahwa ada kemungkinan manfaat pengobatan ARB pada pasien pre-stroke dalam kaitannya dengan luaran stroke iskemik yang lebih baik. Namun, penelitian lebih lanjut dengan penelitian dengan kualitas metode yang lebih baik masih diperlukan. Efisiensi pengobatan ARB dalam kaitannya dengan luaran tipe stroke lain perlu diteliti lebih lanjut.

Keywords: angiotensin receptor blocker - pre-stroke – benefit – prognosis - hypertension

INTRODUCTION

Stroke remains one of the most devastating of all neurological conditions, often causing death or gross physical impairment or disability.[1] Hypertension is the major risk factor and the most important modifiable risk factor for stroke.[2,3] Several clinical trials show that reducing blood pressure (BP) is accompanied by a significant reduction of cardiac and cerebrovascular events.[4,5]

Angiotensin receptor blockers (ARB) are one type of drugs that is now widely used for the treatment of hypertension.[6] A number of studies showed that ARB are powerful neuroprotective agents with potential therapeutic effect for many brain disorders.[7] However, the possible benefits of treatment with ARB before stroke are not clear at the present. In this systematic review, we assessed the potential benefits of pre-stroke use of ARB in relation to stroke prognosis.

MATERIALS AND METHODS

The review was conducted in a series of steps: (i) database search of the published literature, (ii) quality assessment of each retrieved investigation, (iii) data extraction from tables and graphs, and (iv) summary and interpretation of findings. Meta-analysis of the obtained data was not feasible because of the great diversity of settings and extensive heterogeneity of findings between investigations. Therefore, the findings and synthesis of our review are provided as a narrative summary.

Literature search

Major medical databases (PubMed, MEDLINE, Clinical Key, Cochrane Library, EMBASE) were systematically searched using keyword: "**hypertension**", "**ARB**", "**stroke**", and "**outcome**". Search parameters were limited to clinical trial, within last 10 years, and full-text availability. Only English language was included. Manual searches of references and bibliographies

were conducted. All reports were reviewed, irrespective of publications status. Searches were independently conducted by 3 of the authors. Abstracts for all results were reviewed and relevant studies were selected for further review. Any disagreement was resolved by discussion.

Study selection

We included all retrospective studies enrolling hypertensive patients with or without other risk factors that have history of ARB medication before stroke incidence. Included studies must have outcome of patient discharge. Outcome of the studies can be determined into morbidity or mortality. This review excluded studies with no available data on pre-stroke ARB treatment, morbidity, and mortality outcome. Our search returned 57 articles, and 6 additional relevant article was added from the reference list of one of the primary articles, 63 in total. As illustrated in FIGURE 1, of the total number of retired citations, 42 duplicate ones were excluded, leaving 21 articles. Further, examination of the title and abstract of these latter ones according to the inclusion and exclusion criteria resulted in the elimination of an additional 14 publications, leaving 7 articles. Thorough reading of the full content of the latter number of papers culminated in the exclusion of additional 3 articles, because of outcome data unavailability and inappropriate study population, thus, leaving 4 studies for consideration.

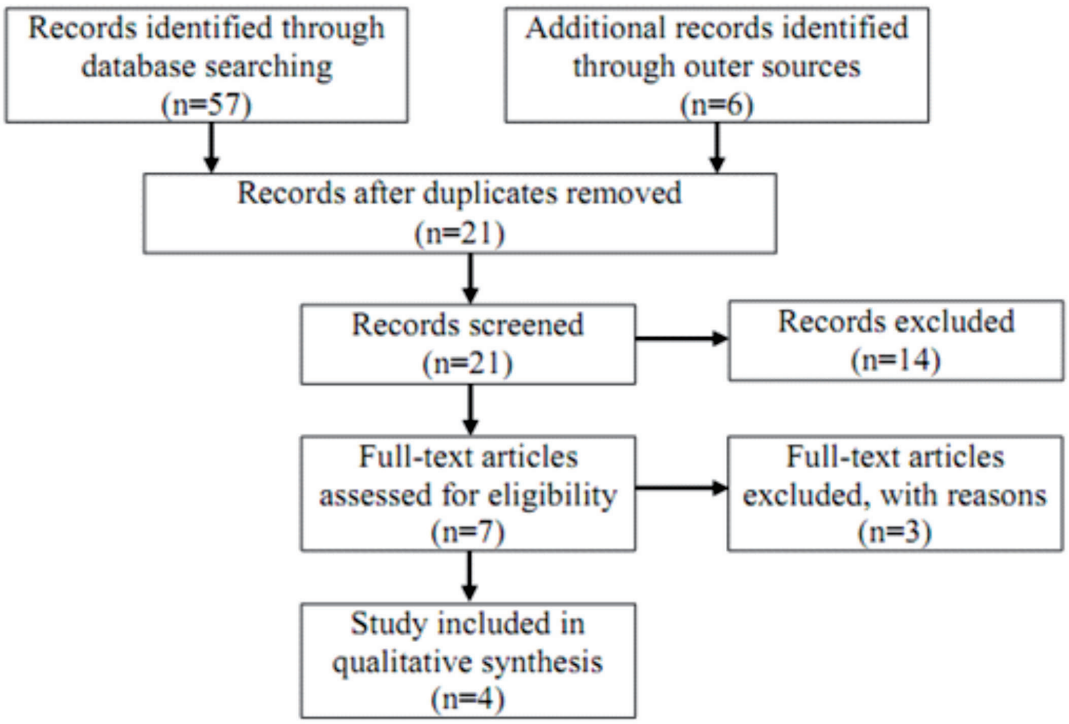

FIGURE 1. Flow diagram of literature search

Assessment of Study Quality

Assessment of the quality of each research articles was conducted by authors. There is no universally accepted gold standard for evaluating and interpreting the quality of research articles. Thus, we choose to assess the quality of the methods and research of articles by using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group (TABLE 1).

TABLE 1. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group

Author (year)	Type of evidence	Quality	Consistency	Directness	Effect size
Miyamoto *et al.*[8]	+2	0	+1	0	+1
Fuentes *et al.*[9]	+2	0	+1	0	+1
Sundboll *et al.*[11]	+2	0	0	0	+1
Tziomalos *et al.*[10]	+2	0	-1	-1	0

Data abstraction and synthesis

The four studies were classified according to author/year, country/setting, methodology of the study, sample cohort, and outcome (TABLE 2).

TABLE 2. Description of the study

Author (year)	Country / Setting	Method (study period)	Patients (n)	Outcomes
Miyamoto *et al.*[8]	Japan/hospital	Retrospective (2 yrs)	151	stroke severity discharge outcome
Fuentes *et al.*[9]	Spain/hospital	Retrospective (7 yrs)	1968	stroke severity discharge outcome
Sundboll *et al.*[11]	Denmark/nation population-based	Cohort (8 yrs 6 mos)	100.043	30-days mortality
Tziomalos *et al.*[10]	Greece/hospital	Retrospective (2 yrs 10 mos)	482	stroke severity discharge outcome in-hospital mortality

RESULTS

Four studies with total 102,644 patients met all inclusion/exclusion criteria. Three were retrospective[8-10] and one was nationwide population-based cohort study.[11] The sample size of the databases varied greatly between studies, from only n=151 in Miyamoto *et al.*[8] to n=100.043 in Sundboll *et al.*[11] The research setting was well defined in all publications. Thus, in TABLE 1, the research setting is classified as hospital (utilizing hospital recordings) and long-term care institutions (utilizing national databased). Outcome of the studies was explored according morbidity to (severity and functional status upon discharge) and mortality (30-days mortality or in-hospital mortality) as summarized in TABLE 1.

Although all of the articles comprising this review were published in peer-review

journals, we, nonetheless, examined their methodological quality using GRADE Working Group as criteria. The four qualifying reports differed rather substantially in the quality of the research method. One was of very low methodological quality in Tziomalos *et al.*[10] one moderate quality in Sundboll *et al*.,[11] and two high quality in Fuentes *et al*.[9] Miyamoto *et al*.[8]

ARB and morbidity of stroke

Three studies addressed ARB and morbidity of stroke. All of them were conducted in a hospital setting with the data of one of them obtained through hospital records of stroke unit[9] and the data of the remaining two studies collected from general hospital records.[8,10] As stated before, morbidity outcome divided into severity and functional status upon discharge which can define as assistance-free state at discharge from the hospital. Fuentes *et al*.[9] evaluated stroke severity using Canadian Neurological Scale (CNS) whereas Miyamoto *et al*.[8] and Tziomalos *et al.*[10] evaluated admission severity using NIH Stroke Scale (NIHSS) score. Both Fuentes *et al.*[9] and Miyamoto *et al*.[8] study considered that previous treatment with ARB had associated with reduced stroke severity (2.6% vs 8.9%, p=0.017 and 16.2% vs 28.2%, p<0.01, respectively). However, the findings of the study by Tziomalos *et al.*[10] differ. In this study the NIHSS score did not differ between patients who were receiving before stroke monotherapy ARBs and those who were not being treated with any hypertensive agent at admission (p=not significant [NS]). Functional status upon discharge, as assessed by a modified Rankin Score (mRS). Two study, Fuentes *et al*.[9] and Miyamoto *et al*.[8] stated that previous use of ARB significantly correlated with better outcome at discharge (OR 0.467, 95%CI 0-262-0.0831, p=0.010 and OR 0.3810, 95%CI 1.111-13.068, p=0.033, respectively). In contrast, Tziomalos *et al.*[10] obtained beneficial effect of ARB to discharge outcome (p=0.088).

ARB and mortality of stroke

Two studies identified mortality rate ratios after stroke event. Sundboll *et al.*[11] who conducted nationwide population-based cohort study to examined the 30-day mortality following stroke, reported current use of ARB was associated with reduced 30-day mortality among patients with ischaemic stroke (MMR 0.85, 95%CI 0.81-0.89). But it found no association with ICH or SAH patients. The publication's by Tziomalos *et al*.,[10] examined in-hospital mortality. It stated that treatment with ARB before stroke did not differ between patients who died during hospitalization and those discharge (p=0.394).

TABLE 3. Summary of 4 studies included in this report

Author	OR/MMR (95%CI), p	Result
Miyamoto *et al.*[8]	0.381 (1.111-13.068), p=0.033	significant lower severity and better outcome at patient's discharge from hospital
Fuentes *et al.*[9]	0.467 (0-262-0.0831), p=0.010	significant lower severity and associated with better outcome
Sundboll *et al.*[11]	0.85 (0.81-0.89), p<0.05	significant reduced 30-day mortality among patient with ischemic stroke
Tziomalos *et al.*[10]	1.442 (0.7112-2.9255), p=0.394	do not appear to affect either stroke severity, discharge outcome, and in-hospital mortality

DISCUSSION

Successful blood pressure control is the most critical factor in stroke prevention and stroke outcomes. It is well established that the renin-angiotensin-aldosterone system plays an important role in the pathophysiology of vascular events.[12] ARB is one class of drugs that may affect renin-angiotensin-aldosterone system through selective blockade of angiotensin II at the type 1 receptor (AT_1R).[6] Several clinical and experimental studies have provided ARB has neuroprotective effect. Even though, ARB achieves a similar benefit of blood pressure reduction, Fournier *et al.*[13] stated that AT_1R blocker is superior over ACEI in the protection against brain ischemia.[13] Neuroprotection may cause by the result of direct blockade of brain AT_1R. Blockade of brain AT_1R could result in improvement of endothelial function mediated by suppression of inflammation and induction of vasodilatation in peripheral area of ischemia.[14,15]

This systematic review evaluated the explicit reporting of beneficial pre-stroke use of ARB and several stroke outcomes. The results showed that these principles were inconsistently reported. Three studies showed pre-stroke use of ARB was considered significant with reducing stroke severity, better outcome at patient's discharge and reduced short-term mortality, only 1 study found different result whereas ARBs do not appear to affect either morbidity and mortality of stroke. In fact, there are differences in outcomes definition. A notable finding of this review is the disparity between published studies in sample size, varying in particular according to the study setting, and period of data's study.

Several limitations were present, including non-random treatment assignment, retrospective study design, and lack of data for longitudinal medication exposure in observational studies. The most effective method is randomized controlled trial (RCT). However, using RCTs is difficult when implementing complex interventions involving multiple components since it is not possible to 'blind' providers or recipients to the control and intervention groups. The results of this review must be interpreted with caution. As this was the first systematic review of its kind, a broad reaching search strategy was necessary in order to capture all potentially relevant studies. One of the disadvantages of this search strategy was that studies of heterogeneous design were included which resulted in the use of a modified version of the GRADE Working Group criteria for quality assessment. Different approaches were explored for presenting the studies in a meaningful way.

CONCLUSION

This systematic review shows evidence that there is possible benefit of pre-medication of stroke using ARB in relation to better ischemic stroke outcomes. However, because lack of data, further studies is needed to examine the efficacy of ARB in relation to stroke outcomes of another other type of stroke (SAH, ICH). RCTs, as well as well-designed observational studies that adjust for nonrandom treatment assignment and longitudinal medication exposure, are also needed.

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