Research Article

Statins on Spontaneous Intracerebral Hemorrhage: A Meta-Analysis

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Objective. In order to explore whether the application of statins can improve the prognosis of patients with intracerebral hemorrhage. Methods. Studies of patients with intracerebral hemorrhage taking statins published in English until December 2021 were searched based on limited search terms, the retrieved literature was screened out based on inclusion and exclusion criteria, and the quality assessment and data extraction were carried out independently by two investigators. The extracted clinical data were then meta-analyzed. Results. A total of 17 literatures were included in this study, with a sample size of 16,988 cases, including 3,001 cases in the statin group and 13,487 cases in the control group. MRS score of mortality was used as the prognostic index to evaluate cerebral hemorrhage. According to the Newcastle-Ottawa Scale (NOS), the score of literature quality evaluation scale was 6–8, indicating good literature quality. Meta-analysis of clinical data extracted from the literature showed that the statin group reduced overall mortality after intracerebral hemorrhage compared with the nonstatin group (\(P < 0.01\)). In terms of improving functional prognosis, the statin group improved functional prognosis 90 days after intracerebral hemorrhage (\(P < 0.01\)). There was no significant difference between the statin and nonstatin groups in reducing the number of intracerebral hematomas. Conclusions. Statins can reduce the total mortality after ICH and improve the survival rate (90 d), without increasing the amount of hematoma.

1. Background

Spontaneous intracerebral hemorrhage (ICH) [1], as a primary nontraumatic parenchymal hemorrhage, is a subtype with the worst prognosis of stroke, the one-month mortality approaching 40% and 75%. Patients with ICH often cannot take care of themselves, mild patients were with disabilities and other sequelae and loss of work ability, and severe patients can die from intracerebral hemorrhage acute phase or long-term complications [2]. Despite the rapid progress in the medical field in recent years, many cerebrovascular diseases can be effectively treated, such as drug therapy and intravascular interventional therapy, but ICH still has a high mortality and disability rate, its prognosis is not optimistic, and there is still a lack of effective treatment [3].

Statins [4], hydroxymethyl glutaryl-CoA (HMG-CoA) reductase inhibitors, originated from fungi and had a history of more than 40 years ago. On the one hand, statins competitively inhibit key steps in the cholesterol biosynthesis pathway by binding to enzyme substrates, limiting cholesterol synthesis, and reducing cholesterol concentration in the liver [5]. On the other hand, statins also increase the clearance rate of LDL-cholesterol particles in the blood by upregulating LDL receptor expression on the liver membrane [6]. Because statins can lower blood lipids well, they play an important role in ischemic heart and cerebrovascular diseases based on antiatherosclerosis, which is also inseparable from the wide range of applications of statins [7]. Therefore, statins are widely used in the primary and secondary prevention of cardiovascular and cerebrovascular diseases [8]. In recent years, some animal
experiments and basic studies have shown that statins can improve the prognosis of cerebral hemorrhage. They have anti-inflammatory activities, maintain vascular endothelial stability, upregulate nitric oxide synthase, and stimulate neurogenesis and synaptic formation, thus achieving neuroprotective effects [9]. An experimental study on stroke in 2004 [10] suggested that statins can be used in a variety of complex situations such as hemorrhage transformation after acute ischemic stroke, hemorrhage after thrombolytic therapy, and acute phase of cerebral hemorrhage. However, a study in 2006 [11] suggested that statins promoted hematoma enlargement, increased the risk of rebleeding, and increased ICH mortality or functional outcomes by inhibiting platelet aggregation and thrombosis. SPARCL test [12] and SPARCL secondary analysis [13] both showed that statins increased the risk of cerebral hemorrhage [14].

There is still a lack of evidence-based medical evidence on whether statins reduce the incidence and improve the prognosis of intracerebral hemorrhage. This paper conducted a meta-analysis of 17 included literature, in order to provide evidence for clinical treatment of intracerebral hemorrhage.

2. Materials and Methods

2.1. Search Strategy. A comprehensive search of PubMed, Medline, Embase, Web of Science, and The Cochrane Library was limited to high-quality studies published until December 2021. The included literature was searched to find the studies that met the inclusion criteria. Search terms included intracerebral hemorrhage, ICH, intracranial bleeding, statins, and prognosis of cerebral hemorrhage.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria are as follows: (1) study type: study comparing the prognosis of intracranial hemorrhage between the statin group and the nonstatin group; (2) there were no statistically significant differences in gender, mean age, past medical history, and other basic characteristics between the statin group and the nonstatin group; (3) the diagnostic criteria were spontaneous intracerebral hemorrhage confirmed by head CT; (4) outcome indicators: mortality (in-hospital, 30 d, 90 d, long-term), functional score (MRS 0–3/MRS 0–2) in different periods after intracerebral hemorrhage (in-hospital, 30 d, 90 d, long-term) and hematoma; (5) original research report; (6) rigorous experimental design and reliable data.

Exclusion criteria are as follows: (1) head CT clearly does not meet the diagnostic criteria of cerebral hemorrhage; (2) the prognosis of intracerebral hemorrhage was affected by other drugs (antiplatelet drugs, anticoagulants, etc.); patients with subarachnoid and subdural hemorrhage, hemorrhagic transformation of ischemic stroke, hemorrhage due to brain tumors and arteriovenous malformations; (3) secondary cerebral hemorrhage, such as brain trauma; (4) case report and review; (5) literatures with repeated reports and poor data quality; (6) the sample size is too small (n < 10), and the original data are incomplete and cannot be obtained through other means.

2.3. Quality Evaluation. The New Castle-Ottawa Scale (NOS) was used to evaluate the literature quality of the included literature, and a score of 6–8 indicated good literature quality [15].

2.4. Data Extraction. After the data extraction criteria were established, two trained evaluators comprehensively searched all databases according to keywords, independently selected the studies that met the inclusion criteria and extracted sample data. The missing data were obtained from the authors as far as possible, and the literature that could not obtain complete data information were abandoned. Finally, the basic features of the selected literature were, respectively, made into data extraction tables, in which part of the data need to be calculated, replaced, and merged, and finally verified the extracted data. In case of any disagreement in the process of data extraction, two people should negotiate to solve it. If there is still any disagreement, the third party (experienced evaluator) should be sought for assistance to solve it.

2.5. Statistical Analysis. Rate ratios (RRs) and 95% confidence intervals (CIs) were a result of categorical variables comparison and standardized mean difference (SMD) was a result of the continuous variable comparison to assess heterogeneity between studies using standard $I^2$ tests. The random effects model (RM) was selected for $I^2 > 50\%$, and the fixed effects model (FM) was selected for $I^2 < 50\%$. After the forest plot and funnel plot were made, studies with high heterogeneity were removed and analyzed again. All calculations were performed using statistical software provided by the Cochrane Collaboration (RevMan 5.3).

3. Results

3.1. Basic Information of the Included Studies. Seventeen studies [12, 16–31] finally met relevant standards, and the screening process is shown in Figure 1. The basic information of the included literature is shown in Table 1.

3.2. Effects of Statins on Mortality after ICH

3.2.1. Effects of Statins on Total Mortality after ICH. Sixteen studies [12, 16–22, 24–31] were included, including 3501 cases in the statin group and 13487 cases in the nonstatin group. The mortality rates during the last recorded period were statistically analyzed, and a meta-analysis was conducted, indicating heterogeneity $P < 0.001$, $I^2 = 84\% > 50\%$. The RM was used for the statistics, and the results were $P = 0.07$, RR = 0.86, 95% CI (0.73, 1.01), with no statistical significance. Results are shown in Figure 2.

3.2.2. Publish Bias Analysis. The funnel plot of literature was drawn by RevMan 5.3 to evaluate the publication bias of the included literature, as shown in Figure 3. Studies by Priglinger et al. and Pan et al. were obviously outside the confidence interval and increased heterogeneity.
After excluding the studies conducted by Priglinger et al. [27] and Pan et al. [26], the forest plot of the other 10 literatures included showed $I^2 = 49\% < 50\%$. The fixed effect model was adopted, $P = 0.0005 < 0.05$, RR = 0.85, 95% CI (0.78, 0.93), indicating that statins are significant in reducing mortality after intracerebral hemorrhage (Figure 4).

After eliminating the studies conducted by Priglinger et al. [27] and Pan et al. [26], the funnel plot was symmetrically distributed with low heterogeneity (Figure 5).

### 3.2.3. Effects of Statins on In-Hospital Mortality after ICH

Six studies [17, 22, 24, 28, 30, 31] including in-hospital mortality were included, and heterogeneity showed $P < 0.01$, $I^2 = 89\% > 50\%$. The random effect model was used to conduct statistics, and the results were $P = 0.14$, RR = 0.79, 95% CI (0.57, 1.08), with no statistical significance (Figure 6).

### 3.2.4. Effects of Statins on 30 d, 90 d, and Long-Term Mortality after ICH

Three studies [17, 21, 25] were included, heterogeneity analysis showed $P = 0.23$, $I^2 = 31\% < 50\%$, fixed effect model was used for analysis. The difference, $P = 0.77$, RR = 1.02, 95% CI (0.88, 1.19), was not statistically significant. There was no significant difference in 30-day mortality after reduced intracerebral hemorrhage between the statin and nonstatin groups.

Ten studies were included [6, 16, 18–20, 24, 26, 27, 29, 30]. Heterogeneity analysis showed $P < 0.01$, $I^2 = 86\% > 50\%$. The random effect model was used to conduct the analysis, and the results were $P = 0.15$, RR = 0.84, 95% CI (0.67, 1.07), with no statistically significant difference. There was no significant difference between statins and non-statins in reducing 90 days post-ICH mortality.

Four studies [17, 24, 26, 31] were included, including 1 study [17] with half-year mortality and 3 studies [24, 26, 31] with 1-year mortality. Heterogeneity analysis showed $P < 0.01$, $I^2 = 92\% > 50\%$. The random effect model was used for analysis, and the results were $P = 0.09$, RR = 0.73, 95% CI (0.50, 1.06), the difference was not statistically significant, indicating that there was no significant difference between statins and non-statins in reducing long-term mortality after ICH (Figure 7).

The source of heterogeneity was analyzed, sensitivity analysis was conducted by funnel plot, and the heterogeneity of Mustanoja et al. [24], Pan et al. [26], Priglinger et al. [27], and Siddiqui et al. [30] with high heterogeneity was eliminated, which significantly reduced the heterogeneity. Results: $I^2 = 13\%$, using the fixed effect model, $P = 0.01 < 0.05$, RR = 0.87, 95% CI (0.78, 0.97), the difference is significant, indicating that statins can reduce the mortality of 90 days after ICH (Figure 8).

### 3.3. Effects of Statins on Functional Recovery after ICH

#### 3.3.1. Effects of Statins on Total Functional Recovery after ICH

Eleven studies [6, 16–18, 20, 22, 24–27, 30] including functional prognosis after ICH were included, and a good functional prognosis was defined as MRS 0–3. The sample size of the statin group was 2779 cases, and that of the nonstatin group was 11387 cases. Meta-analysis showed that heterogeneity was $P < 0.01$, $I^2 = 90\% > 50\%$. The random effects model was used for analysis, and the results were $P = 0.20$, RR = 1.11, 95% CI (0.94, 1.32), with no statistical significance (Figure 9).

Sensitivity analysis was conducted, and heterogeneity was significantly reduced after the studies by Dowlatshahi et al. [17], Pan et al. [26], and Priglinger et al. [27] were removed, $I^2 = 49\% < 50\%$, and the fixed effect model was adopted. The results showed that $P < 0.01$, RR = 1.12, 95% CI (1.05, 1.20) had a significant difference. It indicates that statins can improve the functional prognosis of cerebral hemorrhage (Figure 10).

#### 3.3.2. Effects of Statins on Functional Recovery during Hospitalization after ICH

Four studies [17, 22, 24, 25] including functional prognosis in hospitals after ICH were included. Heterogeneity showed $P < 0.01$, $I^2 = 79\% > 50\%$. The random effect model was used for analysis, and the results were $P = 0.57$, RR = 1.09, 95% CI (0.81, 1.46), with no statistically significant difference (Figure 11).
| Author, year       | Design   | Research center | State       | Group    | Samples | Statin doses | Years | Outcomes                  | Follow-up | NOS |
|-------------------|----------|-----------------|-------------|----------|---------|--------------|-------|---------------------------|-----------|-----|
| Biffi, 2011 [16]  | Prospective | Single-center  | USA          | Statin   | 238     | NA           | 74.2  | Mortality, MRS            | 90 d      | 8   |
|                   |          |                 |             | Control  | 461     |              | 72    |                           |           |     |
| Dowlatshah, 2012  | Prospective | Multicenter    | Canada      | Statin   | 537     | NA           | 74    | Mortality, MRS            | In the hospital, 30 d, 180 d | 8   |
|                   |          |                 |             | Control  | 1929    |              | 70    |                           |           |     |
| Eichel, 2010 [18] | Retrospective | Single-center | Israel      | Statin   | 101     | NA           | 72.4  | Mortality, MRS            | 90 d      | 8   |
|                   |          |                 |             | Control  | 298     |              | 71.8  |                           |           |     |
| FitzMaurice, 2008 | Prospective | Single-center  | USA         | Statin   | 149     | NA           | 72.4  | Mortality, hematoma       | 90 d      | 8   |
|                   |          |                 |             | Control  | 480     |              | 71.9  |                           |           |     |
| Goldstein, 2009   | Retrospective | Single-center | England     | Statin   | 44      | 80 mg        | NA    | Mortality, MRS            | 90 d      | 7   |
|                   |          |                 |             | Control  | 29      |              | NA    |                           |           |     |
| Gomis, 2010 [20]  | Retrospective | Single-center | Spain       | Statin   | 34      | 10–40 mg     | 73.6  | Mortality, MRS            | 90 d      | 8   |
|                   |          |                 |             | Control  | 234     |              | 71.7  |                           |           |     |
| King, 2012 [21]   | Prospective | Single-center  | Singapore    | Statin   | 292     | NA           | 66.7  | Mortality, hematoma       | 30 d      | 8   |
|                   |          |                 |             | Control  | 1089    |              | 63.4  |                           |           |     |
| Leker, 2009 [22]  | Prospective | Multicenter    | Israel       | Statin   | 89      | NA           | 70.9  | Mortality, MRS            | In the hospital | 8   |
|                   |          |                 |             | Control  | 223     |              | 72.75 |                           |           |     |
| Miura, 2011 [23]  | Retrospective | Single-center | Japan        | Statin   | 56      | 80 mg        | 73    | MRS, hematoma             | 30 d      | 7   |
|                   |          |                 |             | Control  | 235     |              | 66.7  |                           |           |     |
| Mustanoja, 2013   | Retrospective | Single-center | Finland      | Statin   | 187     | NA           | 74    | Mortality, MRS, hematoma | In the hospital, 30 d, 1 y | 8   |
|                   |          |                 |             | Control  | 777     |              | 65    |                           |           |     |
| Naval, 2008 [25]  | Retrospective | Single-center | USA         | Statin   | 32      | NA           | 69.8  | Mortality, MRS, hematoma | In the hospital, 30 d | 7   |
|                   |          |                 |             | Control  | 32      |              | 65    |                           |           |     |
| Pan, 2014 [26]    | Prospective | Multicenter    | China        | Statin   | 220     | NA           | 61.3  | Mortality, MRS            | 90 d, 1 y | 8   |
|                   |          |                 |             | Control  | 2998    |              | 60.7  |                           |           |     |
| Priglinger, 2015  | Prospective | Multicenter    | multiple countries | Statin   | 204     | NA           | NA    | Mortality, MRS, hematoma | 90 d      | 7   |
|                   |          |                 |             | Control  | 2980    |              | NA    |                           |           |     |
| Ricard, 2010 [28] | Retrospective | Multicenter  | Canada       | Statin   | 71      | NA           | 71.1  | Mortality, hematoma       | In the hospital | 8   |
|                   |          |                 |             | Control  | 232     |              | 74.9  |                           |           |     |
| Romero, 2011 [29] | Prospective | Single-center  | Brazil       | Statin   | 20      | 2–8 mg/kg   | 68    | Mortality, GCS            | 90 d      | 8   |
|                   |          |                 |             | Control  | 62      |              | 69    |                           |           |     |
| Siddiqui, 2017    | Prospective | Multicenter    | USA          | Statin   | 1093    | NA           | 65.1  | Mortality, MRS, hematoma | In the hospital, 90 d | 9   |
|                   |          |                 |             | Control  | 1364    |              | 60.3  |                           |           |     |
| Winkler, 2013 [31]| Retrospective | Single-center | USA         | Statin   | 190     | NA           | 70.4  | Mortality, hematoma       | In the hospital, 1 y | 8   |
|                   |          |                 |             | Control  | 236     |              | 67    |                           |           |     |
### 3.3.4. Effects of Statins on Functional Recovery 90 Days after ICH (MRS 0–2)

Seven studies [6, 16, 18, 20, 26, 27, 30] containing functional outcomes at 90 days after ICH were included, in which a good functional prognosis was defined as MRS 0–2 points. Heterogeneity was $P < 0.01, \Gamma^2 = 93\% > 50\%$, and random effects model was used. The results showed that $P = 0.04, RR = 1.25, 95\% CI (1.01, 1.55)$, and the difference was statistically significant (Figure 13).

### 4. Discussion

ICH is a fatal disease with no specific treatment to improve the prognosis. Primary ICH etiology can be divided into hypertension and cerebral amyloid vascular disease (CAA), secondary ICH risk factors are brain tumor, aneurysm, arteriovenous malformation, coagulation abnormalities, brain trauma, etc. [32]. HMG-CoA reductase inhibitors (statins) are common lipid-lowering drugs in clinical practice, which can effectively reduce LDL and cholesterol levels, and are widely used in the primary and secondary prevention of cardiovascular and cerebrovascular diseases based on atherosclerosis [33]. However, epidemiological studies have shown that hypocholesterolemia increases the incidence and mortality of hemorrhagic stroke [34]. It is
speculated [35] that cholesterol is necessary for cerebrovascular wall integrity, and low cholesterol levels can increase the risk of cerebrovascular disease. Statins reduce plasma cholesterol levels, increase blood-brain barrier permeability, and inhibit platelet aggregation, thrombosis, and thrombin-linked reaction after acute ICH, resulting in further enlargement of cerebral hematoma and poor prognosis. Other studies [36] reported that statins had neuroprotective effects. Statins exert their pleiotropic function in various ways and have the ability to maintain the integrity of vascular endothelial cells, regulate the immune system and inhibit the inflammatory process. However, the results of these studies are contradictory [37], and the guidelines for cerebrovascular diseases [38] do not give clear...
3.1.1 30-day mortality rate

| Study or Subgroup | Experimental Events | Control Events | Weight (%) | Risk Ratio M-H, Random, 95% CI |
|-------------------|---------------------|----------------|------------|--------------------------------|
| Dowlatshahi 2012  | 193                 | 537            | 9.1        | 0.98 [0.86, 1.11] |
| King 2012         | 92                  | 292            | 8.3        | 1.14 [0.94, 1.36] |
| Naval 2008        | 5                   | 32             | 2.1        | 0.61 [0.25, 1.45] |
| Subtotal (95% CI) | 861                 | 3111           | 19.5       | 1.02 [0.88, 1.19] |
| Total events      | 290                 | 1033           |            |                  |

Heterogeneity: Tau^2 = 0.01; Chi^2 = 2.91, df = 2 (P = 0.23); I^2 = 31%
Test for overall effect: Z = 0.29 (P = 0.77)

3.1.2 90-day mortality rate

| Study or Subgroup | Experimental Events | Control Events | Weight (%) | Risk Ratio M-H, Random, 95% CI |
|-------------------|---------------------|----------------|------------|--------------------------------|
| Biffi 2011        | 109                 | 238            | 8.8        | 0.79 [0.67, 0.93] |
| Eichel 2010       | 43                  | 101            | 7.4        | 0.96 [0.74, 1.25] |
| FitzMaurice 2008  | 68                  | 149            | 8.2        | 1.01 [0.83, 1.24] |
| Goldstein 2009    | 14                  | 44             | 3.9        | 0.62 [0.35, 1.07] |
| Gomis 2010        | 9                   | 34             | 3.6        | 0.81 [0.45, 1.46] |
| Mustanoja 2013    | 63                  | 187            | 7.9        | 1.10 [0.88, 1.39] |
| Pan 2014          | 12                  | 220            | 3.9        | 0.26 [0.15, 0.45] |
| Priglinger 2015   | 42                  | 204            | 7.0        | 1.82 [1.36, 2.42] |
| Romero 2011       | 8                   | 20             | 3.6        | 0.84 [0.46, 1.52] |
| Siddiqui 2017     | 191                 | 1093           | 8.8        | 0.67 [0.57, 0.79] |
| Subtotal (95% CI) | 2290                | 9685           | 63.1       | 0.84 [0.67, 1.07] |
| Total events      | 559                 | 2297           |            |                  |

Heterogeneity: Tau^2 = 0.11; Chi^2 = 66.17, df = 9 (P < 0.00001); I^2 = 86%
Test for overall effect: Z = 1.42 (P = 0.15)

3.1.3 long-term mortality rate

| Study or Subgroup | Experimental Events | Control Events | Weight (%) | Risk Ratio M-H, Random, 95% CI |
|-------------------|---------------------|----------------|------------|--------------------------------|
| Dowlatshahi 2012  | 231                 | 537            | 9.3        | 1.00 [0.90, 1.12] |
| Mustanoja 2013    | 69                  | 187            | 8.1        | 1.07 [0.87, 1.32] |
| Pan 2014          | 19                  | 220            | 0.0        | 0.32 [0.20, 0.49] |
| Winkler 2013      | 64                  | 190            | 0.0        | 0.67 [0.53, 0.85] |
| Subtotal (95% CI) | 724                 | 2706           | 17.4       | 1.02 [0.92, 1.12] |
| Total events      | 300                 | 1096           |            |                  |

Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.75, df = 1 (P = 0.33); I^2 = 13%
Test for overall effect: Z = 0.32 (P = 0.75)

Total (95% CI) 3875 15502 100.0 0.91 [0.79, 1.05]

Total events 1149 4426

Heterogeneity: Tau^2 = 0.05; Chi^2 = 77.44, df = 14 (P < 0.00001); I^2 = 82%
Test for overall effect: Z = 1.24 (P = 0.21)
Test for subgroup differences: Chi^2 = 2.21, df = 2 (P = 0.33), I^2 = 9.4%

3.2.1 30-day mortality rate

| Study or Subgroup | Experimental Events | Control Events | Weight (%) | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|----------------|------------|--------------------------------|
| Biffi 2011        | 109                 | 238            | 8.8        | 0.79 [0.67, 0.93] |
| Eichel 2010       | 43                  | 101            | 7.4        | 0.96 [0.74, 1.25] |
| FitzMaurice 2008  | 68                  | 149            | 8.2        | 1.01 [0.83, 1.24] |
| Goldstein 2009    | 14                  | 44             | 3.9        | 0.62 [0.35, 1.07] |
| Gomis 2010        | 9                   | 34             | 3.6        | 0.81 [0.45, 1.46] |
| Mustanoja 2013    | 63                  | 187            | 7.9        | 1.10 [0.88, 1.39] |
| Pan 2014          | 12                  | 220            | 3.9        | 0.26 [0.15, 0.45] |
| Priglinger 2015   | 42                  | 204            | 7.0        | 1.82 [1.36, 2.42] |
| Romero 2011       | 8                   | 20             | 3.6        | 0.84 [0.46, 1.52] |
| Siddiqui 2017     | 191                 | 1093           | 8.8        | 0.67 [0.57, 0.79] |
| Subtotal (95% CI) | 2290                | 9685           | 63.1       | 0.84 [0.67, 1.07] |
| Total events      | 559                 | 2297           |            |                  |

Heterogeneity: Tau^2 = 0.11; Chi^2 = 66.17, df = 9 (P < 0.00001); I^2 = 86%
Test for overall effect: Z = 1.42 (P = 0.15)

Total (95% CI) 3875 15502 100.0 0.91 [0.79, 1.05]

Total events 1149 4426

Heterogeneity: Tau^2 = 0.05; Chi^2 = 77.44, df = 14 (P < 0.00001); I^2 = 82%
Test for overall effect: Z = 1.24 (P = 0.21)
Test for subgroup differences: Chi^2 = 2.21, df = 2 (P = 0.33), I^2 = 9.4%

Figure 7: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing 30d, 90d, or long-term mortality.

Figure 8: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage after eliminating biased studies, comparing 90d mortality.
recommendations, which leads to conflicts between conventional secondary prevention and drug treatment for patients with previous ischemic cardiovascular and cerebrovascular diseases. Therefore, we conducted a meta-analysis on the mortality, functional prognosis, and other aspects of statins and intracerebral hemorrhage to further guide clinical treatment decisions.

Patients with ICH are always at risk of death, and the common causes of death are cerebral hernia, rebleeding, and related complications (such as pulmonary infection, gastrointestinal stress bleeding, and deep vein thrombosis). Statin is a common drug in the neurology department. In order to explore whether it can reduce the death rate after ICH, this study selected a number of studies for statistical analysis.
analysis of the death rate at each time after ICH as the evaluation index (during hospitalization, 30 d, 90 d, and long-term), and extracted binary variables. Preliminary analysis showed that there was high heterogeneity among studies of total mortality at various periods after ICH, and heterogeneity decreased after the studies by Priglinger and Pan were excluded from sensitivity analysis. The reason for the high heterogeneity of Pan et al.’s study [26] may be that Chinese people have a better understanding of the pharmacokinetics of statins and are better than Westerners in terms of absorption, distribution, and metabolism of statins [39]. The heterogeneity of Priglinger et al.’s study [27] was high because it explored whether lowering blood lipids secondary to statins increased the risk of spontaneous intracerebral hemorrhage. Most of the lipid-lowering drugs used were statins, and lipoprotein reduction was taken as the experimental group standard.

In this study, good functional prognosis in each period after ICH was selected as the evaluation index, and good functional recovery was defined as an MRS score of 0–3. Our results suggest that statins can indeed improve functional recovery after intracerebral hemorrhage, especially in the middle and long term, which is closely related to the enhancement of nerve repair and reduction of cerebral edema.

### Figure 12: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing 90d functional recovery (a good functional prognosis was defined as MRS 0–3).

| Study or Subgroup | Statin Events | Control Events | Weight (%) | Risk Ratio M-H, Random, 95% CI |
|-------------------|---------------|----------------|------------|-------------------------------|
| Eichel 2010       | 28            | 101            | 15.5       | 1.13 [0.78, 1.64]             |
| Goldstein 2009    | 19            | 44             | 9.3        | 1.14 [0.64, 2.02]             |
| Gomis 2010        | 21            | 34             | 18.4       | 1.47 [1.08, 1.99]             |
| Pan 2014          | 187           | 220            | 28.6       | 1.42 [1.33, 1.51]             |
| Siddiqui 2017     | 581           | 1093           | 28.2       | 1.08 [1.00, 1.17]             |
| **Total (95% CI)**| 1492          | 4924           | 100.0      | 1.25 [1.01, 1.53]             |

**Total events** 2648

Heterogeneity: Tau² = 0.04; Chi² = 40.03; df = 4 (P < 0.00001); I² = 90%

Test for overall effect: Z = 2.05 (P = 0.04)

### Figure 13: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage after eliminating biased studies, comparing 90d functional recovery (a good functional prognosis was defined as MRS 0–3).

| Study or Subgroup | Statin Events | Control Events | Weight (%) | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------|----------------|------------|-------------------------------|
| Eichel 2010       | 28            | 101            | 5.5        | 1.13 [0.78, 1.64]             |
| Goldstein 2009    | 19            | 44             | 2.0        | 1.14 [0.64, 2.02]             |
| Gomis 2010        | 21            | 34             | 3.7        | 1.47 [1.08, 1.99]             |
| Siddiqui 2017     | 581           | 1093           | 88.8       | 1.08 [1.00, 1.17]             |
| **Total (95% CI)**| 1272          | 1926           | 100.0      | 1.10 [1.02, 1.18]             |

**Total events** 855

Heterogeneity: Chi² = 3.71; df = 3 (P = 0.29); I² = 19%

Test for overall effect: Z = 2.48 (P = 0.01)

### Figure 14: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing 90d functional recovery (a good functional prognosis was defined as MRS 0–2).

| Study or Subgroup | Statin Events | Control Events | Weight (%) | Risk Ratio M-H, Random, 95% CI |
|-------------------|---------------|----------------|------------|-------------------------------|
| Biffi 2011        | 60            | 238            | 15.2       | 1.34 [1.00, 1.78]             |
| Eichel 2010       | 12            | 101            | 10.2       | 0.80 [0.44, 1.46]             |
| Goldstein 2009    | 12            | 44             | 9.2        | 0.72 [0.37, 1.41]             |
| Gomis 2010        | 17            | 34             | 13.7       | 1.51 [1.03, 2.21]             |
| Pan 2014          | 164           | 220            | 17.7       | 1.52 [1.39, 1.65]             |
| Priglinger 2015   | 65            | 204            | 16.5       | 0.66 [0.54, 0.82]             |
| Siddiqui 2017     | 403           | 1093           | 17.5       | 1.05 [0.94, 1.16]             |
| **Total (95% CI)**| 1934          | 8365           | 100.0      | 1.06 [0.80, 1.42]             |

**Total events** 3604

Heterogeneity: Tau² = 0.12; Chi² = 87.33; df = 6 (P < 0.00001); I² = 93%

Test for overall effect: Z = 0.42 (P = 0.68)
by statins. After ICH occurred, cerebral vascular pressure caused by hematoma led to cerebral hyperperfusion, cerebral ischemia and hypoxia led to brain cell necrosis, enhanced brain free radical reaction, lipid peroxidation, and many other factors can lead to distant cellular brain edema. Statins may inhibit the formation of secondary cerebral edema in multiple ways due to their pleiotropism. Experimental studies [40] have shown that statins can resist thrombosis and fibrinolytic function (original activators inhibition of fibrinolytic enzyme inhibitors-1), in the acute phase, for example, statins can reduce the blood coagulation cascade and blood coagulation factor (organizational factor, V factor, and factor XIII), reduce the blood clot retraction, reducing the volume of hematoma surrounding edema. In rats, statins have also been shown to reduce the activation of glial cells and the release of cytokines such as interleukin and tumor necrosis factor, thereby achieving anti-inflammatory effects [41].

In our study, we evaluated that statins can reduce the total mortality after ICH, and improve the survival rate (90 d), without increasing the amount of hematoma.

### Data Availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

### References

[1] R. Garg and J. Biller, "Recent advances in spontaneous intracerebral hemorrhage," *F1000Research*, vol. 8, 2019.
[2] C. Kurian, K. Kaur, G. Kaur, and R. Sahni, "Assessment of the patient with intracerebral hemorrhage: a review of the literature," *Cardiology in Review*, vol. 29, no. 1, pp. 20–25, 2021.
[3] R. Veltkamp and J. Purrucker, "Management of spontaneous intracerebral hemorrhage," *Current Neurology and Neuroscience Reports*, vol. 17, no. 10, p. 80, 2017.
[4] O. Köhler-Forsberg, C. Otte, S. M. Gold, and S. D. Østergaard, "Statins in the treatment of depression: hype or hope?" *Pharmacology & Therapeutics*, vol. 215, Article ID 107625, 2020.
[5] Q. Xu, Y. Deng, J. Xiao et al., “Three musketeers for lowering cholesterol: statins, ezetimibe and evolocumab,” *Current Medicinal Chemistry*, vol. 28, no. 5, pp. 1025–1041, 2021.
[6] H. X. Yang, M. Zhang, S. Y. Long et al., “Cholesterol in LDL receptor recycling and degradation,” *Clinica Chimica Acta*, vol. 500, pp. 81–86, 2020.
[7] S. H. Lee and J. H. Choi, “Involvement of inflammatory responses in the early development of calcific aortic valve disease: lessons from statin therapy,” *Animal Cells and Systems*, vol. 22, no. 6, pp. 390–399, 2018.
[8] Y. Morofuji, S. Nakagawa, K. Ujifuku et al., “Beyond lipid-lowering: effects of statins on cardiovascular and cerebrovascular diseases and cancer,” *Pharmaceuticals*, vol. 15, no. 2, p. 151, 2022.
[9] C. J. Chen, D. Ding, N. Ironside et al., “Statins for neuroprotection in spontaneous intracerebral hemorrhage,” *Neurology*, vol. 93, no. 24, pp. 1056–1066, 2019.
[10] K. H. Jung, K. Chu, S. W. Jeong et al., “HMG-CoA reductase inhibitor, atorvastatin, promotes sensorimotor recovery, suppressing acute inflammatory reaction after experimental intracerebral hemorrhage,” *Stroke*, vol. 35, no. 7, pp. 1744–1749, 2004.
[11] C. Newman, J. Tsai, M. Szarek, D. Luo, and E. Gibson, “Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients,” *The American Journal of Cardiology*, vol. 97, no. 1, pp. 61–67, 2006.
[12] L. B. Goldstein, P. Amarenco, J. Zivin et al., “Statin treatment and stroke outcome in the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial,” *Stroke*, vol. 40, no. 11, pp. 3526–3531, 2009.
[13] P. Amarenco, O. Benavente, L. B. Goldstein et al., “Results of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial by stroke subtypes,” *Stroke*, vol. 40, no. 4, pp. 1405–1409, 2009.
[14] V. L. Serebruany, A. I. Malinin, and C. H. Hennekens, “Statins increase risk of hemorrhagic stroke by inhibition of the PAR-1 receptor,” *Cerebrovascular Diseases*, vol. 24, no. 5, pp. 477–479, 2007.
[15] C. K. L. Lo, D. Mertz, and M. Loeb, “Newcastle-Ottawa scale: comparing reviewers’ authors’ assessments,” *BMC Medical Research Methodology*, vol. 14, p. 45, 2014.
[16] A. Biffi, W. J. Devan, C. D. Anderson et al., “Statin use and outcome after intracerebral hemorrhage: case-control study and meta-analysis,” *Neurology*, vol. 76, no. 18, pp. 1581–1588, 2011.
[17] D. Dowlatshahi, A. M. Demchuk, J. Fang, M. K. Kapral, M. Sharma, and E. E. Smith, "Association of statins and statin
discontinuation with poor outcome and survival after intracerebral hemorrhage," *Stroke*, vol. 43, no. 6, pp. 1518–1523, 2012.

[18] R. Eichel, S. T. Khoury, T. Ben-Hur, M. Keidar, R. Paniri, and R. R. Leker, "Prior use of statins and outcome in patients with intracerebral haemorrhage," *European Journal of Neurology*, vol. 17, no. 1, pp. 78–83, 2010.

[19] E. FitzMaurice, L. Wendell, R. Smider et al., "Effect of statins on intracerebral hemorrhage outcome and recurrence," *Stroke*, vol. 39, no. 7, pp. 2151–2154, 2008.

[20] M. Gomis, A. Ois, A. Rodriguez-Campello et al., "Outcome of intracerebral haemorrhage patients pre-treated with statins," *European Journal of Neurology*, vol. 17, no. 3, pp. 443–448, 2010.

[21] N. K. King, V. K. S. Tay, J. C. Allen, and B. T. Ang, "Prior statin use has no effect on survival after intracerebral hemorrhage in a multiethnic Asian patient cohort," *Acta Neurochirurgica Supplement*, vol. 114, pp. 343–346, 2012.

[22] R. R. Leker, S. T. Khoury, G. Rafaelli, R. Shwartz, R. Eichel, and D. Tanne, "Prior use of statins improves outcome in patients with intracerebral hemorrhage: prospective data from the national acute stroke israeli surveys (NASIS)," *Stroke*, vol. 40, no. 7, pp. 2581–2584, 2009.

[23] K. Miura, Y. Yoshii, Y. Nakamura, and K. Ikeda, "Clinicoradiological profile and serum lipid levels of intracerebral hemorrhage in prior statin users," *Internal Medicine*, vol. 50, no. 13, pp. 1385–1391, 2011.

[24] S. Mustanoja, D. Strbian, J. Putaala et al., "Association of pre-stroke statin use and lipid levels with outcome of intra-cerebral hemorrhage," *Stroke*, vol. 44, no. 8, pp. 2330–2332, 2013.

[25] N. S. Naval, T. A. Abdelhak, P. Zeballos, N. Urrunaga, M. A. Mirski, and J. R. Carhuapoma, "Prior statin use reduces mortality in intracerebral hemorrhage," *Neurocritical Care*, vol. 8, no. 1, pp. 6–12, 2008.

[26] Y. S. Pan, J. Jing, Y. L. Wang et al., "Use of statin during hospitalization improves the outcome after intracerebral hemorrhage," *CNS Neuroscience and Therapeutics*, vol. 20, no. 6, pp. 548–553, 2014.

[27] M. Priglinger, H. Arima, C. Anderson, M. Krause, and N. S. Naval, T. A. Abdelhak, P. Zeballos, N. Urrunaga, S. Mustanoja, D. Strbian, J. Putaala et al., "Association of statins and outcome in patients with intracerebral hemorrhage," *Stroke*, vol. 40, no. 7, pp. 2151–2154, 2008.

[28] G. Ricard, M. P. Garant, N. Carrier, N. Leblanc, and J. M. Boulanger, "Statins may increase intracerebral hemorrhage volume," *The Canadian Journal of Neurological Sciences*, vol. 37, no. 6, pp. 791–796, 2010.

[29] F. R. Romero, E. D. F. Bertolini, V. N. Veloso, L. Venturini, and E. G. Figueiredo, "Outcomes from intracerebral hemorrhage among patients pre-treated with statins," *Arq Neuropsiquiatr*, vol. 69, no. 3, pp. 452–454, 2011.

[30] F. M. Siddiqui, C. D. Langefeld, C. J. Moomaw et al., "Use of statins and outcomes in intracerebral hemorrhage patients," *Stroke*, vol. 48, no. 8, pp. 2098–2104, 2017.

[31] J. Winkler, J. P. Shoup, A. Czaplak et al., "Long-term improvement in outcome after intracerebral hemorrhage in patients treated with statins," *Journal of Stroke and Cerebrovascular Diseases*, vol. 22, no. 8, pp. e541–e545, 2013.

[32] Y. Chen, S. Chen, J. Chang, J. Wei, M. Feng, and R. Wang, "Perihematoma edema after intracerebral hemorrhage: an update on pathogenesis, risk factors, and therapeutic advances," *Frontiers in Immunology*, vol. 12, Article ID 740632, 2021.

[33] R. Balasubramanian and N. M. P. Maideen, "HMG-CoA reductase inhibitors (statins) and their drug interactions involving CYP enzymes, P-glycoprotein and OATP transporters-an overview," *Current Drug Metabolism*, vol. 22, no. 5, pp. 328–341, 2021.

[34] Y. Ma, Z. Li, L. Chen, and X. Li, "Blood lipid levels, statin therapy and the risk of intracerebral hemorrhage," *Lipids in Health and Disease*, vol. 15, p. 43, 2016.

[35] C. Gurevitz, E. Auriel, A. Ellis, and R. Kornowski, "The association between low levels of low density lipoprotein cholesterol and intracerebral hemorrhage: cause for concern?" *Journal of Clinical Medicine*, vol. 11, no. 3, p. 536, 2022.

[36] M. L. Kim, K. R. Sung, J. Kwon, G. W. Choi, and J. A. Shin, "Neuroprotective effect of statins in a rat model of chronic ocular hypertension," *International Journal of Molecular Sciences*, vol. 22, no. 22, Article ID 12500, 2021.

[37] B. B. Adhyaru and T. A. Jacobson, "Safety and efficacy of statin therapy," *Nature Reviews Cardiology*, vol. 15, no. 12, pp. 757–769, 2018.

[38] L. Liu, W. Chen, H. Zhou et al., "Chinese stroke association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases," *Stroke and Vascular Neurology*, vol. 5, no. 2, pp. 159–176, 2020.

[39] D. A. Godoy, R. A. Núñez-Patiño, A. Zorrilla-Vaca, W. C. Ziai, and J. C. Hemphill, "Intracranial hypertension after spontaneous intracerebral hemorrhage: a systematic review and meta-analysis of prevalence and mortality rate," *Neurocritical Care*, vol. 31, no. 1, pp. 176–187, 2019.

[40] R. Naito, K. Miyauchi, and H. Daida, "Racial differences in the association between low levels of low density lipoprotein cholesterol and intracerebral hemorrhage: cause for concern?" *Journal of Atherosclerosis and Thrombosis*, vol. 24, no. 1, pp. 19–25, 2017.

[41] H. Zheng, C. Chen, J. Zhang, and Z. Hu, "Mechanism and therapy of brain edema after intracerebral hemorrhage," *Cerebrovascular Diseases*, vol. 42, no. 3-4, pp. 155–169, 2016.