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Meta-Analysis of Hypertension as a Risk Factor of Cerebrovascular Disorders in Koreans

This study was conducted to integrate the results of previous studies which evaluated hypertension as a risk factor for cerebrovascular disorders (CVD) in Koreans. We retrieved the Korean literature using a manual search and the English literature using the MEDLINE database concerning the relationship between hypertension and CVD in Koreans from 1980 to 1997. The overall effect size of hypertension as a risk factor of CVD was represented by common odds ratio (OR). Before the integration of each effect size, a heterogeneity test and a sensitivity test was conducted. The materials were nine published epidemiologic studies with a total of 2,271 cases of CVD. The common ORs (95% confidence interval) of overall CVD, hemorrhagic CVD and ischemic CVD associated with hypertension were 4.10 (3.56-4.71), 6.56 (4.92-8.80) and 3.28 (2.77-3.90), respectively. Thus, the common OR of hemorrhagic CVD associated with hypertension was significantly higher than that of overall or ischemic CVD. This suggests that hypertension is an important risk factor for overall CVD and its subtypes in Koreans. Due to the lack of reliable prospective studies, however, longitudinal study is required in this area.

Key Words: *Cerebrovascular Disorders; Hypertension; Meta-Analysis; Korea*

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INTRODUCTION

Cerebrovascular disorders (CVD) are known to be one of the major causes of death in industrialized countries around the world. It is a major cause of mortality and accounts for more than 34,000 deaths per year in Korea (1-4).

Though CVD is a critical and life-threatening disorder, it is considered a disease that can be prevented through effective control of its risk factors (5). This may be primarily due to the extensive cohort research conducted for identifying the attributable risks of each risk factor for cardiovascular disorders, including CVD, and the meta-analyses that quantitatively integrated the results of such research. Many nations that initiated such research, including the U.S.A., have utilized the results to control CVD.

Since the 1960s, Korea has become active in this particular area of research and many original articles have been presented (1, 7). In addition, medical journals that focus on risk factors such as hypertension related with CVD have been initiated in recent years (1, 6-7). Meanwhile, several researchers have attempted a qualitative investigation on relevant research papers that identify research trends and propose directions for future research. However, these researches have not been able to substantially disclose risk factors or integrate useful results. The purpose of such analysis remains a descriptive review or partial reviews of individual papers. Therefore, a methodological approach for integrating the results of the research to date is necessary. For integrating these results, one of the most powerful methods is meta-analysis, which has been vigorously advanced in the U.S.A. (8-10).

The purpose of this study was to integrate the results of previous studies which evaluated hypertension as a risk factor for CVD in Koreans.

MATERIALS AND METHODS

Data collection

The process (Fig. 1) of this study followed the pattern

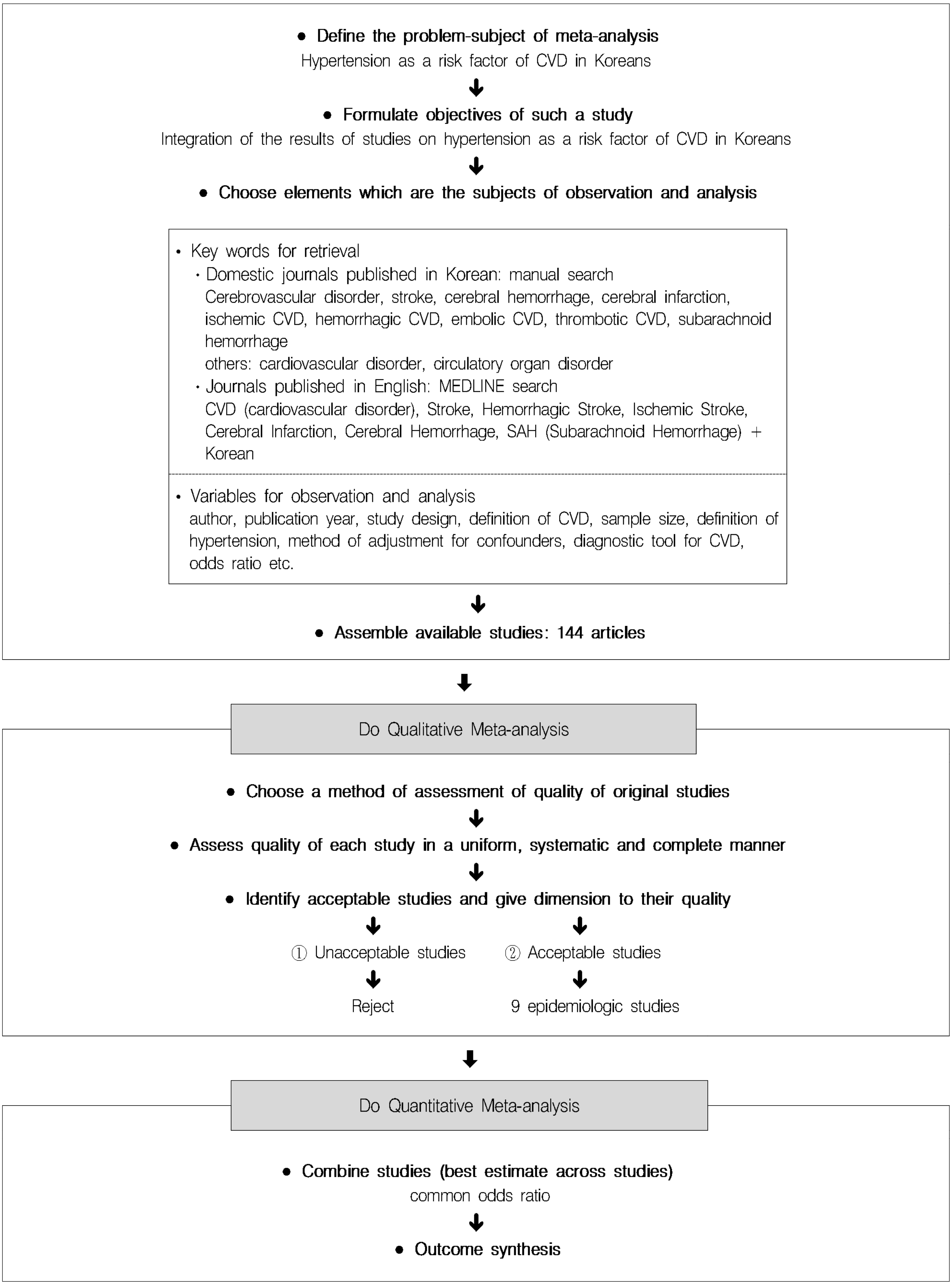

Fig. 1. Overall flowchart of meta-analysis.

of meta-analysis proposed by Jenicek (11).

The materials were articles concerning the relationship between hypertension and CVD in Koreans that were published in either Korean or English from 1980 to 1997. Information was retrieved by manual searching of Korean publications (including the Korean Index Medicus) and MEDLINE (only English publications) databases. There were included *Korean J Intern Med, Korean J Epidemiol, Korean J Prev Med, Korean J Nutrition, Yonsei Med J,* etc. as the major domestic journals, and *Stroke, Hypertension, Am J Epidemiol, BMJ,* etc. as the major international journals. The medical subject headings for this search were CVD, stroke, ischemic CVD (cerebral infarction: thrombotic, embolic, and lacunar cerebral infarctions included), hemorrhagic CVD (cerebral hemorrhage, intracranial hemorrhage), subarachnoid hemorrhage, cardiovascular disorder, circulatory organ disorder, etc. according to the method proposed by Counsell (12).

Meta-analysis method

A total of 144 articles which contained information on the risk factors of CVD were selected in this search and evaluated thoroughly by two reviewers. The agreement rate to the quality evaluation of each article between the two reviewers was 91.8% by blinding of quality assessors, and disagreements were adjusted by mutual consensus. These were then divided into two categories depending on whether the CVD-related risk factors were clarified or not in the title, key words, or purpose of the study. The criteria for selecting articles for quantitative meta-analysis were; i) original articles or ii) articles that clarified the risk factors (hypertension etc.) for CVD in the research purpose. In particular, the following standards were used for judging the quality of articles before applying meta-analysis. Those that did not meet the standards were excluded from the analysis even though they provided information for calculating the effect size. First, a normal control group was set, and the case group and control group in the study came from the same community or hospital. Second, studies that were controlled for major confounding factors (gender and age) during the study design or analysis process. Through this process, 9 epidemiologic studies were included in meta-analysis.

The following informations were collected from each publication: names of authors, publication year, design of study, sample size and sampling methods, definition of hypertension, subtype of stroke assessed by diagnostic method (including computer tomography or MRI), gender ratio, and controlled confounders, etc.

The relationship between hypertension and CVD was assessed by estimation of the common OR and 95% confidence interval (CI). For the sensitivity test on the common OR, we adopted both methods of comparing the results in fixed and random effect model and the method of calculating the cumulative ORs in chronological order by publication years of the articles.

Meta-Analysis$^{0.988}$ (1990-1995), a computer program for meta-analysis developed by Lau (13), was used for calculating the study-specific OR, 95% CI, cumulative OR, common OR and Q statistic. In addition, the samples and ORs of each article were illustrated using funnel plots to assess the publication bias (14).

RESULTS

Table 1 presents the details of the nine epidemiologic studies used in meta-analysis. The study design of the articles was case-control studies. The diagnostic method of CVD in these studies was mostly computer tomography or MRI, whereas in the community-based studies family physicians diagnosed according to clinical judgment. A total of 2,271 CVD cases were included in the analysis.

Both random and fixed effect model were used in order to assess the relationship between hypertension and overall CVD. The Q and χ^2 test statistics of the two models were used for the evaluation of homogeneity. The Q value in the random effect model was 16.43 ($p<0.001$, Table 2). However, the χ^2 value in the homogeneity test according to the fixed effect model was 15.02 (d.f.=8, $p>0.05$, Table 3). Thus, the data of each article were considered homogeneous in the fixed effect model. Therefore, the fixed effect model was selected as a more suitable model for the integration of the results.

According to the fixed effect model, the common OR of overall CVD associated with hypertension was 4.10 (95% CI: 3.56-4.71). Of nine articles, three offered information for the ORs of hemorrhagic CVD and seven offered those of ischemic CVD. Also, the results of homogeneity test in both subtypes of CVD were similar to that in overall CVD. The common ORs (95% CI) of hemorrhagic and ischemic CVD were 6.56 (4.92-8.80) and 3.28 (2.77-3.90), respectively. Thus, the common OR of hemorrhagic CVD was higher than that of ischemic or overall CVD (Table 3).

The common OR and study-specific ORs for the relationship between hypertension and CVD are shown in the log scale on the left side of Fig. 2. The ORs of individual studies varied widely, but the 95% CI for the nine studies overlapped each other. Likewise, when calculating the cumulative ORs in chronological order by publication years from 1984 to 1997, we found consistent results that all the cumulative ORs were significant

Table 1. Characteristics of 9 epidemiological studies on relationship between hypertension and CVD in Koreans

Author, year (Ref. No)[‡]	Design	Sample size	Definition of hypertension (mmHg)	CT diagnosed (stroke) %	Male (%)	Ischemic (%)	Controlled for
Kim JS, 1984 (15)	Case -control	community survey Cases, 154; Controls, 154	160/95	0 (diagnosed by symptom & P/E)	59.1	55	sex, age 1:1 matching
Shin GM, 1988 (16)*,†	Case -control	hospital survey Cases, 260; Controls, 262	diastolic BP - higher than 90	100	50.4	48.1	sex, age frequency matching
Han SH, 1988 (17)	Case -control	community survey Cases, 80; Controls, 80	160/95	0 (diagnosed by family physicians)	51.3	not reported	sex, age, occupation individual matching
Kim JS, 1989 (18)*	Case -control	hospital survey Cases, 208; Controls, 208	past history or 160/90 (WHO standard)[§]	partial	54.8	100	sex, age, DM duration matching (DM patients)
Lee HC, 1991 (19)*,†	Case -control	hospital survey ICVD, 546, Controls, 383	past history or 160/90 (WHO standard)[§]	100	43.8	100	sex, age matching
		HCVD 459, Controls, 383		100	58.8	0	
O KY, 1992 (20)*	Case -control	hospital survey Cases, 303; Controls, 207	160/90	100	50.8	100 lacunae 92; thrombotic 170; embolic 41	sex, age matching
Kim JR, 1995 (21)*,†	Case -control	hospital survey Cases, 127; Controls, 127	160/90 (WHO standard)[§] or fundoscopy abnormality	100	50.4	58.3	sex, age matching
O SW, 1996 (22)*	Case -control	hospital survey Cases, 102; Controls, 102	160/90 (WHO standard)[§]	partial (& MRI)	50.0	100	sex, age 1:1 matching
Rhee KH, 1997 (23)*	Case -control	NIDDM cases with ICVD, 32; NIDDM cases without ICVD, 32	160/90	partial (& MRI)	65.5	100	age matching

ICVD indicates ischemic CVD; HCVD hemorrhagic CVD; NIDDM noninsulin-dependent diabetes mellitus
*articles that provide data for ICH besides that of overall CVD; †articles that provide data for ICVD besides that of overall CVD; ‡a number of articles are presented in references; §confirm the definition of hypertension by direct contact with authors

Table 2. Common odds ratios of CVD and its subtype in relation to hypertension in Koreans (random effect model)

Stroke subtype	N	OR (95% CI)	Test for homogeneity	
			Q	*p**
Hemorrhagic	3	7.25 (3.99-8.68)	4.77	$p<0.05$
Ischemic	7	3.33 (2.28-4.86)	23.57	$p<0.001$
Total†	9	4.35 (3.45-5.50)	16.43	$p<0.001$

OR, indicates odds ratio (common OR); CI, confidence interval; N, number of studies
*the estimated range of the *p*-value can be found in the χ^2 table (degree of freedom=1)
†actual number of articles excluding overlapping articles

Table 3. Common odds ratios of CVD and its subtype in relation to hypertension in Koreans (fixed effect model)

Stroke subtype	N	OR (95% CI)	Test for homogeneity	
			χ^2*	*p*
Hemorrhagic	3	6.56 (4.92-8.80)	5.06	$p>0.05$
Ischemic	7	3.28 (2.77-3.90)	21.17	$p>0.05$
Total†	9	4.10 (3.56-4.71)	15.02	$p>0.05$

OR, indicates odds ratio (common OR); CI, confidence interval; N, number of studies
*degree of freedom=N-1
†actual number of articles excluding overlapping articles

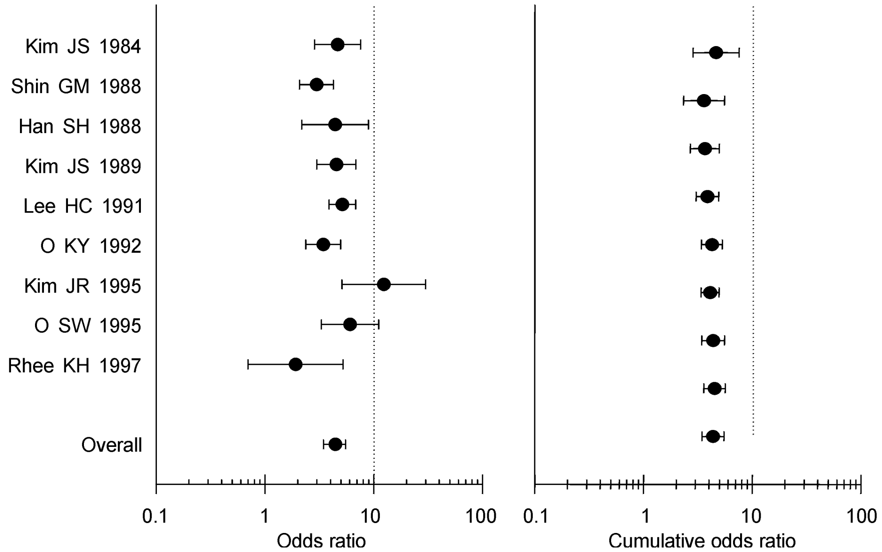

Fig. 2. Odds ratio, common odds ratio and 95% confidence interval **(left)**, cumulative OR **(right)** of CVD in relation to hypertension in Koreans.

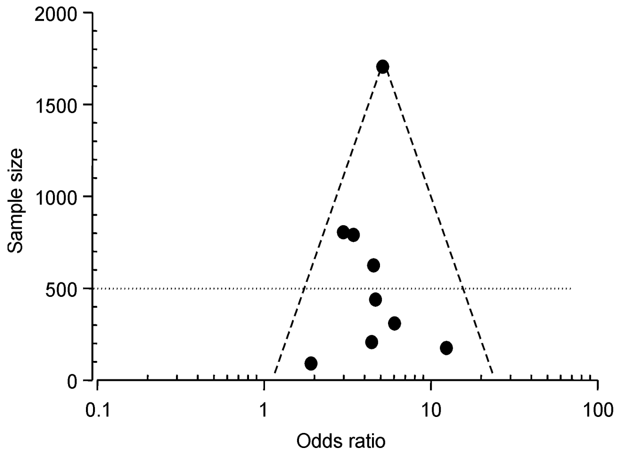

Fig. 3. Inverse funnel plotting between sample size and OR of CVD in relation to hypertension.

($p<0.0001$) and 95% CI were decreased continuously (Fig. 2, right side).

Inverse funnel plotting between sample size and the ORs for each study is shown in the log scale (Fig. 3). The scatter of points showed that the studies were concentrated at the left lower part of the triangle. Therefore, it seemed that studies with a large number of samples and high ORs were lacking.

DISCUSSION

In Korea, we found few attempts which have been made for quantitative meta-analysis (24-27). Therefore, this study may be considered pioneering attempt to integrate the results of previous studies which evaluate hypertension as a risk factor for CVD in Koreans through quantitative meta-analysis.

The materials of this study were limited to those articles published after 1980. The primary reason for this was securing homogeneity in the relationship between hypertension and CVD. It is known that there was a transition of trends in disorders from infectious diseases to chronic degenerative diseases after the 1970s. The second reason was that since 1982, various relevant medical professional societies have been launched, including the Korean Neurological Association, and a growing number of articles in this field began to be published, accordingly.

The primary targets of meta-analysis are randomized clinical trials (RCTs) in which there is little possibility of a bias intervening in the individual research projects. Thus, quite a few drawbacks were indicated in the application of this method to observational research and considerable debate continues as to the merits of meta-analysis in observational studies (28, 29). Nonetheless, many researchers emphasize the significance of meta-analysis in contributing to knowledge by studying features across studies that may account for the variation in results (30, 31). Also, although meta-analysis restricted to RCTs is usually preferred to meta-analyses of observational studies (29), the number of published meta-analyses concerning observational studies in health has increased substantially during the past 4 decades (32).

Meta-analyses of observational studies present particular challenges because of inherent biases and differences in study designs (33); yet, they may provide a tool for helping to understand and quantify sources of variability in results across studies (34). Generally, the assessment method for bias which may have intervened in the study should be considered when applying meta-analysis to observational studies. After considering various meta-analysis studies, Egger et al. (14) divided the bias into five categories. Therefore, this assessment method was considered in this study to control various biases. At first, in order to minimize citation bias, the materials included all relevant medical journals that were published in either Korean or English. In addition, to eliminate multiple publication bias when there were several articles based on a single project, information from the most recent publication was used.

Because case-control studies were used in the study design, the logit estimate and the stratification analysis was used to integrate the study results in meta-analysis. In particular, this study calculated the integrated estimate according to the fixed effect model because this model was selected as a more suitable model in homogeneity test (13, 35).

The community attributable risk of hypertension on CVD has been estimated at 26% in the U.S.A. (36). By using both the OR of this study and the estimated prevalence (19.8%) of hypertension in Koreans 30 yr or over (15), the community attributable risk in Koreans may be estimated at 36.0%. In addition, the results of meta-analysis in People's Republic of China (a total of 12 epidemiological studies with 2,379 stoke cases), revealed the common relative risk of stroke associated with hypertension was 5.43 (95% CI: 4.62-6.39) (37). The common OR of overall CVD associated with hypertension in our study was 4.10, which was much lower than the common relative risk estimated in studies of Chinese populations. However, it was much greater than the corresponding relative risk (2.3-3.6) in studies of western populations (38-41). Of course, this estimate was based on a very conservative definition of hypertension including past history of cases or the recommendations of the WHO by articles review or direct contact with authors, i.e., an average systolic blood pressure $\geq$160 mmHg or diastolic blood pressure $\geq$90 mmHg (42, 43). Because of this definition, it should be considered that the estimated OR of CVD associated with hypertension seems to have been underestimated (37).

The results of the fixed effect model and the random effect model showed similar aspects. Generally, the integrated estimate and 95% CI according to the random effect model are greater and wider than those according to the fixed effect model (13). Our study results were in accordance with these observations.

We recognize that the use of quality scoring in meta-analyses of observational studies is controversial, as it is for RCTs (44, 45), because scores constructed in ad hoc fashion may lack demonstrated validity, and results may not be associated with quality (46). Nevertheless, the quality of this study was primarily dependent upon the quality of the sample articles. Since the design of sample articles was case-control study, blood pressure was assessed after the occurrence of CVD. Consequently, there may be problems in reliability and validity of blood pressure, as well as the estimated common effect size. To overcome these problems, a well-designed and prospective study is required.

It is still rare to find a large cohort study of high quality targeted at Koreans. Therefore, what we should emphasize is not just a simple methodological application of meta-analysis, but conducting high quality cohort studies. Only when high quality studies are performed as such, will quantitative meta-analysis contribute to the integration of high quality results.

In conclusion, hypertension is an important risk factor for overall CVD and its subtypes in Koreans.

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