Research Article

Combined Association of Low-Density Lipoprotein Cholesterol Levels and Systolic Blood Pressure to the Outcome of Intracerebral Hemorrhage: Data from the China Stroke Center Alliance

Yarong Ding,1,2,3 Yu Wang,1,2,4 Liping Liu,1,2,5 Hongqiu Gu,1,2 Kaixuan Yang,2,6,7 Zixiao Li,1,2,5 and Xingquan Zhao1,2,5

1Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
2China National Clinical Research Center for Neurological Diseases, Beijing, China
3Department of Neurology, Beijing Luhe Hospital, Capital Medical University, Beijing, China
4Department of Neurology, Beijing Hospital, National Center of Gerontology, Beijing, China
5Research Unit of Artificial Intelligence in Cerebrovascular Disease, Chinese Academy of Medical Sciences, Beijing, China
6Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, Beijing, China
7Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing, China

Correspondence should be addressed to Zixiao Li; lizixiao2008@hotmail.com and Xingquan Zhao; zxq@vip.163.com

Received 5 February 2022; Revised 14 March 2022; Accepted 28 May 2022; Published 18 June 2022

Copyright © 2022 Yarong Ding et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Limited data were available about the combined impact of systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C) levels on intracerebral hemorrhage (ICH) prognosis. The objective of this study is to explore whether the relationship between LDL-C and ICH outcomes was modified by SBP levels in a Chinese population. From August 1, 2015, to July 31, 2019, 75,443 ICH patients enrolled from the Chinese Stroke Center Alliance program were included in our study. Patients were divided into LDL-C levels of <70 mg/dL, 70-100 mg/dL, and ≥100 mmol/L. SBP was stratiﬁed as <140 mmHg, 140–180 mmHg, and ≥180 mmHg. The primary outcome was the occurrence of hematoma expansion (HE), and the second outcome was in-hospital mortality. Correlation between LDL-C levels and SBP on ICH outcomes were assessed by logistic regression. 6,116 (8.1%) and 1,576 (2.1%) patients suffered HE and in-hospital mortality. Compared with the ≥100 mg/dL group, patients with LDL-C concentrations under 70 mg/dL had a 19% and 24% increase in the relative risk of HE (crude OR 1.19, 95% CI 1.11-1.28) and in-hospital mortality (crude OR 1.24, 95% CI 1.08-1.42). When SBP was added as a stratiﬁcation variable, the above-mentioned association was attenuated in patients under a threshold SBP of 140 mmHg (P > 0.05). However, no statistical interaction was detected between SBP and LDL-C levels. Lower LDL-C levels (<70 mg/dL) are related to a higher risk of HE and in-hospital mortality conﬁned to ICH patients with elevated SBP (≥140 mmHg).

1. Introduction

Intracerebral hemorrhage (ICH) has signiﬁcant high morbidity and mortality [1–3]. Interventional trials, involving intensive antihypertensive treatment [4], hypoglycemic therapy [5], hemostatic agents [6, 7], and hematoma evacuation [8, 9], achieved only marginally therapeutic efﬁcacy. As interest in multifactorial interventions is increasing, integrated approaches to the management of ICH are urgently needed.

Elevated blood pressure (BP), especially systolic BP (SBP), is the cornerstone of ICH prevention as is closely related to the occurrence of hematoma expansion (HE) and subsequent poor prognosis [10]. Meanwhile, growing attention has been paid to the effect of low-density lipoprotein...
cholesterol (LDL-C) on ICH prognosis [11–13]. In the series of China Stroke Center Alliance (CSCA) studies, we found that in acute ICH patients, lower LDL-C levels are related to a high risk of HE and mortality [14]. Researches regarding the joint effects of SBP and LDL-C on atherosclerotic cardiovascular risk showed an additive, even synergetic association [15–17]. While limited data were available about the combined impact of SBP and LDL-C levels on ICH prognosis. It is worth noting that one observational research indicated that the proportional risk of cerebral hemorrhage associated with lower LDL-C was confined to patients with elevated BP [18]. Therefore, the purpose of our study was to investigate whether the association between LDL-C and ICH prognosis was modified by SBP levels in a Chinese population.

Figure 1: Flow chart for selection of study participants. TIA: transit ischemic attack; CSCA: Chinese Stroke Center Alliance; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; ICH: intracerebral hemorrhage.

Figure 2: Prevalence of (a) hematoma expansion and (b) in-hospital mortality according to LDL-C levels across systolic blood pressure subgroups. LDL-C: low-density lipoprotein cholesterol.
2.2. LDL-C, SBP, and Other Baseline Covariates. Laboratory variables were collected within 24 hours after admission to each subcenter. LDL-C levels were categorized into three groups regarding the 2018 American Heart Association guidelines for the management of cholesterol: <70 mg/dL, 70–100 mg/dL, and ≥100 mg/dL [20].

Three BP readings were recorded separately in the supine position after at least two-minute resting by trained nurses at baseline, and the average of the three measurements was


groups regarding the 2018 American Heart Association guidelines for the management of cholesterol: <70 mg/dL, 70–100 mg/dL, and ≥100 mg/dL [20].

Three BP readings were recorded separately in the supine position after at least two-minute resting by trained nurses at baseline, and the average of the three measurements was


groups regarding the 2018 American Heart Association guidelines for the management of cholesterol: <70 mg/dL, 70–100 mg/dL, and ≥100 mg/dL [20].

Three BP readings were recorded separately in the supine position after at least two-minute resting by trained nurses at baseline, and the average of the three measurements was
regarded as the admission BP. Admission SBP was then classified into three categories based on the 2018 European Society of Hypertension as <140 mmHg, 140-180 mmHg, and ≥180 mmHg [21].

Other baseline characteristics including demographic information, body mass index (BMI), smoking and drinking history, medical and medication history, Glasgow coma scale (GCS) score on admission, and time from symptom onset to arrival were also extracted.

### 2.3. Outcomes

The primary outcome was HE event, and the second outcome was in-hospital mortality. A cranial CT scan was obtained in the emergency department and repeated after admission. Hematoma volume was estimated using the ABC/2 method by two experienced neurologists. Differences were considered to be significant if they were observed in different SBP categories, an interaction term (LDL-C × SBP, both as a polytomous variable) was added among all the included patients as well as patients admitted within 24 h of symptom onset. Differences were considered to be significant at $P < 0.05$. Analyses were performed using the SAS software (version 9.4; SAS Institute, Cary, NC, USA).

### 3. Results

75,443 patients were finally enrolled in our study; 6,116 (8.1%) and 1,576 (2.1%) of them were identified as HE and in-hospital mortality, separately. Among them, the lowest LDL-C group (<70 mg/dL) together with the highest SBP group (≥180 mmHg) tended to have more events. The prevalence of adverse outcomes according to LDL-C levels across SBP subgroups is shown in Figure 2.

### 3.1. Baseline Characteristics

Significant differences were found in age, sex, BMI, BP, behavior history, previous history, medication history, in-hospital treatment, creatinine,
and GCS score on admission among LDL-C groups. Baseline characteristics and ICH prognosis according to LDL-C categories are shown in Table 1.

### Table 3: Association between LDL-C and ICH outcomes in different blood pressure levels among all the included patients.

| SBP          | LDL-C levels | Case (%) | Univariate analysis | Multivariate analysis | Model 1 | Model 2 | Model 3 |
|--------------|--------------|----------|---------------------|-----------------------|---------|---------|---------|
|              |              |          |                     |                       |         |         |         |
| Hematoma expansion |              |          |                     |                       |         |         |         |
| <70 mg/dL    | 214 (9.18)   | 1.18 (0.99, 1.39) | 1.17 (0.99, 1.38) | 1.14 (0.96, 1.35) | 1.16 (0.90, 1.49) |
| 70-100 mg/dL | 364 (8.45)   | 1.07 (0.93, 1.24) | 1.07 (0.93, 1.23) | 1.07 (0.93, 1.24) | 0.98 (0.79, 1.22) |
| ≥100 mg/dL   | 477 (7.92)   | Ref.     | Ref.                | Ref.                  | Ref.    | Ref.    | Ref.    |
| <70 mg/dL    | 563 (8.93)   | 1.23 (1.11, 1.36) | 1.23 (1.11, 1.36) | 1.20 (1.08, 1.33) | 1.33 (1.14, 1.54) |
| 140-180 mmHg | 70-100 mg/dL | 996 (7.51) | 1.02 (0.94, 1.11) | 1.02 (0.94, 1.11) | 1.04 (0.96, 1.13) | 1.13 (1.00, 1.28) |
| ≥100 mg/dL   | 1515 (7.36)  | Ref.     | Ref.                | Ref.                  | Ref.    | Ref.    | Ref.    |
| <70 mg/dL    | 325 (9.97)   | 1.16 (1.02, 1.32) | 1.15 (1.01, 1.31) | 1.16 (1.02, 1.33) | 1.14 (0.97, 1.35) |
| ≥180 mmHg    | 70-100 mg/dL | 617 (8.35) | 0.95 (0.86, 1.06)  | 0.95 (0.86, 1.06)  | 0.97 (0.87, 1.07) | 0.93 (0.81, 1.06) |
| ≥100 mg/dL   | 1045 (8.71)  | Ref.     | Ref.                | Ref.                  | Ref.    | Ref.    | Ref.    |

P for interaction:

- Hematoma expansion: 0.649
- In-hospital mortality: 0.646

Data are OR (95% CI) unless otherwise stated. Model 1 adjusted for age and sex. Model 2 adjusted for variables in model 1 plus body mass index (≥25.0 or ≥25.0 kg/m²), systolic blood pressure, diastolic blood pressure, smoking status, drinking status, hypertension, diabetes mellitus, previous ICH, medication history (including prior use of antiplatelet, anticoagulant, antihypertensive agent, and stains), and creatinine. Model 3 adjusted for variables in model 2 plus GCS score on admission as a sensitivity analysis.

3.2. Independent Association of LDL-C and SBP Levels for ICH Outcomes. Lower LDL-C levels had a significant correlation with ICH outcomes in the univariate analysis (P < 0.001). Compared with the ≥100 mg/dL group, patients with LDL-C concentrations under 70 mg/dL had a 19% and 24% increase in the relative risk of HE (OR 1.19, 95% CI 1.11-1.28) and in-hospital mortality (OR 1.24, 95% CI 1.08-1.42). In the multivariate analysis, similar results were obtained after adjusting for potential covariates in model 1 and 2. The adjusted ORs of HE were 1.17 (95% CI 1.09-1.26) for LDL-C levels <70 mg/dL, 1.02 (95% CI 0.96-1.08) for LDL-C levels of 70 mg/dL to 100 mg/dL, and 1.0 (reference) for LDL-C levels ≥100 mg/dL in model 2. Correspondingly, the adjusted ORs of in-hospital mortality were 1.16 (95% CI 1.01-1.33), 0.96 (95% CI 0.86-1.08), and 1.0 (reference) among the three LDL-C groups from low to high. However, increasing mortality risk with lower LDL-C levels (<70 mg/dL) was not pronounced when further adjusted for admission GCS score in the sensitivity analysis.

The fully adjusted ORs of the lowest SBP group (<140 mmHg) were 0.82 (95% CI 0.73-0.93) and 0.74 (95% CI 0.60-0.90) for HE and in-hospital mortality, respectively. Additional detailed information was given in Table 2.

3.3. Combined Association of LDL-C and SBP to ICH Outcomes. When examining the association of LDL-C with ICH outcomes across SBP categories, it was noteworthy that no statistical significance was obtained in those with SBP under 140 mmHg, irrespective of LDL-C concentration (P > 0.05). While for those with SBP between 140 mmHg and 180 mmHg and SBP above 180 mmHg, lower LDL-C levels (<70 mg/dL) conferred a 1.23-fold, 1.16-fold greater likelihood of HE presence (P < 0.001, Table 3). When it comes to in-hospital mortality, its significant correlation with lower LDL-C levels diminished among the highest SBP category (≥180 mmHg). In multivariate analyses, the results were essentially unaltered in both model 1 and model 2. While after further adjustment for admission GCS score in model 3, the association became nonsignificant between lower LDL-C levels and adverse outcomes among ICH patients with normal SBP. There was, however, no apparent interaction detected between LDL-C and SBP with either HE (P = 0.649) or in-hospital mortality (P = 0.667).

To differentiate the effect of time from symptom onset to admission, additional sensitivity analyses were performed among the 60,024 patients admitted within 24 h of symptom
In-hospital mortality.

‡ towards "intensive control of SBP is recommended."

With lower LDL-C levels and uncontrolled BP, for whom comes occurs commonly in the high-risk ICH patients, those LDL-C levels. Our results indicated that the adverse outcome presented robust consistent results. However, no statistical interaction was detected between SBP and LDL-C levels across SBP categories in acute ICH. Observational studies with small sample size demonstrated that lower LDL-C levels were independently related to HE in ICH patients [25, 26]. What is more, recent studies suggested that lower LDL-C levels carried an increased hazard of mortality [12, 25]. Of the 75,443 ICH patients enrolled in our study, the fully adjusted OR of HE for the lowest versus the highest LDL-C group was 1.22 (95% CI 1.10-1.35). When it comes to in-hospital mortality, full adjustment with admission GCS score attenuated the significant association with LDL-C. In the series of CSCA studies, the correlation between LDL-C and adverse events weakened with the aggravation of ICH [14].

4. Discussion

We provided evidence of ICH risk stratification regarding LDL-C concentrations across SBP categories in acute ICH patients. Those with LDL – C < 70 mg/dL conferred a higher risk of HE and in-hospital mortality compared to patients with LDL – C ≥ 100 mg/dL. When SBP was added as a stratification variable, it was noteworthy that the abovementioned association was attenuated in patients under a threshold SBP of 140 mmHg. Patients admitted within 24 h of symptom onset presented robust consistent results. However, no statistical interaction was detected between SBP and LDL-C levels. Our results indicated that the adverse outcome occurs commonly in the high-risk ICH patients, those with lower LDL-C levels and uncontrolled BP, for whom intensive control of SBP is recommended.

Although with the popular belief of lipid-lowering goal towards "the lower, the better" in atherosclerotic cardiovascular disease [24], appropriate LDL-C levels are still a matter of debate when weighing atherosclerosis and bleeding in acute ICH. Observational studies with small sample size demonstrated that lower LDL-C levels were independently related to HE in ICH patients [25, 26]. What is more, recent studies suggested that lower LDL-C levels carried an increased hazard of mortality [12, 25]. Of the 75,443 ICH patients enrolled in our study, the fully adjusted OR of HE for the lowest versus the highest LDL-C group was 1.22 (95% CI 1.10-1.35). When it comes to in-hospital mortality, full adjustment with admission GCS score attenuated the significant association with LDL-C. In the series of CSCA studies, the correlation between LDL-C and adverse events weakened with the aggravation of ICH [14].

Research about the strength and shape of the joint effects of SBP and LDL-C levels on hemorrhagic risk was limited. Data from the China Kadoorie Biobank prospective study showed that lowering LDL-C by 1 mmol/L increased the risk of ICH by about one-seventh, irrespective of baseline BP level [11], while another Korean observational study suggested that the inverse association between serum cholesterol and hemorrhagic stroke was restricted to hypertensive [18]. The results of our study added to the evidence that the bleeding risk associated with lower LDL-C (<70 mg/dL) in acute ICH patients with elevated SBP (≥140 mmHg). BP in the hyperacute phase of ICH was strongly related to adverse outcomes [10]; we thus performed a sensitivity analysis among patients admitted within 24 h of symptom onset which yielded identical results to the overall population. However, no apparent modification effect of SBP subgroups was discovered in the relationship between LDL-C and ICH prognosis. Our investigation suggested that acute ICH patients with lower LDL-C and elevated BP are more susceptible to HE and ensuing mortality; simultaneous control of these two factors may have therapeutic potential.

Hypertension is a well-recognized hazard factor for adverse outcomes in ICH patients, and intensive BP reduction was associated with reduced HE and improved functional outcomes [10]. Furthermore, cholesterol is important for the

| SBP          | LDL-C levels | Case (%) | Univariate analysis | Odds ratio (95% CI) |
|--------------|--------------|----------|---------------------|---------------------|
| Hematoma expansion | < 70 mg/dL | 158 (9.72) | 1.21 (1.00, 1.48) |  |
|              | 70-100 mg/dL | 254 (8.66) | 1.07 (0.90, 1.27) |  |
|              | ≥ 100 mg/dL  | 339 (8.15) | Ref.                |  |
| 140-180 mmHg | < 70 mg/dL | 480 (9.52) | 1.26 (1.13, 1.41) |  |
|              | 70-100 mg/dL | 811 (7.76) | 1.01 (0.92, 1.10) |  |
|              | ≥ 100 mg/dL  | 1237 (7.71) | Ref.                |  |
| ≥ 180 mmHg   | < 70 mg/dL | 307 (10.51) | 1.17 (1.02, 1.33) |  |
|              | 70-100 mg/dL | 569 (8.76) | 0.95 (0.85, 1.06) |  |
|              | ≥ 100 mg/dL  | 947 (9.15) | Ref.                |  |
| In-hospital mortality | < 70 mg/dL | 45 (2.77) | 1.40 (0.97, 2.02) |  |
|              | 70-100 mg/dL | 56 (1.91) | 0.96 (0.68, 1.35) |  |
|              | ≥ 100 mg/dL  | 83 (2.00) | Ref.                |  |
| 140-180 mmHg | < 70 mg/dL | 120 (2.38) | 1.40 (1.13, 1.74) |  |
|              | 70-100 mg/dL | 183 (1.75) | 1.03 (0.85, 1.24) |  |
|              | ≥ 100 mg/dL  | 274 (1.71) | Ref.                |  |
| ≥ 180 mmHg   | < 70 mg/dL | 114 (3.90) | 1.11 (0.90, 1.38) |  |
|              | 70-100 mg/dL | 222 (3.42) | 0.97 (0.82, 1.13) |  |
|              | ≥ 100 mg/dL  | 364 (3.52) | Ref.                |  |

Figure 3: Association of LDL-C with HE or in-hospital mortality across SBP categories among patients admitted within 24 h of symptom onset. LDL-C: low-density lipoprotein cholesterol; HE: hematoma expansion; SBP: systolic blood pressure. P = 0.747 for HE; P = 0.604 for in-hospital mortality. 60,024 (79.6%) patients were admitted within 24 h of symptom onset.
integrity of vessel walls. While in the pathological state of ICH with poor BP control, decreased cholesterol levels could lead to the fragility of cerebrovascular endothelium [27], promote the necrosis of arterial smooth muscle cells [28], inhibit platelet aggregation [29], affect erythrocyte osmotic fragility [30], and eventually cause bleeding [31]. A combined but noninteractive effect of circulating LDL-C and SBP levels on ICH outcomes was observed in our study. Intensive control of SBP to 140 mmHg is rational and necessary, especially for acute ICH patients with lower LDL-C levels.

Our study confirmed and extended the results of our previous investigation by further adding SBP categories; lower LDL-C levels are related to an increased hazard of HE and in-hospital mortality in patients with poorly-controlled BP. Nonetheless, there are still some limitations. First, hematoma volume at baseline and follow-up were unaccessible, and the determination of HE relied on subcenters. Meanwhile, the time from symptom onset to CT scans was unobtainable, and the determination of HE relied on subcenters.

5. Conclusions

A combined but noninteractive effect of LDL-C and SBP levels on ICH outcomes was observed in our study. Lower LDL-C levels (<70 mg/dL) are associated with a higher risk of HE and in-hospital mortality confined to ICH individuals with elevated SBP (>140 mmHg).

Data Availability

Data are available to researchers on request for purpose of reproducing the results or replicating the procedure by directly contacting the corresponding author.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors’ Contributions

Yarong Ding and Yu Wang contributed equally to this article.

Acknowledgments

We gratefully appreciate all the participating centers in the CSCA program for their hard work in data collection. The Chinese Stroke Center Alliance program was supported by grants from the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-029), Beijing Natural Science Foundation (Z200016), Beijing Municipal Committee of Science and Technology (Z201100005620010), and National Key R&D Programme of China (2018YFC1705003).

Supplementary Materials

See Table S1 in the Supplementary Material for baseline characteristics between included and excluded ICH patients.

References

[1] V. L. Feigin, C. M. Lawes, D. A. Bennett, S. L. Barker-Collo, and V. Parag, “Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review,” Lancet Neurology, vol. 8, no. 4, pp. 355–369, 2009.

[2] W. Wang, B. Jiang, H. Sun et al., “Prevalence, incidence, and mortality of stroke in China,” Circulation, vol. 135, no. 8, pp. 759–771, 2017.

[3] W. J. Tu, B. H. Chao, L. Ma et al., “Case-fatality, disability and recurrence rates after first-ever stroke: a study from bigdata observatory platform for stroke of China,” Brain Research Bulletin, vol. 175, pp. 130–135, 2021.

[4] T. J. Moullaali, X. Wang, R. H. Martin et al., “Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data,” Lancet Neurology, vol. 18, no. 9, pp. 857–864, 2019.

[5] C. S. Gray, A. J. Hildreth, P. A. Sandecock et al., “Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK),” Lancet Neurology, vol. 6, no. 5, pp. 397–406, 2007.

[6] M. N. Diringer, B. E. Skolnick, S. A. Mayer et al., “Thromboembolic events with recombinant activated factor VII in spontaneous intracerebral hemorrhage: results from the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial,” Stroke, vol. 41, no. 1, pp. 48–53, 2010.

[7] N. Sprigg, K. Flaherty, J. P. Appleton et al., “Tranexamic acid for hyperacute primary intracerebral haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial,” Lancet, vol. 391, no. 10135, pp. 2107–2115, 2018.

[8] A. D. Mendelow, B. A. Gregson, E. N. Rowan et al., “Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial,” Lancet, vol. 382, no. 9980, pp. 397–408, 2013.

[9] D. F. Hanley, R. E. Thompson, M. Rosenblum et al., “Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial,” Lancet, vol. 393, no. 10175, pp. 1021–1032, 2019.

[10] Q. Li, A. D. Warren, A. I. Qureshi et al., “Ultra-early blood pressure reduction attenuates hematoma growth and improves outcome in intracerebral hemorrhage,” Annals of Neurology, vol. 88, no. 2, pp. 388–395, 2020.

[11] L. Sun, R. Clarke, D. Bennett et al., “Causal associations of blood lipids with risk of ischemic stroke and intracerebral
hemorrhage in Chinese adults,” *Nature Medicine*, vol. 25, no. 4, pp. 569–574, 2019.

[12] J. M. Ramirez-Moreno, I. Casado-Naranjo, J. C. Portilla et al., “Serum cholesterol LDL and 90-day mortality in patients with intracerebral hemorrhage,” *Stroke*, vol. 40, no. 5, pp. 1917–1920, 2009.

[13] H. Noda, H. Iso, F. Irie et al., “Low-density lipoprotein cholesterol concentrations and death due to intraparenchymal hemorrhage: the Ibaraki prefectural health study,” *Circulation*, vol. 119, no. 16, pp. 2136–2145, 2009.

[14] Y. Wang, J. Wu, H. Gu et al., “Lower low-density lipoprotein cholesterol levels are associated with an increased risk of hematoma expansion and ensuing mortality in acute ICH patients,” *Neurological Sciences*, vol. 43, pp. 3121–3129, 2021.

[15] A. P. C. S. Collaboration, “Joint effects of systolic blood pressure and serum cholesterol on cardiovascular disease in the Asia Pacific region,” *Circulation*, vol. 112, no. 22, pp. 3384–3390, 2005.

[16] B. A. Ference, D. L. Bhatt, A. L. Catapano et al., “Association of genetic variants related to combined exposure to low low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease,” *Journal of the American Medical Association*, vol. 322, no. 14, pp. 1381–1391, 2019.

[17] K. Musunuru, K. Nasir, S. Pandey et al., “A synergistic relationship of elevated low-density lipoprotein cholesterol levels and systolic blood pressure with coronary artery calcification,” *Atherosclerosis*, vol. 200, no. 2, pp. 368–373, 2008.

[18] S. Ebrahim, J. Sung, Y. M. Song, R. L. Ferrer, D. A. Lawlor, and S. G. Davey, “Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study,” BMJ, vol. 333, no. 7557, p. 22, 2006.

[19] Y. Wang, Z. Li, Y. Wang et al., “Chinese Stroke Center Alliance: a national effort to improve healthcare quality for acute stroke and transient ischaemic attack: rationale, design and preliminary findings,” *Stroke and Vascular Neurology*, vol. 3, no. 4, pp. 256–262, 2018.

[20] S. M. Grundy, N. J. Stone, A. L. Bailey et al., “2018 AHA/ACC/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines,” *Circulation*, vol. 139, no. 25, pp. e1082–e1143, 2019.

[21] B. Williams, G. Mancia, W. Spiering et al., “2018 ESC/ESH guidelines for the management of arterial hypertension,” *European Heart Journal*, vol. 39, no. 33, pp. 3021–3104, 2018.

[22] R. U. Kothari, T. Brott, J. P. Broderick et al., “The ABCs of measuring intracerebral hemorrhage volumes,” *Stroke*, vol. 27, no. 8, pp. 1304-1305, 1996.

[23] D. Dowlatshahi, A. M. Demchuk, M. L. Flaherty et al., “Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes,” *Neurology*, vol. 76, no. 14, pp. 1238–1244, 2011.

[24] C. P. Cannon, “Low-density lipoprotein cholesterol,” *Journal of the American College of Cardiology*, vol. 75, no. 17, pp. 2119–2121, 2020.

[25] D. Rodriguez-Luna, M. Rubiera, M. Ribo et al., “Serum low-density lipoprotein cholesterol level predicts hematoma growth and clinical outcome after acute intracerebral hemorrhage,” *Stroke*, vol. 42, no. 9, pp. 2447–2452, 2011.