Original Article

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Hypolipidemia and Risk of Intracerebral Hemorrhage: A Meta-Analysis

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Objective: The risk of hemorrhagic stroke is linked to low cholesterol levels. However, majority of studies primarily concentrate on assessing the safety of statin medications in reducing blood cholesterol levels. This meta-analysis aimed to investigate the impact of pre-existing hypolipidemia on the prognosis of patients diagnosed with primary intracerebral hemorrhage (ICH).

Methods: We conducted a comprehensive search of Medical Literature Analysis and Retrieval System Online (MEDLINE®), Public Medicine (PubMed®) and Excerpta Medica Database (EMBASE®) and included studies that compared the mortality rates of patients with ICH with and without pre-existing hypolipidemia. Adjusted or unadjusted odds ratios (ORs) for mortality were pooled along with their corresponding 95% confidence intervals (CIs) to determine the overall effect of this meta-analysis.

Results: In the nine trials analyzed, hypolipidemia was associated with a significantly higher risk of ICH (OR 2.048; 95% CI 1.159 – 3.617). Additionally, meta-regression analysis revealed that the adjusted OR for mortality among patients with hypolipidemia was 1.429 times (95% CI 1.109 – 1.843, $p = 0.006$) higher compared to that for patients with non-hypolipidemia.

Conclusions: Hypolipidemia was found to be associated with both the risk of ICH and mortality rates among patients with ICH.

Key words: cholesterol, hypolipidemia, stroke, intracerebral hemorrhage, meta-analysis

Introduction

Spontaneous intracerebral hemorrhage (ICH) is the second most prevalent form of stroke after ischemic stroke. Within one month of stroke, the mortality rate ranges from 35% to 52%, and only 20% of those who survive manage to regain functional independence within six months.[1,2] Despite numerous clinical trials investigating medical and surgical interventions to improve mortality and functional outcomes, no observed changes have been reported in the ICH fatality or long-term mortality rates over time.[3-5]

Hypolipidemia is a prevalent condition

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affecting approximately 2% – 3% of seemingly healthy individuals.[6] In contrast to hyperlipidemia, physicians often lack awareness of hypolipidemia or primarily concentrate on the safety of statin medications. Recent meta-analysis have explored the association between the use of statin-induced hypolipidemia and risk of ICH.[3]

Hypolipidemia is a recognized risk factor for ICH. Implementing effective primary stroke prevention measures remains the most effective approach to reduce the overall burden of stroke. Therefore, we conducted a meta-analysis to examine the association between various categories of hypolipidemia and the risk of ICH.

Materials and Methods

To investigate the association between low-density lipoprotein cholesterol (LDL-C) and ICH, we conducted systematic literature searches using the Medical Literature Analysis and Retrieval System Online (MEDLINE®), Public Medicine(PubMed®) and Excerpta Medica Database (EMBASE®). Our search strategy utilized specific keywords, including ([LDL-C] OR [hypolipidemic] OR [LDL]) AND ([intracerebral hemorrhage] OR [hemorrhagic stroke] OR [ICH]) to identify potentially relevant studies. The search was limited to articles published between January 1980 and June 2021, focusing on those published in English. In addition to observational studies and case series, we reviewed the reference lists of the selected studies and previously published meta-analysis on similar topics for additional relevant information.

Inclusion criteria

Our study included published articles that examined the clinical aspects of low LDL-C levels including mortality, ischemic stroke, and ICH. We calculated the risk estimate based on the data presented in each article. The definition of low LDL-C levels was not restricted to severity levels.

Exclusion criteria

We excluded studies that met any of the following criteria: (1) they specifically investigated the relationship between lipid-lowering therapy and the risk of ICH; (2) they were review articles; (3) they solely involved a follow-up study of a cohort comprising patients with low LDL-C levels without a comparison group; or (4) there was insufficient information provided to enable the calculation of risk estimates.

Data analysis

Two authors (H. K. Wang and W. L. Chin) independently reviewed the titles and abstracts of selected studies. The full articles of potentially relevant studies were thoroughly assessed to determine their eligibility based on these criteria. Our study followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) Reporting Guidelines and adhered to a systematic review approach. The selection process of studies reporting hemorrhagic stroke in relation to low LDL-C levels was documented using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

The fixed effects model was selected based on the absence of heterogeneity among studies, whereas the random effects model was chosen in the presence of heterogeneity. Funnel plots were used to assess the potential presence of publication bias or systematic heterogeneity in the studies included in our analysis. An asymmetric funnel plot indicated a systematic disparity between the studies with higher and lower precision. Egger regression is a statistical tool used to quantify asymmetry in a funnel plot.

Results

Systematic search

Our literature search, along with an examination of the reference lists, resulted in 201 references. Following evaluation of the

Table 1. Individual for all included studies in intracerebral hemorrhage (ICH) or hematoma growth/transformation and mortality.

Author, year of publication, country	Study design	Participants (% of statin user)	Age range or mean (year)	Follow-up (year)	Cut-off points of LDL (mg/dl)	Outcomes definition
Ma C, et al. 2019, China[6]	Prospective cohort study	96,043 subjects who were free of stroke, myocardial infarction, and cancer (2.0%)	51.3	9	< 50	Incident of ICH
Sun L, et al. 2019, China[14]	Nested case-control study	16,541 subjects without prior history of cardiovascular disease (CVD), cancer, lipid-lowering, anticoagulant, or antiplatelet treatment at baseline (0%)	51	9	88.9	Incident of ICH
Lee JG, et al. 2012, Korea[12]	Retrospective study	959 subjects with low-density lipoprotein cholesterol (LDL-C) level ≤ 70 mg/dL (48.4%)	61.5	6	≤ 40	Incidence of ICH
Rodriguez-Luna D, et al. 2011, Spain[7]	Prospective study	108 patients with primary supratentorial ICH presenting within 6 hours From symptoms onset between April 2009 and June 2010 (15.7%)	71.6	24 hours	< 91	Hematoma growth
Kim BJ, et al. 2009, Korea[13]	Retrospective study	377 subjects with stroke attributable to large artery atherothrombosis and cardioembolism who admitted to hospital within 7 days after ictus between October 2002 and March 2006	66	1 week	< 89.7	Hematoma transformation
Wieberdink RG, et al. 2011, Netherlands[8]	Prospective population-based cohort study	9,068 stroke-free community-dwelling persons (4.9%)	55+	9.7	< 123.7	ICH
Ramírez-Moreno JM, et al. 2009, Spain[9]	Prospective cohort study	88 patients over age 18 with ICH without traumatism, brain tumor, previous ICH, hemorrhagic transformation of ischemic stroke, vascular cerebral malformations, and patients who required neurosurgical procedures (30.7%)	73.8	90 days	< 100	90-day mortality
Penson PE, et al. 2018, US[10]	Longitudinal prospective cohort study	30,239 participants with 'high risk' for coronary events with a Framingham Coronary Risk Score of ≥ 10% or atherosclerotic cardiovascular disease (ASCVD) risk ≥ 7.5%	67.6	7.14	< 50	All-cause mortality
Johannesen CDL, et al. 2020, Denmark[11]	Prospective cohort study	108,243 Individuals randomly selected from the national Danish Civil Registration System (12%)	20 – 100	9.4	< 70	All-cause mortality

abstracts and, when indicated, full-text articles, 30 studies were identified as potentially eligible for inclusion. Nine studies were ultimately selected for the final meta-analysis (Table 1).

Study characteristics

The meta-analysis included individual participant data from nine trials comprising 261,666 participants. Table 1 presents the characteristics of the included studies and their participants. Among the nine trials, six were prospective cohort studies,[6-11] two were retrospective studies,[12,13] and one was a case-control study.[14] Geographically, 4 studies were conducted in Asian countries,[6,12,13,14] whereas five were conducted in Western countries.[7-11] The percentage of statin users ranged from 2.0% to 48.8% in six studies,[6-9,11,12] whereas one study[10] did not provide clear information on this aspect. One study initially excluded statin users,[14] while another study specifically included participants with a history of hyperlipidemia or prior use of lipid-lowering medications.[13]

Meta-analysis of Low LDL-C and ICH or hematoma transformation/growth

The heterogeneity test yielded a significant result (I_2 = 93.155%, $p < 0.05$) based on six studies,[6,7,8,12,13,14] leading to the selection of a random-effects model. The pooled estimate of odds ratios (ORs) for ICH or hematoma transformation/growth among individuals with lower LDL-C was 1.885 (95% confidence interval [CI] 1.037 – 3.427). This finding indicated a significantly higher risk (p = 0.038) of ICH or hematoma transformation/growth in this particular group (Fig. 1). Sensitivity analysis revealed that the effect size of the pooled estimate was not influenced by the removal of any specific study. The funnel plot assessed using Egger's test (p = 0.293) did not reveal any statistical evidence of publication bias among the studies regarding ICH incidence or hematoma transformation/growth (Fig. 2).

Meta-analysis of Low LDL-C and mortality

The heterogeneity test yielded non-significant results (I_2 = 42.371%, $p > 0.05$) based on the studies,[9-11] leading to the selection of a fixed-effects model. The pooled estimate of the relative risks (RRs) for mortality among individuals with lower LDL-C levels was 1.273 (95% CI 1.177 – 1.378), indicating a significantly higher risk ($p < 0.001$) of mortality in this particular group (Fig. 3). Sensitivity analysis revealed that the effect size of the pooled estimate was not influenced by the removal of any specific study. The funnel plot assessed using Egger's test (p = 0.033) demonstrated statistical evidence of publication bias among the studies regarding mortality (Fig. 4). After imputation, the adjusted effect size was 1.250.

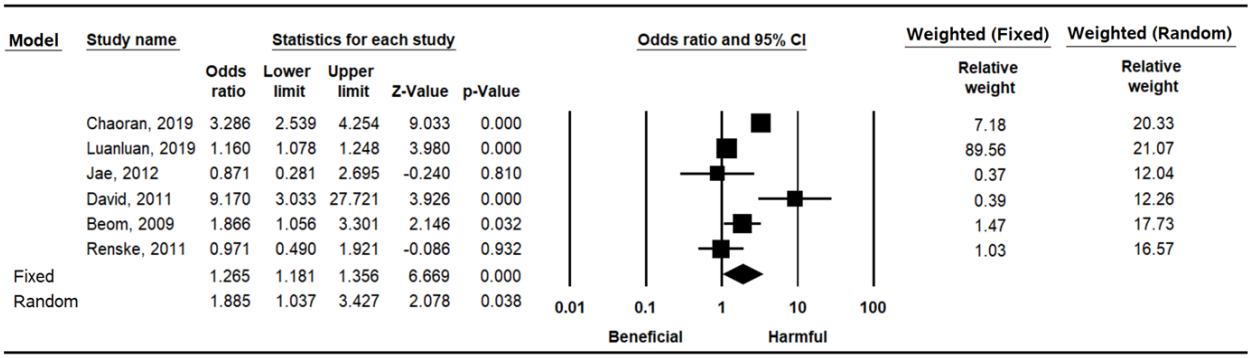

Fig. 1 Individual and pooled odds ratios for ICH.

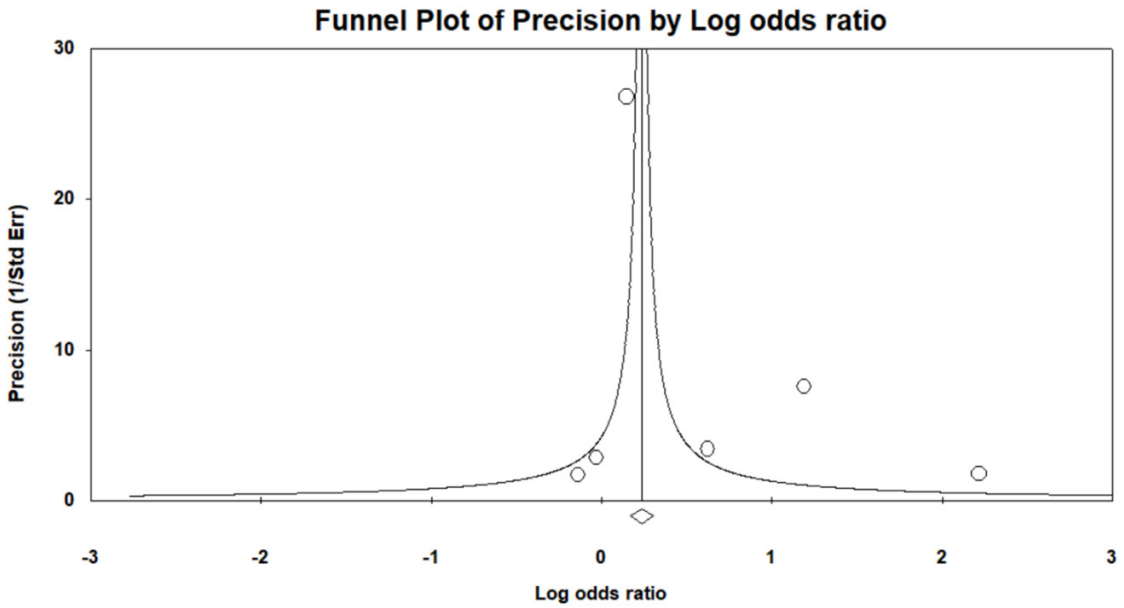

Fig. 2 Funnel plot, using the six trials of LDL-C and ICH or hematoma transformation/growth.

Model	Study name	Statistics for each study					Hazard ratio and 95% CI	Weighted (Fixed)
		Hazard ratio	Lower limit	Upper limit	Z-Value	*p*-Value		Relative weight
	Jose, 2009	3.070	1.042	9.041	2.035	0.042		0.53
	Penson, 2018	1.410	1.117	1.781	2.886	0.004		11.38
	Camilla, 2020	1.250	1.149	1.359	5.215	0.000		88.09
Fixed		1.273	1.177	1.378	6.017	0.000		

Fig. 3 Individual and pooled odds ratios for mortality.

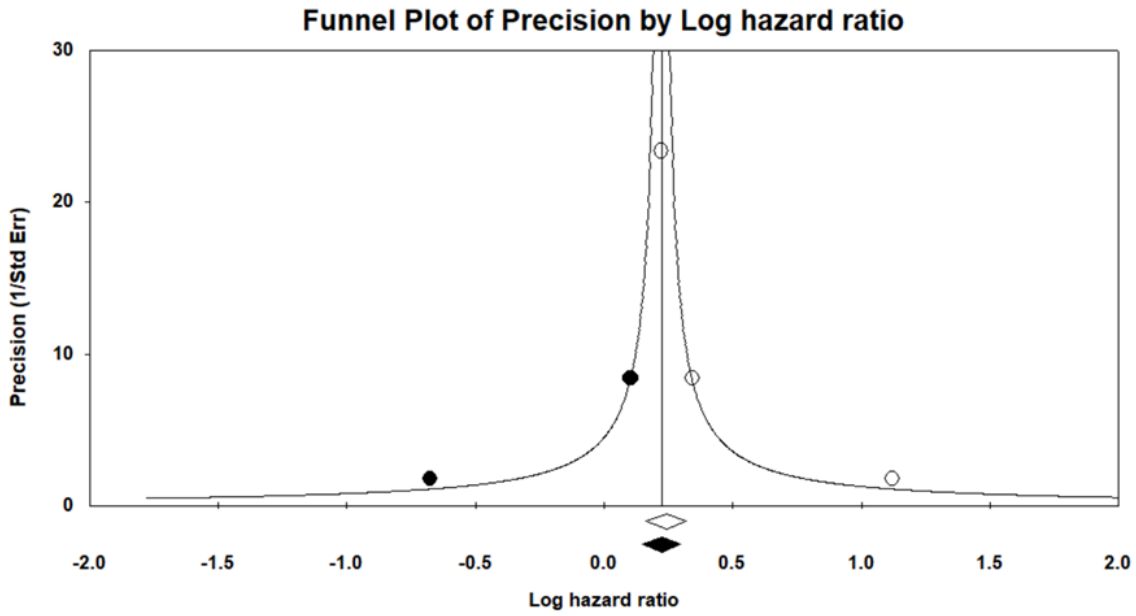

Fig. 4 Funnel plot, using the three trials of LDL-C and mortality.

Discussion

The relationship between hypolipidemia and the incidence of ICH has long been a subject of concern. We conducted a meta-analysis to investigate this association and found that hypolipidemia was associated with an increased risk of ICH (OR 2.048; 95% CI 1.159 – 3.617). Furthermore, hypolipidemia was also found to be significantly associated with an increased risk of mortality in patients with ICH (OR 1.429; 95% CI 1.109 – 1.843). The key finding of our study is that hypolipidemia is not only a potential risk factor for the incidence of ICH, but also for mortality in these patients.

Our findings are consistent with those of previous epidemiological studies investigating the relationship between hypolipidemia and ICH, which consistently demonstrated higher rates of ICH and ICH-related mortality in populations with low cholesterol levels.[6,14-18] One possible mechanism that may explain this relationship is the effect of serum cholesterol levels. Cholesterol plays a crucial role in maintaining the integrity and fluidity of the cell membranes. Lower cholesterol levels can lead to necrosis of medial smooth muscle cells and decrease the resistance to rupture of the vascular wall.[7,12,14,19] In addition, it can influence platelet-activating factors, that mediate platelet aggregation and degranulation. Very low cholesterol levels can lead to platelet dysfunction, making it more difficult for blood to clot properly. Therefore, low cholesterol levels may increase the risk of ICH.

Furthermore, the relationship between hypolipidemia and ICH is complex and not well-established. Numerous epidemiological studies have highlighted the role of LDL-C, commonly referred to as "bad" cholesterol, in the development of arterial plaque and increased risk of ischemic stroke and coronary artery occlusion.[13,20] Medical professionals are advised to adhere to the 2018 guidelines jointly developed by multiple societies for blood cholesterol management in patients with established atherosclerotic cardiovascular disease or those at high risk of myocardial infarction or thrombotic stroke. To address hyperlipidemia, more potent and recently developed hypolipidemic medications are used for aggressive treatment. However, there may be situations where extremely low lipid levels are a risk factor, particularly in the absence of other known risk factors. Although previous studies have primarily focused on the safety of statins, they have also indicated an inverse association between LDL-C and ICH.[3] In our analysis, we discovered a statistically significant increased risk of ICH in individuals with low LDL-C levels (OR 2.048; 95% CI 1.159 – 3.617).

Our study revealed a higher mortality rate in patients with low levels of LDL-C following an ICH. Several studies have indicated that low LDL-C levels are associated with an increased risk of hematoma growth,[8,9,21-24] which significantly affects mortality. Conversely, other studies have shown that higher LDL-C levels are independently associated with a reduced likelihood of hematoma expansion and decreased in-hospital mortality after acute spontaneous ICH.[25-28] A U-shaped association is observed between low LDL-C levels and overall mortality in patients with ICH. Our findings align with those of community-based studies that investigated the relationship between LDL-C levels and mortality.

Nonetheless, our study had certain limitations. First, it remains unclear whether low levels of LDL-C are primarily a result of genetic factors or serve as a marker for underlying nutritional or disease processes (e.g., liver dysfunction). Low cholesterol levels often occur because of preexisting conditions, particularly cancer and liver diseases.[10,11,29-31] In cancer cases, the gradual consumption and depletion of serum cholesterol during cancer cell proliferation can lead to low cholesterol levels. These factors were not adjusted in the analysis.

Second, Asians exhibit a higher prevalence of low cholesterol than non-Asians,[31] making it challenging to discern the effect of race on the findings. Finally, it is important to recognize that, like other epidemiological studies of this nature, our findings establish an association rather than a cause-and-effect relationship.

Conclusions

The results of the meta-analysis and meta-regression analysis demonstrated a significant association between hypolipidemia and an elevated risk of ICH. Furthermore, hypolipidemia is associated with an increased risk of all-cause mortality. Corroborated by further studies, these findings have significant clinical and public-health implications.

Author Contributions

Wei-Leng Chin, Han-Jung Chen, and Hao-Kuang Wang designed research; Po-Yuan Chen, Cheng-Kai Lin, Yu-Ying Wu, Cheng-Chun Wu, Yi-Che Lee, and Chi-Wei Lin analyzed data; Wei-Leng Chin, and Hao-Kuang Wang wrote the paper.

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Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

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Conflicts of Interest

The authors declare no conflict of interest.

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