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Retinal vein occlusion and risk of cerebrovascular disease and myocardial infarction: A meta-analysis of cohort studies

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ABSTRACT

Background and aims: Retinal vein occlusion (RVO) has been hypothesized to be associated with cerebrovascular disease and myocardial infarction (MI), but the results are inconclusive. We thus systematically evaluated the effect of RVO on the development of cerebrovascular disease and MI by a meta-analysis of cohort studies.

Methods: PubMed, Embase and Web of Science databases were searched from inception to October 2015. Reference lists of retrieved papers were also reviewed. Cerebrovascular disease and MI were considered as the endpoints. Either fixed- or random-effects models were used to calculate the overall summary risk estimates. Subgroup and sensitivity analysis were performed to assess the potential sources of heterogeneity and the robustness of the pooled estimation.

Results: Overall, a total of 9 cohort studies were included. Of these, 8 reported results on cerebrovascular disease and 5 reported on MI. The summary adjusted relative risks (RRs) for patients with RVO compared with the reference group were 1.50 (95% confidence interval [CI]: 1.32–1.69) for cerebrovascular disease and 1.28 (95% CI: 1.17–1.41) for MI. These associations were not significantly modified by geographic area, sample size, length of follow-up, and adjustment for potential confounding factors. Sensitivity analyses according to various inclusion criteria yielded similar results. No evidence of publication bias was observed.

Conclusions: This meta-analysis provides further evidence supporting that RVO is associated with increased risk of future cerebrovascular disease and MI.

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1. Introduction

Retinal vein occlusion (RVO), including central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), is one of the foremost cause of severe visual impairment and blindness, especially in the elderly [1]. A recent pooled analysis of individual population-based data suggested that approximately 16 million people are affected by RVO worldwide [2]. In particular, RVO has received considerable attention for the unique characteristic of retinal vessels that can be directly and noninvasively examined via ophthalmoscopy [3]. Meanwhile, cardiovascular disease (CVD) has become a major public health issue and is responsible for approximately 30% of all deaths worldwide [4]. It is reported that the leading causes of death in 2030 are predicted to be ischemic heart disease and cerebrovascular disease [5].

It has been shown that the retinal blood vessels share similar anatomic and physiologic characteristics with cerebral vessels [6], and many systemic risk factors for RVO are also associated with arterial thromboembolic events, such as cerebrovascular disease and myocardial infarction (MI) [7,8], which indicate a possible link between RVO and development of cerebrovascular disease and MI.

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During the past decade, a number of epidemiologic observational studies have investigated the associations between RVO and future cerebrovascular disease and/or MI [9–22]. Recently, a nationwide population-based longitudinal study in Korea showed that RVO was significantly associated with stroke development based on a 9-year follow-up period after adjusting for potential confounders [12]. While several cohort studies from United States or Taiwan found RVO was not independently associated with increased risk of stroke and acute MI [16,18,19]. The inconsistent results may due to differences in sample size, study design, study population or residual confounding among these studies. Clarifying these associations have important clinical and public health implication for primary prevention of cerebrovascular disease and MI. Hence, we systematically evaluated current available cohort studies to evaluate the associations between RVO and risk of cerebrovascular disease and MI by a meta-analysis.

2. Methods

2.1. Literature search and study selection

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [23]. We conducted a systematic literature search by using the electronic databases PubMed (from 1965 to October 2015), Embase (from 1965 to October 2015) and Web of Science (from 1986 to October 2015). The following search terms were used: “cardiovascular disease”, “stroke”, “cerebral infarction”, “brain infarction”, “cerebrovascular disease”, “cerebral hemorrhage”, “intracranial hemorrhage”, “cerebrovascular disorders”, “myocardial infarction”, “coronary heart disease”, “ischemic heart disease” in combined with “retinal vein occlusion”, “retinal vein obstruction” (Supplemental Table 1). No language restriction was imposed. We also conducted manual searches of the reference lists of selected articles to identify additional eligible studies.

We first performed an initial review of titles and/or abstracts, and then a second review was based on full texts of the articles if there was uncertainty about relevance. Studies were considered eligible for analysis if they met the following criteria: (1) the study design was a cohort study (prospective or retrospective cohort); (2) the exposed population was patients with RVO; (3) the study outcomes were cerebrovascular disease and/or MI (fatal or nonfatal or both); (4) enrolled participants were free of cerebrovascular disease and MI at baseline; (5) risk estimates and the corresponding 95% CIs of the association between RVO and cerebrovascular disease or MI were reported.

2.2. Data collection and quality assessment

Data were collected using a standard electronic form. The following data elements were extracted from each study: first author, publication year, location, study design (prospective vs retrospective), sample size, follow-up years, RVO types, study endpoint, exposure and endpoint assessment, and covariates in the fully adjusted model. The Newcastle-Ottawa Scale (NOS) was used to evaluate study quality [24]. The NOS is a comprehensive tool that has been partially validated for evaluating the quality of observational studies in meta-analyses and a higher score represents better methodological quality [25]. Data extraction and quality assessment were independently performed by CKZ and SJY, and independently checked for accuracy by YHZ.

2.3. Statistical analysis

The relative risk (RR) was used as the common measure of the association between RVO and risk of cerebrovascular disease and MI. The hazard ratios and incidence rate ratios were considered equivalent to RRs. For one study that reported stratified risk estimates of different RVO forms only, we used a fixed-effects model to calculate a combined adjusted RR and then included this combined RR in the meta-analysis [19]. Heterogeneity across studies was examined by using the Cochrane Q and I^2 statistic [26]. For the Q statistic, a P-value <0.1 was considered statistically significant heterogeneity; and for the I^2 statistic, the following cutoff points were used: <30% (little or no heterogeneity), 30–75% (moderate heterogeneity), and >75% (high heterogeneity) [27]. The combined RRs were computed using either fixed-effects models or, in the presence of heterogeneity, random-effects models [28]. Forest plots were produced to visually assess the RRs estimates and corresponding 95% CIs across studies for individual studies and all combined.

To explore potential sources of heterogeneity, subgroup analyses based on adjusted RRs were conducted according to geographic area, sample size, length of follow-up, adjusted hypertension, adjusted diabetes mellitus, adjusted hyperlipidemia, and adjusted renal disease. To test the robustness of the associations between RVO and risk of cerebrovascular disease and MI, sensitivity analyses were performed according to various inclusion criteria. Additional sensitivity analyses were performed by removing each individual study from the meta-analysis. Several methods were used to check for potential publication bias, including visual inspection of funnel plots, and Begg rank correlation test and Egger linear regression test [29,30]. All reported P values were 2-sided, and $P < 0.05$ were considered statistically significant. Statistical analyses were performed using STATA software (version 12.0; STATA Corporation, College Station, TX, USA).

3. Results

3.1. Studies and patient characteristics

Overall, a total 682 articles were identified from the initial PubMed database search. After the first screening based on titles and abstracts, we excluded 631 records and retained 51 studies for further evaluation by reading the full text. Of these, 42 were excluded because data (risk estimates and/or 95% CIs) were not available in 7 publications, the exposure of interest was not RVO in 15 publications, the outcome of interest was not cerebrovascular disease or MI in 19 publications, and 1 study enrolled participants with preexisting stroke at baseline [31]. Finally, 9 cohort studies were included in this meta-analysis [12–20]. The results of the study selection process are shown in Fig. 1.

Characteristics of the selected studies are presented in Table 1. All studies were published between 2007 and 2015. The follow-up durations ranged from 1.5 to 12 years. Four studies were conducted in Asia [12,14,18,19], three in Europe [13,15,17], one in the Unite States [16], and one was a multinational study [20]. Of the included studies, six were prospective cohorts, while the other three were retrospective cohorts. Study quality was assessed by using the NOS. Overall, three studies had a score of 9 [12,14,18], three studies had a score of 8 [16,17,19], and one study had a score of 7 [13], and the remaining two studies had a score of 6 [15,20] (Supplemental Table 2).

3.2. RVO and risk of cerebrovascular disease

A total of 8 cohort studies with 183 135 participants and 11 229 incident cases reported an association between RVO and cerebrovascular disease. Fig. 2 presents the combined unadjusted and multivariable-adjusted RRs for cerebrovascular disease. Compared

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