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Adherence to Antihypertensive Medications and Stroke Risk: A Dose-Response Meta-Analysis

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***Background*—**Inconsistent findings have been obtained for previous studies evaluating the association between antihypertensive medication (AHM) adherence and the risk of stroke. This dose-response meta-analysis was designed to investigate the association between AHM adherence and stroke risk.

***Methods and Results*—**MEDLINE and Embase databases were systematically searched to identify relevant studies. The quantification of adherence to AHM was calculated as the percentage of the sum of days with AHM actually taken divided by the total number of days in a specific period. Summary relative risks (RR) and 95% CIs were estimated using a random-effects model. Stratified and dose-response analyses were also performed. A total of 18 studies with 1 356 188 participants were included. The summary RR of stroke for the highest compared with the lowest AHM adherence level was 0.73 (95% CI, 0.67–0.79). Stratified by stroke subtype, a higher AHM adherence was associated with lower risks of ischemic stroke (RR, 0.74; 95% CI, 0.69–0.79) and hemorrhagic stroke (RR, 0.55; 95% CI, 0.42–0.72). Moreover, both fatal (RR, 0.51; 95% CI, 0.36–0.73) and nonfatal stroke (RR, 0.52; 95% CI, 0.28–0.94) were lower in participants with higher AHM adherence. The results of a dose-response analysis indicated that a 20% increment in AHM adherence level was associated with a 9% lower risk of stroke (RR, 0.91; 95% CI, 0.86–0.96).

***Conclusions*—**Higher AHM adherence is dose-dependently associated with a lower risk of stroke in patients with hypertension.
(*J Am Heart Assoc*. 2017;6:e006371. DOI: 10.1161/JAHA.117.006371.)

Key Words: antihypertensive medication • dose response • medication adherence • meta-analysis • stroke

Despite significant improvements in diagnosis and treatment, stroke remains one of the most important causes of mortality worldwide.[1] Patients with stroke typically experience a loss of body function, which finally contributes to long-term morbidity and disability. Therefore, an increased risk of stroke and subsequent adverse events are associated with increased burden for the patients themselves, their family members, and healthcare systems, particularly in low- and middle-income countries.[1,2]

Hypertension is a reversible risk factor underlying the pathogenesis of stroke.[3,4] Previous clinical trials have confirmed the role of antihypertensive medications (AHMs) for the prevention of stroke.[3,4] AHM adherence, defined as the extent to which patients take medications as prescribed by their physicians, is also an important determinant for the preventative effect of AHM for stroke.[5] Previous studies have reported that poor adherence to AHM appeared to be associated with an increased risk for stroke incidence or recurrence in patients with hypertension.[6,7] However, inconsistent findings were retrieved for previous studies evaluating the association between AHM adherence and the risk of stroke.

A systematic evaluation of the association between AHM adherence and the risk of stroke is of significance for understanding the role of AHM adherence in stroke prevention. Importantly, confirmation of the dependent association between the AHM adherence magnitude and the preventative efficacy of stroke may provide more detailed guidelines and education information for patients with hypertension who are taking AHM to reduce the risk of stroke. A quantitative analysis of AHM adherence and stroke risk can also provide critical information for the design of future large-scale prospective cohort studies to explore the association between

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Accompanying Data S1, Tables S1 through S4, and Figures S1 and S2 are available at http://jaha.ahajournals.org/content/6/7/e006371/DC1/embed/inline-supplementary-material-1.pdf

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Received April 13, 2017; accepted June 14, 2017.

Clinical Perspective

What Is New?

- This meta-analysis reveals a significant inverse association between antihypertensive medication (AHM) adherence and stroke risk.
- Higher AHM adherence is beneficial for the prevention of ischemic stroke and hemorrhagic stroke.
- Higher AHM adherence is associated with lower risks of both fatal and nonfatal stroke.
- The dose-response analysis suggests that a 20% increment in the AHM adherence level is associated with a 9% lower risk of stroke.

What Are the Clinical Implications?

- This meta-analysis strengthens and extends the understanding of the positive impact of AHM adherence on stroke prevention, further supporting the notion that improved AHM adherence is associated with improve stroke prevention in patients with hypertension.

AHM adherence and the risk of stroke. However, a systematic evaluation of the association between AHM adherence and the risk of stroke is rare, and whether AHM adherence is dose-dependently associated with stroke risk remains to be determined. Therefore, we investigated the association between AHM adherence and risk of stroke in a quantitative dose-response meta-analysis.

Methods

We followed the previously published guidelines for a Meta-Analysis of Observational Studies in Epidemiology for conducting meta-analyses and reporting the results.[8]

Literature Search and Study Selection

The MEDLINE and Embase electronic databases were searched using predefined terms and search criteria (Data S1). The latest search was conducted on January 30, 2017. Studies were included if they met all of the following criteria: (1) publication in the English language; (2) studies with either cohort, case-control, or controlled trial design; (3) the exposure of interest was AHM adherence in patients with hypertension; (4) the outcome of interest was fatal/nonfatal stroke; and (5) reported the relative risk (RR) and the corresponding 95% CI for the association between AHM adherence and stroke risk (or these data could be estimated). Nonoriginal articles, articles with insufficient data or irrelevant outcomes, or case reports were excluded. No restriction on time of publication was applied.

Data Extraction, Exposure Assessment, and Quality Assessment

The following data were extracted from each study independently by 2 of the authors (T.X. and S.O.): first author, publication year, location, population demographics, data source, stroke type, follow-up time, primary or secondary prevention for stroke, strategies for the assessment of AHM adherence, RR from the most fully adjusted model for the categories with the highest compared with the lowest adherence level to AHM and the corresponding 95% CI, and confounders adjusted for in the multivariate analysis. According to previous definitions, AHM adherence was primarily assessed by quantifying the adherence level or determining whether AHM was persistently taken during the treatment period.[9] Medication adherence is defined as the extent to which a patient participates in a treatment regimen after this patient agrees to that regimen.[9] Both low adherence level and the discontinuation of AHM use were considered poor adherence to AHM.[9] The AHM adherence level usually refers to data from a quantitative analysis, and a low AHM adherence level was considered nonpersistence rather than the discontinuation of AHM.[5,9] Different studies may have different names for the quantitative assessment of AHM adherence (eg, proportion of days covered,[10] medication possession ratio,[11] cumulative medication adherence,[12] and medication refill adherence[13]). However, proportion of days covered, medication possession ratio, cumulative medication adherence, and medication refill adherence were similarly obtained by calculating the percentage of days exposed to AHM in a given follow-up period.[9] Therefore, proportion of days covered, medication possession ratio, cumulative medication adherence, and medication refill adherence were considered equally for the evaluation of AHM adherence level. Adherence level of AHM ranges from 0% to 100%, and a higher percentage reflects better adherence. A 9-star system based on the Newcastle-Ottawa scale was used to assess the quality of the included studies.[14] The full score was 9 stars, and a high-quality study was defined as a study with $\geq$8 awarded stars.

Statistical Analysis

We used RRs with 95% CIs for the highest versus lowest adherence level to assess the association between adherence to AHM and the risk of stroke.[15] For studies that assessed the exposure of interest based on whether AHM was persistently taken during a specific period, the estimation from persistent AHM use compared with discontinuation of AHM use was only used to calculate the pooled RRs from the highest compared with the lowest AHM adherence level. The heterogeneity between the included studies was evaluated with the

Cochrane Q statistic. The I^2 statistic was used to quantify magnitude.[16] We recognize the potential heterogeneity between the included studies; thus, we used a random-effects model to pool the estimates.[17] We conducted predefined subgroup analyses according to stroke subtype (ischemic stroke [IS] and hemorrhagic stroke [HS]), stroke outcome (fatal and nonfatal stroke), geographic region, follow-up time, age distribution, sex, and quality score to evaluate the potential effect of these variables on the results. We also assessed the relationship between AHM adherence and stroke risk in the primary prevention or secondary prevention of stroke. Primary prevention was defined as patients taking AHM to prevent new-onset stroke, and secondary prevention was defined as patients with a history of stroke events taking AHM to prevent stroke recurrence.[18] Moreover, meta-regression analyses were also performed to investigate the influence of the above predefined variables on the heterogeneity of the studies, and *P* interaction was used to assess the heterogeneity between subgroups.[19] Subsequently, a dose-response meta-analysis was performed in accordance with the methods proposed by Greenland and Longnecker[20] and Berlin et al[21] to compute the trend from the correlated log RR estimates across the category of adherence level. For each study, the adjusted RR with a corresponding 95% CI for each median or mean level of exposure was used. If the median or mean adherence level per category was not available, the midpoint of the upper and lower boundaries was considered the dose of each category. If the highest category was open-ended, the midpoint of the category was set to 1.2-fold the lower boundary. We examined a potential nonlinear relationship between adherence level and stroke risk by modeling the adherence level using restricted cubic splines with 3 knots at percentiles 10%, 60%, and 90% of the distribution. We calculated the *P* value for nonlinearity by testing the null hypothesis that the coefficient of the solid line is equal to 0. A *P* value <0.050 was considered statistically significant. Publication bias was investigated visually with funnel plots and statistically with Begg's tests.[22] STATA version 12.0 (StataCorp) was used for the statistical analyses.

Results

Literature Search and Characteristics of Studies

A flow chart of the selection procedure is shown in Figure 1. A total of 18 studies met our inclusion criteria and were eligible for meta-analysis.[10–13,23–36] The characteristics of the included studies are summarized in Table 1. A total of 18 studies involving 1 356 188 participants were examined. Seventeen studies were cohort studies, and only 1 had a nested case-control design.[11] The exposure measure was the percentage of days covered by prescribed AHM (proportion of days covered [n=9], medication possession ratio [n=5], medication refill adherence [n=1], cumulative medication

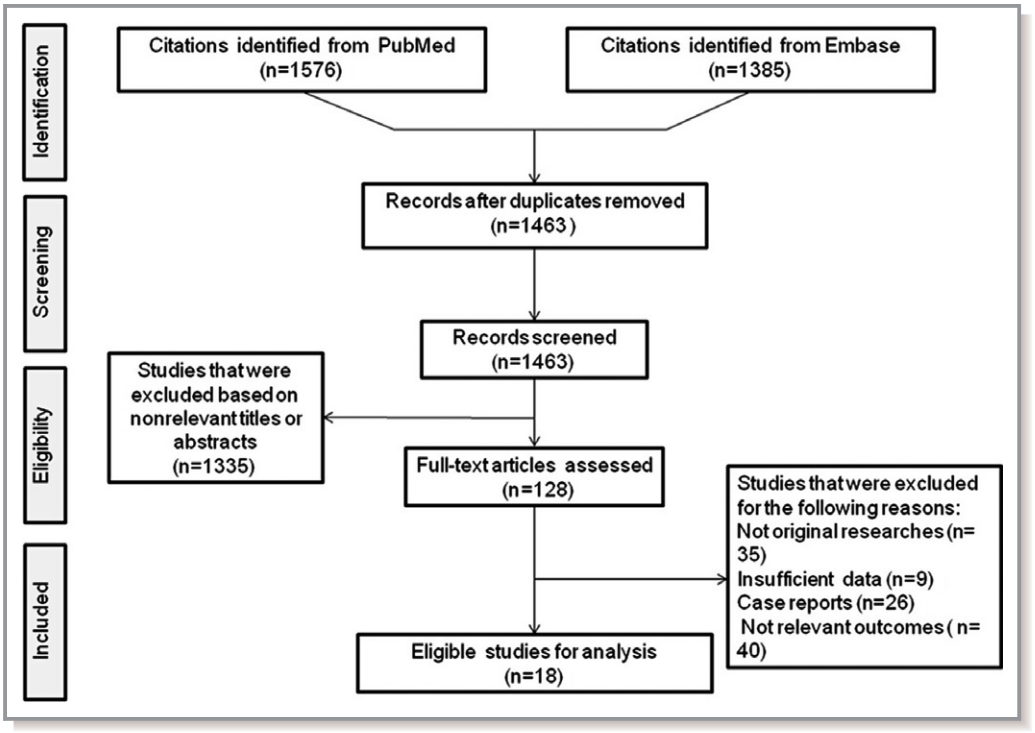

Figure 1. Flowchart of the literature search process.

Table 1. Characteristics of the Studies Included in the Meta-Analysis

First Author, y of Publication	Design	Country	Study Period	Age, y/Women, %/No. in Cohort	Assessment of AHM Adherence	Levels of Prevention and Stroke Type	Outcomes
Yang 2016[23]	CS	United States	2007–2012	18–62/67.3/59 037	MPR	PP for all stroke	Stroke events
Kim 2016[12]	CS	South Korea	2002–2010	≥20/53.4/33 728	CMA	PP for all stroke, IS, HS	Stroke events; fatal stroke events
Herttua 2016[24]	CS	Finland	1995–2007	≥30/54.0/58 266	PDC	PP for all stroke	Fatal stroke events
Krousel–Wood 2015[25]	CS	United States	2006–2011	≥65/59.8/2075	MPR	PP for all stroke	Stroke events
Gosmanova 2015[26]	CS	United States	2004–2013	53.8 (mean age)/ 0.9/312 489	PDC	PP for all stroke	Stroke events
Xu 2013[27]	CS	China	2007–2008	≥18/40.0/8409	PDC	SP for IS	IS events; fatal IS
Wong 2013[28]	CS	China	2001–2012	All age group/ 54.9/218 047	PDC	PP for all stroke	Fatal stroke events
Shin 2013[29]	CS	China	2003–2007	≥18/49.7/40 408	MPR	PP for all stroke	Stroke events
Herttua 2013[30]	CS	Finland	1995–2007	≥30/54.0/73 527	PDC	PP for all stroke	Stroke events; nonfatal and fatal stroke events
Perreault 2012[11]	NCCS	Canada	1999–2007	≥65/46/14 227	MPR	PP for all stroke, IS	Stroke events; nonfatal and fatal stroke events
Degli Esposti 2011[31]	CS	Italy	2004–2006	≥18/52.0/31 306	PDC	PP for all stroke	Stroke events
Corrao 2011[32]	CS	Italy	2000–2007	≥18/56.0/242 594	PDC	PP for all stroke	Stroke events
Khan 2010[10]	CS	Canada	2003–2006	≥66/51.6/3571	PDC	SP for all stroke	Fatal stroke events
Bailey 2010[13]	CS	United States	1994–2000	18–64/67.7/49 479	MRA	PP for all stroke	Stroke events; fatal stroke events
Mazzaglia 2009[33]	CS	Italy	2000–2005	≥35/58.4/18 806	PDC	PP for all stroke	Stroke events
Liu 2009[34]	CS	China	1999–2004	≥30/48.2/29 759	PMC	PP for all stroke, IS	Stroke events
Kettani 2009[35]	CS	Canada	1999–2004	45–85/62.7/83 267	MPR	PP for all stroke, IS, and HS	Stroke events
Breekveldt–Postma 2008[36]	CS	Netherlands	1993–2002	≥18/59.9/77 193	Discontinuation or not	PP for all stroke	Stroke events

AHM indicates antihypertensive medication; CMA, cumulative medication adherence; CS, cohort study; HS, hemorrhagic stroke; IS, ischemic stroke; MPR, medication possession ratio; MRA, medication refill adherence; NCCS, nested case-control study; PDC, proportion of days covered by prescribed AHM; PMC, proportion of months covered by prescribed AHM; PP, primary prevention; SP, secondary prevention.

adherence [n=1]) in 16 studies. In one study,[34] the AHM adherence level was calculated as the percentage of months covered by prescribed AHM, and in another study,[36] the adherence to AHM was evaluated based on whether AHM was taken persistently during a follow-up period. The data source, disease classification, and confounders adjusted in the multivariate analysis for each study are listed in Tables S1 and S2. Quality scores of the included studies are listed in Table S3. The mean score of the included studies was 8.06 (SD, 1.06; range, 6–9).

AHM Adherence and Stroke Risk

The estimation for each study and the pooled RR for the highest compared with the lowest categories of AHM adherence level are shown in Figure 2.[10–13,23–36] Overall, compared with participants in the lowest AHM adherence categories, those in the highest categories had a significantly lowered risk of stroke events (RR, 0.73; 95% CI, 0.67–0.79).

Stratification analyses for the association between AHM adherence and stroke risk are shown in Table 2. A higher AHM adherence rate was associated with lower risks for both the IS (RR, 0.74; 95% CI, 0.69–0.79) and HS (RR, 0.55; 95% CI, 0.42–0.72), and the protective effect of high AHM adherence was more remarkable in HS than IS (45% reduction in HS versus 26% reduction in IS). Improved AHM adherence was associated with lower risks of both nonfatal stroke (RR, 0.52; 95% CI, 0.28–0.94) and fatal stroke (RR, 0.51; 95% CI, 0.36–0.73). For age distribution, the preventative effect of improved AHM adherence against stroke was more significant in patients 65 years and older compared with those younger than 65 years (32% reduction in those ≥65 years versus 13%

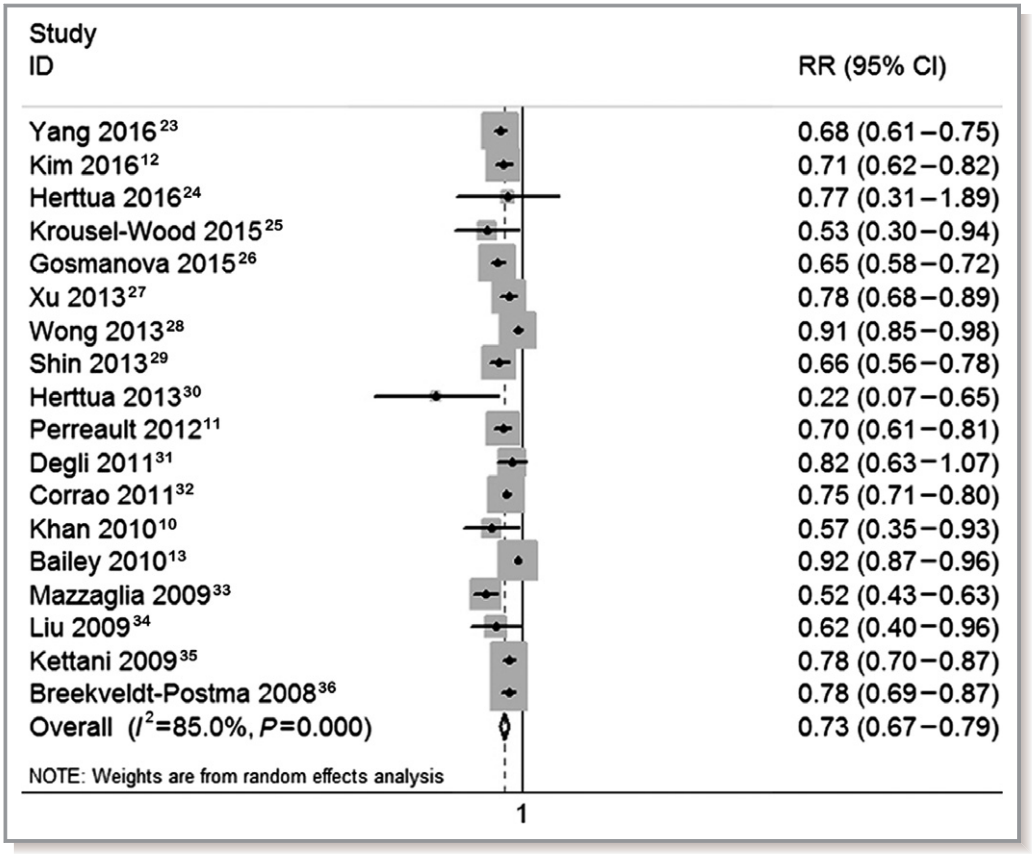

Figure 2. Forest plot of the association between antihypertensive medication adherence and stroke risk. RR indicates relative risk.

reduction in those <65 years). Subsequent analyses indicated that a higher AHM adherence was associated with a reduced risk of stroke regardless of geographic region, follow-up duration, sex, and levels of stroke prevention (primary prevention or secondary prevention).

Dose-Response Meta-Analysis

Ten studies were included in the dose-response analysis of the association between AHM adherence level and risk of stroke.[12,23,25,27,28,30–34] Using a restricted cubic splines model, we found no evidence for the nonlinear relationship between the AHM adherence level and the risk of stroke (P_{trend}<0.001, $P_{nonlinearity}$=0.755). The dose-response analysis indicated that a 20% increment in AHM adherence level was associated with a 9% lower risk of stroke (RR, 0.91; 95% CI, 0.86–0.96) (Figure 3). Three studies were included to estimate the dose-response analysis of AHM adherence and risk of IS.[12,27,34] We also did not detect a nonlinear relationship between AHM adherence and the risk of IS (P_{trend}<0.001, $P_{nonlinearity}$=0.629), and a 20% increment in the AHM adherence level was associated with a 6% lower risk of IS (RR, 0.94; 95% CI, 0.91–0.96) (Figure 4).

Heterogeneity Assessment and Sensitivity Analyses

A meta-regression analysis was conducted to explore the potential sources of heterogeneity. The varied stroke subtype, quality of the included studies, and age distribution accounted for the main heterogeneity among the included studies, respectively. Adherence to AHM does not represent the only factor influencing the risk of stroke. The number and class of prescribed AHMs and the use of other cerebrovascular preventive medications (eg, antiplatelet agents, anticoagulants, lipid-lowering agents, and antidiabetic agents) were also primary factors that may influence stroke risk.[2] When we excluded the studies that did not report details of adjusted confounders in multivariate analysis, the inverse association between high AHM adherence and stroke risk remained significant (Table S4).

Publication Bias

The funnel plot was asymmetric (Figure S1) on visual inspection. However, Begg's test showed no evidence of publication bias in our meta-analysis (P=0.495) (Figure S2).

Table 2. Stratification Analyses of AHM Adherence and Stroke Risk*

Group	No. of Studies	RR	95% CI	I^2, %	PI
Stroke type					0.090
Ischemic stroke	5	0.74	0.69–0.79	11.7	
Hemorrhagic stroke	2	0.55	0.42–0.72	0.0	
Stroke outcome					0.999
Nonfatal	2	0.52	0.28–0.94	96.4	
Fatal	8	0.51	0.36–0.73	98.2	
Geographic region					0.781
Europe	6	0.70	0.60–0.81	73.3	
North America	7	0.72	0.61–0.83	90.3	
Eastern Asia	5	0.75	0.65–0.88	81.3	
Follow-up time					0.594
<5 y	3	0.77	0.69–0.87	0.0	
5 to 9 y	11	0.70	0.63–0.78	89.0	
≥10 y	4	0.81	0.67–0.98	73.1	
Age distribution					0.337
<65 y	2	0.87	0.83–0.91	96.5	
≥65 y	3	0.68	0.60–0.78	0.0	
Women, %					0.419
<50	6	0.69	0.65–0.74	2.5	
≥50	12	0.74	0.67–0.82	87.5	
Levels of prevention					0.888
PP for stroke	15	0.73	0.66–0.80	87.1	
SP for stroke	3	0.73	0.66–0.81	9.2	
Quality score					0.065
<8	5	0.81	0.72–0.91	82.0	
≥8	13	0.70	0.65–0.75	58.1	

AHM indicates antihypertensive medication; PI, *P* interaction; PP, primary prevention; SP, secondary prevention.
*Pooled relative risks (RRs) and 95% CIs were estimated using a random-effects model.

Discussion

To the best of our knowledge, this is the first dose-response meta-analysis to investigate the association between AHM adherence and stroke risk. By incorporating 18 observational studies involving 1 356 188 patients, we found a significant inverse association between AHM adherence and stroke risk. The dose-response analysis suggested that a 20% increment in the AHM adherence level was associated with a 9% lower risk of stroke. This meta-analysis strengthens and extends the understanding of the positive impact of AHM adherence on stroke prevention, further supporting the notion that improved AHM adherence may be associated with improve stroke prevention in patients with hypertension.

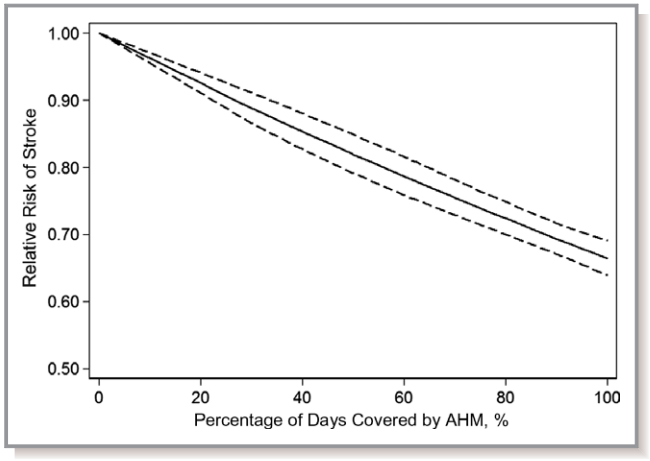

Figure 3. Pooled dose-response analysis of antihypertensive medication (AHM) adherence and total stroke risk (solid line). Dashed lines represent the 95% CI.

Adherence to certain medication has been defined as the extent to which a patient takes medication as prescribed by their healthcare providers, which has a direct influence on the prognosis of a disease, especially for the prevention or treatment of chronic diseases.[5] Hypertension, one of the most prevalent chronic diseases worldwide, could cause serious and irreversible vasculopathy in the brain, thereby representing a known risk factor and treatment target for stroke.[2,3] AHM can effectively control blood pressure and has been confirmed as a major strategy for stroke prevention among patients with hypertension.[3,30] However, in both developed and developing countries, poor adherence to AHM has been raised as a serious concern.[7,12,30] Notably, a high prevalence rate of poor adherence to AHM has been reported in previous studies (ranging from 20% to 60% among the included studies of this meta-analysis), primarily because

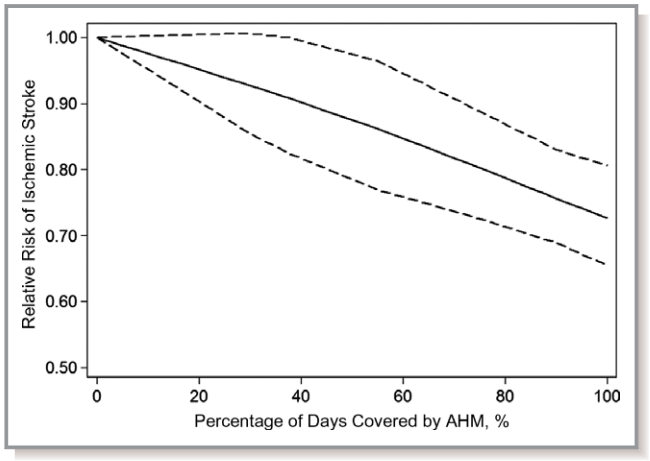

Figure 4. Pooled dose-response analysis of antihypertensive medication (AHM) adherence and ischemic stroke risk (solid line). Dashed lines represent the 95% CI.

of the deficiencies in health systems, poor health education, and issues related to the patient's income.[7] Poor adherence to AHM limited the efficacy of AHM against stroke and has been highlighted as a remarkable obstacle to achieve better stroke prevention outcomes.[11,30,37] Therefore, better adherence to AHM treatment should be highlighted in the clinical prevention of stroke.

This meta-analysis was based on studies in real-world practice, and its results support the importance of improved AHM adherence in preventing stroke among patients with hypertension. Increasing evidence has indicated that AHM not only could ameliorate hypertension and improve vascular structure and function but also have neuroprotective effects, such as the regulation of endothelial NO synthase, anti-inflammatory effects, and cerebral hemodynamics-improving effects, which may be potential mechanisms underlying their preventative effects against stroke.[3,38,39] The results of stratified analyses indicated that higher AHM adherence was associated with lowered risks of both IS and HS, but more remarkably in HS. This is consistent with a previous study showing that hypertension was more associated with HS than IS.[2] In addition, the results of our subgroup analyses showed that higher AHM adherence was associated with lower risks of both fatal and nonfatal stroke. This is important considering that stroke has become one of the most important causes of mortality all over the world.[1] The subgroup analysis also indicated that the stroke prevention effect of high AHM adherence was more significant in patients 65 years and older compared with patients younger than 65 years, partly because patients from the 2 age groups had different stroke causes, risk factors, and comorbidities.

We subsequently evaluated whether the association between AHM adherence and stroke risk was dose dependent. The inverse association between AHM adherence and stroke risk was linear, and a 20% increment in AHM adherence level was associated with a 9% reduction in stroke risk. Moreover, a 20% increment in AHM adherence level was associated with a 6% reduction in IS risk. Based on our comprehensive review of the literature, only 2 studies[12,35] to date have reported a significant benefit for improved AHM adherence in the prevention of HS, and only 1 of these studies[12] found a dose-response relationship between AHM adherence and the risk of HS. Therefore, whether the association between AHM adherence and risk of HS is dose dependent deserves further investigation. In addition to the quantification of AHM adherence, the discontinuation of AHM use also indicated poor AHM adherence. Of the studies included in this meta-analysis, the study by Breekveldt-Postma et al[36] investigated the effect of AHM discontinuation on the risk of stroke, and the results of this study suggested that AHM discontinuation was significantly associated with a higher risk of stroke.

Study Limitations

Several limitations of this meta-analysis should be considered when interpreting the results. First, 4 of the included studies evaluated the risk of cardiovascular morbidity in general, including the risk of stroke, but not exclusively on the risk of stroke.[25,28,32,33] Sensitivity analysis indicates that when the 4 studies were excluded the inverse association between AHM adherence and stroke risk was also significant (RR, 0.73; 95% CI, 0.66–0.80). Second, the information regarding AHM adherence was primarily from administrative data and not directly from face-to-face interviews with patients. These administrative data do not necessarily indicate whether the patients actually took the AHM, which may cause a misclassification of the AHM adherence level. In addition, of the included studies, 2 had relatively different assessments of AHM adherence compared with the others.[34,36] The sensitivity analysis indicates that when the 2 studies were excluded, the pooled estimation had no significant change. Third, a detailed category of the adherence level is important for a dose-response meta-analysis. However, the long interval between the boundaries of the category of the adherence level in several studies may increase the heterogeneity of the results from dose-response meta-analysis and lead to an underestimation of the true association between AHM adherence level and stroke risk. Fourth, different classes of AHM may have different effects on stroke prevention; therefore, a different class of AHM is a key confounder for the association between AHM adherence and stroke risk. It is critical to make a separately quantitative assessment for the associations of different classes of AHM. However, none of the included studies in this meta-analysis reported the association in different classes of AHM. Of the included studies in this meta-analysis, 5 made an adjustment for the class of AHM in their analysis,[13,27–29,36] and the pooled estimation of these studies indicated that the inverse association between AHM adherence and stroke risk was also significant. Fifth, the adherence to AHM is not the only factor that influences the effect of AHM on the risk of stroke. Other confounders (eg, baseline blood pressure, severity of hypertension, and whether target blood pressure values in patients with hypertension were achieved) also influence stroke prevention in patients with hypertension. However, most of the included studies did not report whether they made adjustments for these confounders, which may have reduced the strength of our results. Only the study by Gosmanova et al[26] reported an adjustment for the baseline blood pressure in their analysis, and the results of this study also indicated a significantly inverse association between AHM adherence and stroke risk.

Conclusions

Higher AHM adherence is dose-dependently associated with lower risk of stroke in patients with hypertension. These findings highlight the need to optimize AHM treatment strategies to maximize the beneficial effects of AHM for the prevention of stroke. According to the data reported by the included studies in this meta-analysis, the prevalence of poor adherence to AHM was high in patients with hypertension (ranging from 20% to 60%). Therefore, more efforts should be encouraged to improve adherence to AHM, which may provide significant long-term benefits for patients with hypertension.

Sources of Funding

This work was supported by the National Science Foundation of China (No. 81571259).

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1. Literature search terms:

The following search terms used were in the Medline database:

(adherence [All Fields] OR medication adherence [Mesh] OR patient compliance [Mesh] OR persistence [All Fields])

AND (hypertension [Mesh] OR antihypertensive agents [Mesh] OR angiotensin-converting enzyme inhibitors [Mesh] OR calcium channel blockers [Mesh] OR angiotensin receptor antagonists [Mesh] OR adrenergic beta-antagonists [Mesh] OR diuretics [Mesh] OR antihypertensive medications [All Fields])

AND (stroke [Mesh] OR cerebrovascular disorders [Mesh] OR cardiovascular diseases [Mesh]).

The search strategy for the Embase database was similar to that used for the Medline database.

Table S1 The data source and diseases classification in each included study

First author (year of publication)	Data source	Diseases classification
Yang 2016 [1]	MarketScan Medicaid database from 11 geographically dispersed states in the USA	ICD-9
Kim 2016 [2]	Korea National Health Insurance program in Korea	ICD-10
Herttua 2016 [3]	The Statistics Finland Labor Market database; National Death Register in Finland; National Drug Reimbursement Register in Finland; the Drug Prescription Register by the Social Insurance Institution of Finland; National Institute for Health and Welfare in Finland	ICD-10
Krousel–Wood 2015 [4]	The Cohort Study of Medication Adherence in Older Adults (CoSMO) in the southeastern Louisiana, USA	ICD-9
Gosmanova 2015 [5]	Racial and Cardiovascular Risk Anomalies in CKD (RCAV) study examining risk factors of incident CKD in USA veterans	ICD-9
Xu 2013 [6]	The China National Stroke Registry database	Self-reported
Wong 2013 [7]	A territorywide database in Hong Kong	ICD-9
Shin 2013 [8]	Korean National Health Insurance Claims Database	ICD-10
Herttua 2013 [9]	The Statistics Finland Labor Market database; National Drug Reimbursement Register in Finland; the Drug Prescription Register by the Social Insurance Institution of Finland; National Institute for Health and Welfare in Finland	ICD-10
Perreault 2012 [10]	A linked administrative health database from the RAMQ (Régie Assurance Maladie Québec) in	ICD-9

	Quebec, Canada	
Degli 2011 [11]	Medications Prescription Database maintained by the Local Health Unit of Florence, Italy	ICD-9
Corrao 2011[12]	The health service databases of Lombardy in Italy	Self-reported
Khan 2010[13]	The Registry of the Canadian Stroke Network	Self-reported
Bailey 2010[14]	Tennessee's Medicaid program in USA	ICD-9
Mazzaglia 2009[15]	The Health Search/Thales Database in Italy	ICD-9
Liu 2009 [16]	NHI Research Database in Taiwan	ICD-9
Kettani 2009 [17]	A linked administrative health database from the RAMQ (Régie Assurance Maladie Québec) in Quebec, Canada; Med-Echo databases in Canada	ICD-9
Breekveldt–Postma 2008[18]	PHARMO Record Linkage System in Netherlands	ATC codes

ICD, International Classification of Diseases; CKD, chronic kidney disease; ATC, Anatomical Therapeutic Chemical.

Table S2 The confounders adjusted for the multivariate analysis in each included study.

First author (year of publication)	Adjustment for confounders
Yang 2016 [1]	Age, sex, race, previous CVD, and comorbidities (dyslipidemia, diabetes, chronic respiratory disease, chronic kidney disease, depression)
Kim 2016 [2]	Age, sex, income, residential regions, comorbidities (diabetes, dyslipidemia, and CCI), and the number of AHM
Herttua 2016 [3]	Age, sex, education, comorbidity (diabetes), and a history of cancer
Krousel–Wood 2015 [4]	Age, sex, race, marital status, education, comorbidities (depressive symptoms and CCI), the number of AHM, BMI, and lifestyle behaviors
Gosmanova 2015 [5]	Age, sex, race, marital status, income, public service, baseline glomerular filtration rate, BMI, SBP and DBP, and comorbidities (diabetes, CAD, PAD, chronic respiratory disease, dementia, liver disease, cancers, HIV/AIDS, and depression)
Xu 2013 [6]	Age, education, income, marital status, a history of stroke, comorbidities (myocardial infarction, atrial fibrillation, and diabetes), AHM history, the class of AHM at discharge, severity of stroke, dysphagia, co-medication at discharge (antiplatelet agents, anticoagulants, lipid-lowering agents, and antidiabetic agents)
Wong 2013 [7]	Age, sex, public service, and the class of first AHM
Shin 2013 [8]	Age, sex, type of health insurance, cardiovascular risk at baseline, comorbidities (diabetes, dyslipidemia, and CCI), and the number and class of AHM
Herttua 2013 [9]	Age, sex, length of AHM, education, income, comorbidity (diabetes), and a history of cancer
Perreault 2012 [10]	Age, sex, adherence to other medications (e.g. statins, antidiabetic agents, proton pump inhibitors, and antiresorptive agents for osteoporosis)

Degli 2011 [11]	Age, sex, comorbidities (diabetes, dyslipidemia, heart disease, and atherosclerotic disease), and use of antidiabetic agents, lipid-lowering agents, cardiac therapy, and antiplatelet agents
Corrao 2011[12]	Sex, age, the number of AHM, comorbidity (CCI), and drugs prescribed for heart failure or coronary heart disease
Khan 2010[13]	Age, AHM history, comorbidities (depression and other conditions), total number of baseline drugs used, socioeconomic status, and severity and type of previous stroke
Bailey 2010[14]	Age, sex, race, income, residential regions, type of health insurance, comorbidities (obesity, diabetes, dyslipidemia, CHF, myocardial infarction, atrial fibrillation, TIA, and CCI), history of substance abuse, the class of AHM
Mazzaglia 2009[15]	Age, sex, use of antithrombotics, ≥ 5 concurrent medications, and comorbidities (diabetes, dyslipidemia, and PAD), prior hospitalization, and the number of AHM
Liu 2009 [16]	Age, sex, the number of AHM, and comorbidities (diabetes, CAD, other heart, dyslipidemia, and renal diseases)
Kettani 2009 [17]	Sex , public assistance, comorbidities (CAD, CHF, PAD, other CVD, diabetes, and dyslipidemia), antiplatelet agents, antidiabetic agents, and lipid-lowering agents
Breekveldt–Postma 2008[18]	Sex, age, type of prescriber, cardiovascular co-medication, initial AHM and number of AHM classes, and comorbidity (myocardial infarction)

AHM, antihypertensive medication; CVD, cardiovascular disease; CCI, Charlson Comorbidity Index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; PAD, peripheral artery diseases; CAD, coronary artery disease.

Table S3 Quality assessment of the included studies*

Reference	Is the exposed cohort representative?	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of important factors†	Assessment of outcome	Follow up period	Adequacy of follow up of cohorts	Total quality scores
Yang 2016 [1]	☆	☆	☆	☆	☆☆	—	☆	☆	8
Kim 2016 [2]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Herttua 2016 [3]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Krousel–Wood 2015 [4]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Gosmanova 2015 [5]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Xu 2013 [6]	☆	☆	☆	☆	☆	☆	—	—	6
Wong 2013 [7]	☆	☆	☆	☆	—	☆	☆	☆	7
Shin 2013 [8]	☆	☆	☆	☆	☆☆	☆	—	—	7
Herttua 2013 [9]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Perreault 2012 [10]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Degli 2011 [11]	☆	☆	☆	☆	☆	☆	☆	☆	8
Corrao 2011[12]	☆	☆	☆	☆	☆	☆	☆	☆	8
Khan 2010[13]	☆	☆	☆	☆	—	☆	—	☆	6
Bailey 2010[14]	☆	☆	☆	☆	—	☆	☆	☆	7
Mazzaglia 2009[15]	☆	☆	☆	☆	☆	☆	☆	☆	8
Liu 2009 [16]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Kettani 2009 [17]	☆	☆	☆	☆	☆	☆	☆	☆	8

Breekveldt–Postma 2008[18]	☆	☆	☆	☆	☆☆	☆	☆	☆	9

*Newcastle-Ottawa Scale was used to assess the study quality in this meta-analysis. The full score was 9 stars, and the high-quality study was defined as a study with 8 awarded stars.

† A maximum of two stars could be awarded for this item. One star with adjustment for age and sex, two stars if there was additional comorbidity.

Table S4 Sensitivity analysis for the main confounders*

Group	No. of studies	RR	95% CI	I^2,%	PI
Adjusted for the number of AHM					0.188
Yes	7	0.69	0.62-0.76	64.0	
No	11	0.76	0.68-0.84	86.4	
Adjusted for the class of AHM					0.020
Yes	5	0.82	0.74-0.91	83.0	
No	13	0.69	0.64-0.74	55.9	
Adjusted for other co-medications†					
Yes	6	0.73	0.65-0.81	68.3	0.997
No	12	0.72	0.65-0.81	87.9	

AHM, antihypertensive medication; RR, relative risk; CI, confidence interval; PI, P interaction.

* Pooled RRs and 95% CIs were estimated using a random-effects model.

†Other co-medications included antiplatelet agents, antidiabetic agents, lipid-lowering agents, and anticoagulants.

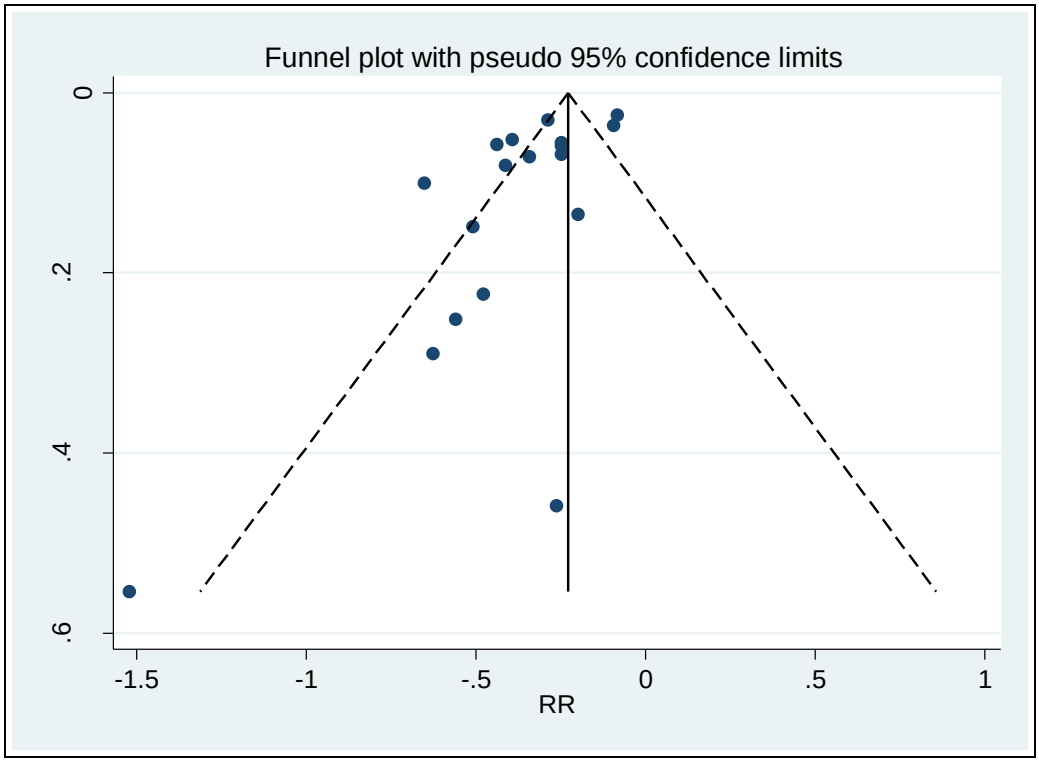

Figure S1. Funnel plot for publication bias test.

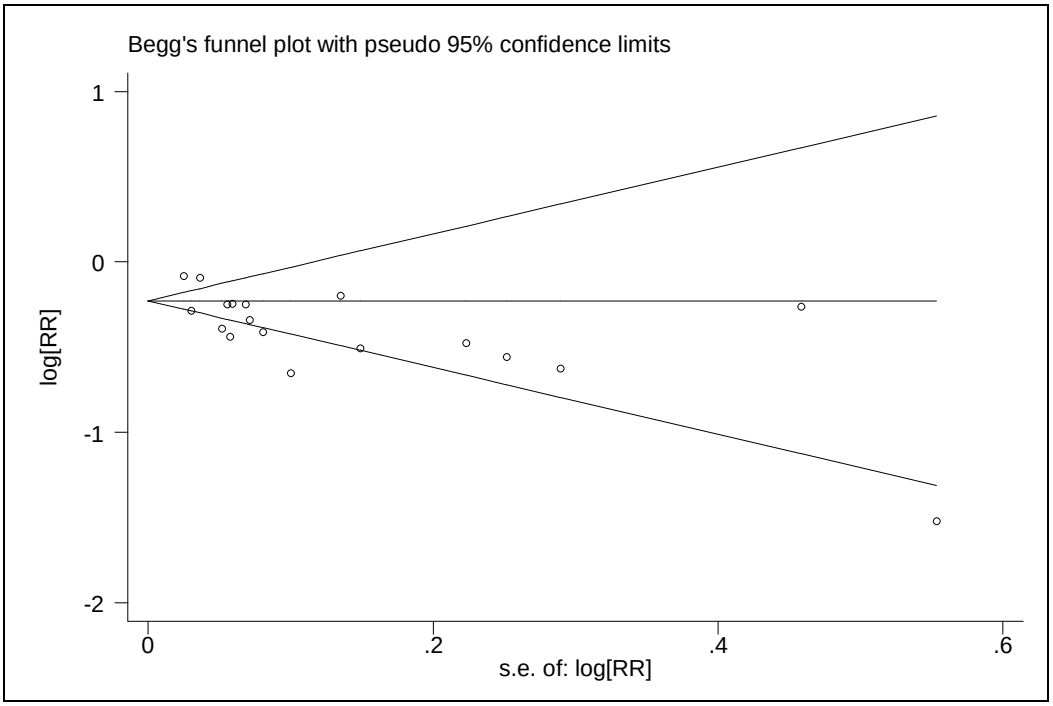

Figure S2. Publication bias test for the association between antihypertensive agents adherence and stroke risk. Begg's test, z = 0.680 (continuity corrected); $p > |z| = 0.495$ (continuity corrected).

Supplemental References

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