Relationships between statins and risk reduction of aortic dissection in patients with hypertension

Yujie Dang (903871914@qq.com)
People's Hospital of Xinjiang Uygur Autonomous Region https://orcid.org/0000-0003-0051-0783
Nanfang Li
People's Hospital of Xinjiang Uygur Autonomous Region https://orcid.org/0000-0003-1505-8566
Qing Zhu
People's Hospital of Xinjiang Uygur Autonomous Region
Shasha Liu
People's Hospital of Xinjiang Uygur Autonomous Region
Mulalibieke Heizhati
People's Hospital of Xinjiang Uygur Autonomous Region
Lin Gan
People's Hospital of Xinjiang Uygur Autonomous Region
Xintian Cai
People's Hospital of Xinjiang Uygur Autonomous Region
Wen Wen
People's Hospital of Xinjiang Uygur Autonomous Region
Menghui Wang
People's Hospital of Xinjiang Uygur Autonomous Region
Junli Hu
People's Hospital of Xinjiang Uygur Autonomous Region
Delian Zhang
People's Hospital of Xinjiang Uygur Autonomous Region
Jing Hong
People's Hospital of Xinjiang Uygur Autonomous Region
Qin Luo
People's Hospital of Xinjiang Uygur Autonomous Region

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Abstract

Purpose

Statins have cardiovascular protective effects in addition to lipid-lowering effects. However, no human studies have examined whether statins prevent aortic dissection. This study aimed to explore the association between statins and aortic dissection.

Methods

This nested case–control study was based on data extracted from the UHDATA (Hypertension Database at Urumchi) in Xinjiang of China. Cases (patients who developed aortic dissection) and controls (patients without aortic dissection; matched for age, sex, and date of aortic dissection diagnosis) were selected from among the 52,146 adult patients with hypertension and hyperlipidemia or high-risk hypertension registered in the database between January 1, 2006, and December 31, 2018. Follow-up data were collected up to April 30, 2022. Multivariable logistic regression analysis was used to assess the relationship between statin use and aortic dissection.

Results

A total of 7049 patients (75.6% men; mean age, 54.6 years) were selected for the study: 647 patients who developed aortic dissection during the follow-up period and 6402 patients who did not develop aortic dissection. The proportion of patients using statins was higher in the case group than in the control group (21.2% vs. 29.9%, $P < 0.001$). However, in multivariable logistic regression analysis, statin use was independently associated with decreased risk for aortic dissection (adjusted OR = 0.538, 95% CI: 0.418–0.692, $P < 0.001$).

Conclusions

Statins appear to reduce risk of aortic dissection, and clinicians should consider early use of statins in hypertensive patients, especially those with hyperlipidemia and multiple risk factors.

Introduction

Aortic dissection is a relatively rare and potentially life-threatening cardiovascular disease [1–4], with incidence in the range of 0.5–3.2/100,000 per year. Males are more commonly affected than females (male-to-female ratio, 2–5:1) [5–8]. The risk of mortality in acute aortic dissection is reported to be about 50% within the first 24 hours, increasing to 68.2% at 48 hours [9]. Identification of the risk factors for aortic dissection in patients could help in prevention of this serious disease.

In addition to congenital diseases such as Marfan syndrome and connective tissue diseases, the known risk factors for aortic dissection include older age, smoking, hypertension, atherosclerosis, inflammation, drug use, and pregnancy [10, 11]. Among them, hypertension and atherosclerosis are the most important risk factors. Hypertension and hyperlipidemia are the main causes of atherosclerosis. Epidemiological surveys show that 81.2% of hypertensive patients have at least one type of dyslipidemia. Because hypertension and hyperlipidemia are risk

factors for cardiovascular disease, active lipid-lowering therapy and antihypertensive therapy is recommended for prevention of cardiovascular and cerebrovascular events [12].

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and are widely used as hypolipidemic drugs. Statins provide cardiovascular protection via various mechanisms, including anti-inflammatory and antioxidant action, stabilizing effect on vulnerable plaque, improvement of vascular endothelial function, and restriction of vascular smooth muscle proliferation and migration. Several animal and clinical trials have confirmed that statins prevent aortic apoptosis and inflammation by down-regulating the PERK-p-EIF2α-CHOP–related ER stress signaling pathway, and may thus protect against abdominal aorta dissection [13]. Furthermore, statins diminish vascular endothelial inflammatory response and progression of aortic dissection by acting on MMP-9, MCP-2, and CXCL5 via the RAC1/NF-kB pathway in the aortic wall [14–18].

The association between lipid-lowering therapy and aortic dissection has not been fully investigated. Therefore, in this study, we attempted to determine the relationship between statin use and aortic dissection in patients with hypertension and hyperlipidemia.

Methods

Data source

This population-based nested case–control study was based on data extracted from the Urumqi Hypertension Database (UHDATA) established by the Hypertension Research Institute of People's Hospital of Xinjiang Uygur Autonomous Region, China. This database, which is updated continuously, was created in December 2019 by our hospital and Yidu Cloud Company, using customized natural language processing (NLP) software. The database includes all patients with definite diagnosis of hypertension who have visited our hospital since 2004 when our hospital began using an electronic medical records system. The database contains 1458 elements. including data from outpatient and inpatient electronic medical records, parameters of Hospital Information System, Laboratory Information System, Picture Archiving and Communication System (PACS), and Radiology Information System; and nursing records.

Study Population

The study population was assembled using the UHDATA. Patients were eligible for inclusion if they 1) were ≥ 18 years old; 2) had hypertension complicated by hyperlipidemia and/or were classified as high risk; 3) had been longitudinally observed from January 1, 2006, to December 31, 2018; and 4) had at least two hospitalization records. Hyperlipidemia and high-risk hypertension were defined per the 2019 ESC/EAS dyslipidemia management guidelines. From among the 52,146 patients that met these criteria, 11,466 patients were excluded because of 1) previous history of aortic dissection, 2) hepatic insufficiency, 3) vasculitis, 4) Marfan syndrome, and 5) incomplete data. The remaining 40,680 patients were observed from January 1, 2006, until the diagnosis of aortic dissection, death, or end of the study period (April 30, 2022), whichever came first. (Fig. 1).

Identification and definition of outcomes

The primary outcome was the first mention of aortic dissection in UHDATA, i.e., International Classification of Diseases 10 revision (ICD-10) diagnostic codes 171.0, I71.004, I71.0002, and I71.404 (aortic dissection); I71 .0011 (type A aortic dissection); I71.0021 (type B aortic dissection); I71.404 (abdominal aortic dissection); I71.900 and

I71.902 (aortic aneurysm); I71.201 (ascending aortic aneurysm); I71.207 (descending aortic aneurysm); I71.210 (aortic root aneurysm); I71.211 (thoracic aortic aneurysm); I71.600 (thoracoabdominal aortic aneurysm); and I71.400 and I71.402 (abdominal aortic aneurysm) [19]. The results of aortography and computed tomography and the classification of cases were cross-checked by two investigators to exclude false positive cases. A total of 647 patients who developed aortic aneurysm were identified; these patients comprised the case group. The hospital admission date or the event date was the index date of case diagnosis. For each case, 10 controls matched for age, sex, and index date of case diagnosis were selected from among the 40,033 patients who did not develop aortic aneurysm.

Exposure

Exposure to statins was defined as use of any statin prior to the date of aortic dissection diagnosis (or the corresponding date in controls) either during hospitalization (i.e., long-term medical orders in inpatient records) or as outpatient (i.e., statin prescription more than once in outpatient records). Statins were classified as lipophilic or hydrophilic using the drug distribution pharmacokinetic parameter logP (partition coefficient). Lipophilic statins (atorvastatin, fluvastatin, lovastatin, simvastatin, and pitavastatin) were defined as those with logP > 0, and hydrophilic statins as those with logP < 0 [20–22].

Data collection and covariables

Selection of covariates in this study was based on previous literature and included the following: general data (age, sex, smoking status, alcohol consumption, body mass index, systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, duration of hypertension); biochemical parameters (total cholesterol [TC], triglycerides, and high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], serum creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST]); comorbidities such as coronary artery disease [CAD], cerebrovascular disease, diabetes, and renal insufficiency; and use of medications such as antihypertensive drugs, statins, aspirin, and so on).

Statistical analysis

Continuous variables (age, pulse rate, SBP, DBP, body mass index, ALT, AST, serum creatinine, TC, triglycerides, HDL-C, LDL-C) were expressed as means ± standard deviation and compared using the t test (for normally distributed variables) or the Mann–Whitney U test (for non-normally distributed variables). Categorical variables were expressed as frequencies and proportions and compared using the chi-square test. The variance inflation factor (VIF) was used to test for collinearity among TC, triglycerides, HDL-C, and LDL-C (tolerance < 0.1 and VIF > 10 was taken as indication of multicollinearity). Conditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Additionally, stratified analysis was carried out to evaluate the association between statins and aortic dissection in subgroups of age (< 50 years/≥50 years), sex, body mass index (BMI; <24/≥24), smoking (never/current), alcohol drinking (never/current), duration of hypertension (5 years/5–10 years/>10 years), SBP (< 140 mmHg/140–159 mmHg/160–179 mmHg/≥180 mmHg), DBP (< 90 mmHg/≥90 mmHg), LDL-C (< 1.56 mmol/L/≥1.56 mmol/L) and comorbidities such as CAD and diabetes (present/absent). In addition, sensitivity analysis was performed after excluding patients taking different types of antihypertensive drugs. Statistical analysis was performed using SPSS 26 (IBM Corp., Armonk, NY, USA) and R 4.2 (https://www.r-project.org/).

Missing data

Missing data is an inevitable feature of observational studies. In this study, 7.88% of covariate data were missing. To minimize resulting bias, the missing data were filled using multiple interpolations, and five imputations were filled employing multiple interpolations. The imputation data were not significantly different from the original data (Table S1). The Rubin method was applied for statistical analysis [23].

Results

Characteristics of the study participants

A total of 7049 patients (75.6% males; mean age, 54.6 years) were included in this study. There were 647 in the aortic dissection group and 6402 in the control group; Table 1 shows the characteristics of the patients in the two groups. The proportion of current smokers (defined as those who had stopped smoking < 5 years ago and those with medical record of history of smoking and no report of having quit) was significantly higher in the case group than in the control group (28.6% vs. 25.9%, P = 0.038). The proportion of patients with duration of hypertension of 5–10 years was higher in the case group (6.0% vs. 4.9%), whereas the proportion of patients with hypertension duration > 10 years was higher in the control group (6.6% vs. 5.2%). The case group had lower proportion of patients with diabetes (5.4% vs. 17.4%, P < 0.001); lower mean BMI (25.2 ± 7.3 vs. 25.9 ± 6.6 kg/m2, P = 0.015); higher mean SBP (147 ± 28.9 mmHg vs. 140 ± 22.2 mmHg, P < 0.001) and DBP (88.8 ± 18.4 mmHg vs. 86.6 ± 14.5 mmHg, P < 0.001); lower mean triglyceride (1.5 ± 1.2 mmol/L vs. 1.7 ± 1.9 mmol/L, P = 0.013); lower proportion of patients taking statins (21.2% vs. 29.9%, P 0.001); higher proportion taking ARB (50.1% vs. 42.9%, P 0.001); lower proportion taking ACEI (10.0% vs. 16.1%, P 0.001); and lower proportion taking aspirin (44.0% vs. 48.3%, P = 0.038).

Table 1
Characteristics of cases and controls

Characteristics	Case Group	Control Group	
	(N = 647)	(N = 6402)	*P* value
Sociodemographics			
Age, y	54.4 ± 13.0)	54.7 ± 12.8	0.456
Sex (female/male), n (%)	148/499(22.9/77.1)	1534/4868(24.0/76.0)	0.537
Smoking status, n (%)			0.038
Never	462(71.4)	4744(74.1)	
Current	185(28.6)	1658(25.9)	
Drinking habit, n (%)			0.428
Never	517(79.9)	5030(78.6)	
Current	130(20.1)	1372(21.4)	
Disease characteristics, n (%)			
Duration of HP			0.125
< 5 years	565(87.3)	5754(89.9)	
5–10 years	39(6.0)	315(4.9)	
≥ 10 years	43(6.6)	333(5.2)	
CAD	35(5.4)	404(6.3)	0.366
Cerebral infarction	15(2.3)	218(3.4)	0.141
Cerebral hemorrhage	5(0.8)	46(0.7)	0.877
Chronic renal insufficiency	300(46.4)	3219(50.3)	< 0.001
Diabetes	35(5.4)	1117(17.4)	< 0.001
Clinical parameters, mean (SD)			
BMI, kg/m^2	25.2 ± 7.3	25.9 ± 6.6	0.015
SBP, mmHg	147 ± 28.9	140 ± 22.2	< 0.001
DBP, mmHg	88.8 ± 18.4	86.6 ± 14.5	< 0.001
pulse, bits/min	83.3 ± 12.7	82.8 ± 11.6	0.347
AST, U/L	19.3(15.0–27.0)	19.0(14.4–28.0)	0.046

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor; BMI, body mass index; β-block, beta adrenergic blocker; CAD, coronary heart disease; Cr, creatinine; blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure

Characteristics	Case Group	Control Group	
	(N = 647)	(N = 6402)	*P* value
Sociodemographics			
ALT, U/L	22.0(14.0–34.0)	22.8(14.0-36.7)	0.430
Total Cholesterol, mmol/L	3.8 ± 1.5	3.7 ± 2.1	0.434
Triglyceride, mmol/L	1.5 ± 1.2	1.7 ± 1.9	0.013
HDL-C, mmol/L	0.9 ± 0.4	0.8 ± 0.5	< 0.001
LDL-C, mmol/L	2.2 ± 1.0	2.2 ± 1.3	0.978
Cr, mmol/L	78.0(60.1–89.2)	73.1(65.1-101.3)	0.541
eGFR, mL/min/1.73m^2	92.8(61.4-140.1)	78.7(52.7-115.6)	0.605
Treatment modalities, n (%)			
Statins	137(21.2)	1915(29.9)	< 0.001
ACEI	65(10.0)	1029(16.1)	< 0.001
ARB	324(50.1)	2748(42.9)	< 0.001
Spironolactone	36(5.6)	376(5.9)	0.749
β-block	135(20.9)	1279(20)	0.591
CCB	510(78.8)	4017(62.7)	< 0.001
Aspirin	285(44.0)	3094(48.3)	0.038

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor; BMI, body mass index; β-block, beta adrenergic blocker; CAD, coronary heart disease; Cr, creatinine; blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure

Regression analysis

In unadjusted logistic regression analysis, age, smoking, drinking, duration of hypertension, diabetes, CAD, SBP, BMI, ALT, triglyceride, LDL-C, creatinine, CCB, β-blocker, and aspirin use were all significantly associated with risk of aortic dissection (all P < 0.05). Unadjusted regression suggested that statins protect against aortic dissection (OR = 0.629,

95% CI: 0.517–0.766; P < 0.001; Table 2). After multivariate adjustment, the protective effect of statins remained significant (OR = 0.531, 95% CI: 0.413–0.682; P < 0.001).

Table 2
Conditional logistic regression analysis of the association of statins with aortic dissection and aneurysm

	Unadjusted		Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Statins (-)	1		1		1		1	
Statins (+)	0.629(0.517–0.766)	< 0.001	0.632(0.519–0.769)	< 0.001	0.627(0.514–0.764)	< 0.001	0.531(0.413–0.682)	< 0.001
Model 1 adjusted age, sex, BMI, smoking, and drinking;								
Model 2 adjusted for variables in Model 1 plus duration of hypertension; CAD, cerebral infarction, cerebral hemorrhage, and diabetes;								
Model 3 adjusted for variables in Model 2 plus pulse, SBP, DBP, TC, TG, HDL, LDL, Cr, spironolactone, ACEI, ARB, β-block, CCB, and aspirin.								

Both types of statins showed protective effect against aortic dissection (Table S2 and Table S3). For hydrophilic statins, the unadjusted and adjusted ORs were 0.772 (95% CI: 0.685–0.870; P < 0.001) and 0.750 (95% CI: 0.650–0.865; P < 0.001), respectively. For lipophilic statins, the unadjusted and adjusted ORs were 0.482 (95% CI: 0.332-0.700; P < 0.001) and 0.516 (95% CI: 0.426–0.816; P = 0.005), respectively.

Stratified analysis

Figure 2 shows the results of stratified analysis. Statin use showed significant protective effect against aortic dissection in both age groups (OR = 0.424, 95% CI: 0.272–0.661, P < 0.001 for < 50 years and OR = 0.584, 95% CI: 0.425–0.801, P = 0.001 for age ≥ 50 years) and in both sexes (OR = 0.510, 95% CI: 0.290–0.897, P = 0.020 for females and OR = 0.548 95% CI: 0.412–0.727, P < 0.001 for males); in high BMI individuals (OR = 0.474, 95% CI: 0.350–0.641, P < 0.001); in current smokers (OR = 0.481, 95% CI: 0.304–0.760, P = 0.002); in never drinkers (OR = 0.521, 95% CI: 0.390–0.697, P < 0.001) and current drinkers (OR = 0.582, 95% CI: 0.345–0.981, P = 0.042); in those with hypertension duration < 5 years (OR = 0.528, 95% CI: 0.404–0.691, P < 0.001); in those with SBP < 140 mmHg (OR = 0.475, 95% CI: 0.316–0.715, P < 0.001), SBP 140–159 mmHg (OR = 0.580, 95% CI: 0.363–0.925, P = 0.022), and SBP ≥ 180 mmHg (OR = 0.406, 95% CI: 0.176–0.934, P = 0.034); in those with LDL-C < 1.56 mmol/L (OR = 0.369, 95% CI: 0.190–0.716, P = 0.003) or LDC-C ≥ 1.56 mmol/L (OR = 0.556, 95% CI: 0.420–0.735, P < 0.001); in those without diabetes (OR = 0.521, 95% CI: 0.401–0.677, P < 0.001); and in those without CAD (OR = 0.518, 95% CI: 0.399–0.673, P < 0.001). None of the variables, nevertheless, significantly changed the association (P > 0.05 for all interactions).

Sensitivity analysis

In sensitivity analysis conducted after excluding patients taking anti-hypertensive drugs (ACEI, ARB, CCB, β-blockers, and spironolactone), the association between statins and aortic dissection remained stable (P < 0.001; Table 3). The results remained stable even after excluding patients followed up for < 1 year (adjusted OR = 0.716, 95% CI: 0.518–0.988, P = 0.042; Table S4).

Table 3
Association of statins with aortic dissection and aneurysm Sensitivity analysis

	Unadjusted Model		Adjusted Model	
	OR (95%CI)	P value	OR (95%CI)	P value
Excluded patients with ACEI (N = 1094)				
Statins (-)	1		1	
Statins (+)	0.644(0.507–0.817)	< 0.001	0.487(0.366–0.649)	<0.001
Excluded patients with ARB (N = 3072)				
Statins (-)	1		1	
Statins (+)	0.533(0.382–0.744)	< 0.001	0.473(0.313–0.714)	<0.001
Excluded patients with β-block (N = 1414)				
Statins (-)	1		1	
Statins (+)	0.450(0.329–0.617)	< 0.001	0.496(0.355–0.693)	<0.001
Excluded patients with CCB (N = 4527)				
Statins (-)	1		1	
Statins (+)	0.621(0.379–1.018)	0.059	0.426(0.231–0.788)	0.007
Excluded patients with Spironolactone (N = 3379)				
Statins (-)	1		1	
Statins (+)	0.607(0.491–0.751)	< 0.001	0.536(0.411–0.699)	<0.001
Adjusted age, sex, BMI, smoking, drinking, duration of hypertension, CAD, cerebral infarction, cerebral hemorrhage, diabetes, pulse, SBP, DBP, TC, TG, HDL, LDL, Cr, spironolactone, ACEI, ARB, β-block, CCB, and aspirin				

Discussion

This nested case–control study based on data from the Chinese province of Xinjiang aimed to determine whether statins can reduce risk of aortic dissection. The results showed that statin use can decrease risk of aortic dissection by 46.2%. While lipophilic statins reduce the risk by 48.4%, hydrophilic statins lower the risk by 25.0%. The protective effect was evident irrespective of duration of hypertension. Hierarchical and sensitivity analyses confirmed the findings.

Statins improve atherosclerosis by decreasing the number of OxLDL-containing macrophages and increasing the content of smooth muscle cells and collagen in vessel wall [19, 24, 25]. Thus, statins protect blood vessels not only by lowering blood lipids, but also by promoting vascular remodeling and decreasing oxidative stress [25, 26]. In addition, statins inhibit macrophage adhesion and expression of mechano-metalloproteinases, and decrease the expression of IL-6 messenger RNA [28].

We have previously demonstrated that hyperaldosteronism is associated with aortic dissection [24], and animal experiments have shown that statins lower serum aldosterone level [28]. Data from separate cohorts of

hypertensive and diabetic patients suggest that lipophilic statins might be highly efficient in blocking aldosterone secretion [29]. The lipophilic statins atorvastatin and simvastatin appear to reduce angiotensin II sensitivity and to downregulate AT1R in humans [30]. Lipophilic statins (particularly simvastatin)—but not hydrophilic statins—are associated with lower aldosterone levels [29, 31]. We speculate that the aldosterone-lowering effect may be another mechanism by which statins protect against aortic dissection. In the UHDATA, the reason for measurement of aldosterone level is not mentioned; further, only baseline aldosterone data were available, so we do not know whether aldosterone levels changed after statin use. We intend to examine this possibility in a future RCT. This study showed that both hydrophilic and lipophilic statins protect against aortic dissection but lipophilic statins appear to be greater protective effect, probably due to larger reduction in LDL cholesterol level.

Traditional belief is that the prevention of aortic dissection is mainly achieved through lowering of blood pressure with antihypertensive drugs. We therefore conducted sensitivity analysis after excluding those taking antihypertensive drugs [21, 23] and confirmed that statins independently protect against aortic dissection.

Study strengths and limitations

This study is a retrospective nested case–control study with a large sample size, with 95% of reliable data on 1458 variables. However, the study has limitations. First, since aortic dissection is a rare condition, large cohort studies and randomized trials are difficult to organize. We therefore chose the nested case–control design, which allowed us to combine the advantages of a case–control study and a cohort study. Second, unidentified confounding variables might have impacted the results. Third, data on dosage and duration of use of the statins were not available; this is important information that could have a major impact on the results. To minimize bias, we performed sensitivity analysis. Fourth, the study does not clarify whether statins protect blood vessels by lowering blood lipid or via other effects such as anti-inflammatory action. Despite these limitations, we believe that this study provides useful information that could help guide selection of drugs for the prevention of aortic dissection.

Conclusions

Statins—especially lipophilic statins—reduce risk of aortic dissection in patients with hypertension and should therefore be prescribed in the early stages of hypertension.

Declarations

Statement

All data supporting the findings are in the manuscript. More detailed information and raw data can be obtained from the corresponding author upon reasonable request.

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Competing Interests

The authors declare no conflict of interest.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yujie Dang, Nanfang Li and Qing Zhu. The first draft of the manuscript was written by Yujie Dang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval

This is an observational study. The hospital ethics committee (People's Hospital of Xinjiang Uygur Autonomous Region) has confirmed that no ethical approval is required.

Informed Consent Statement

The Institutional Ethics Review Board of People's Hospital of Xinjiang Uygur Autonomous Region approved this study and waived the requirement for informed consent because of the retrospective study design.

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Figures

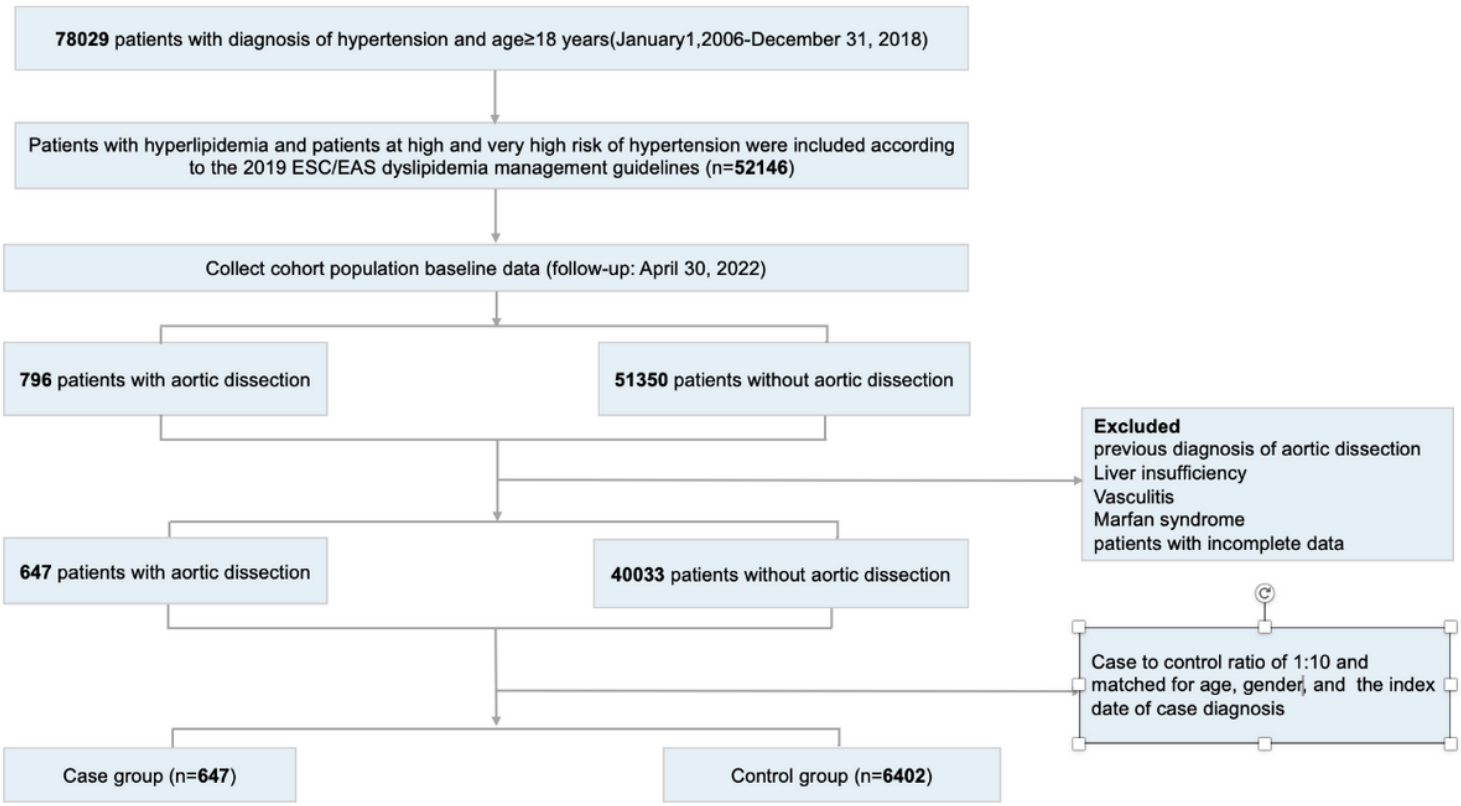

Figure 1

Patient selection flowchart

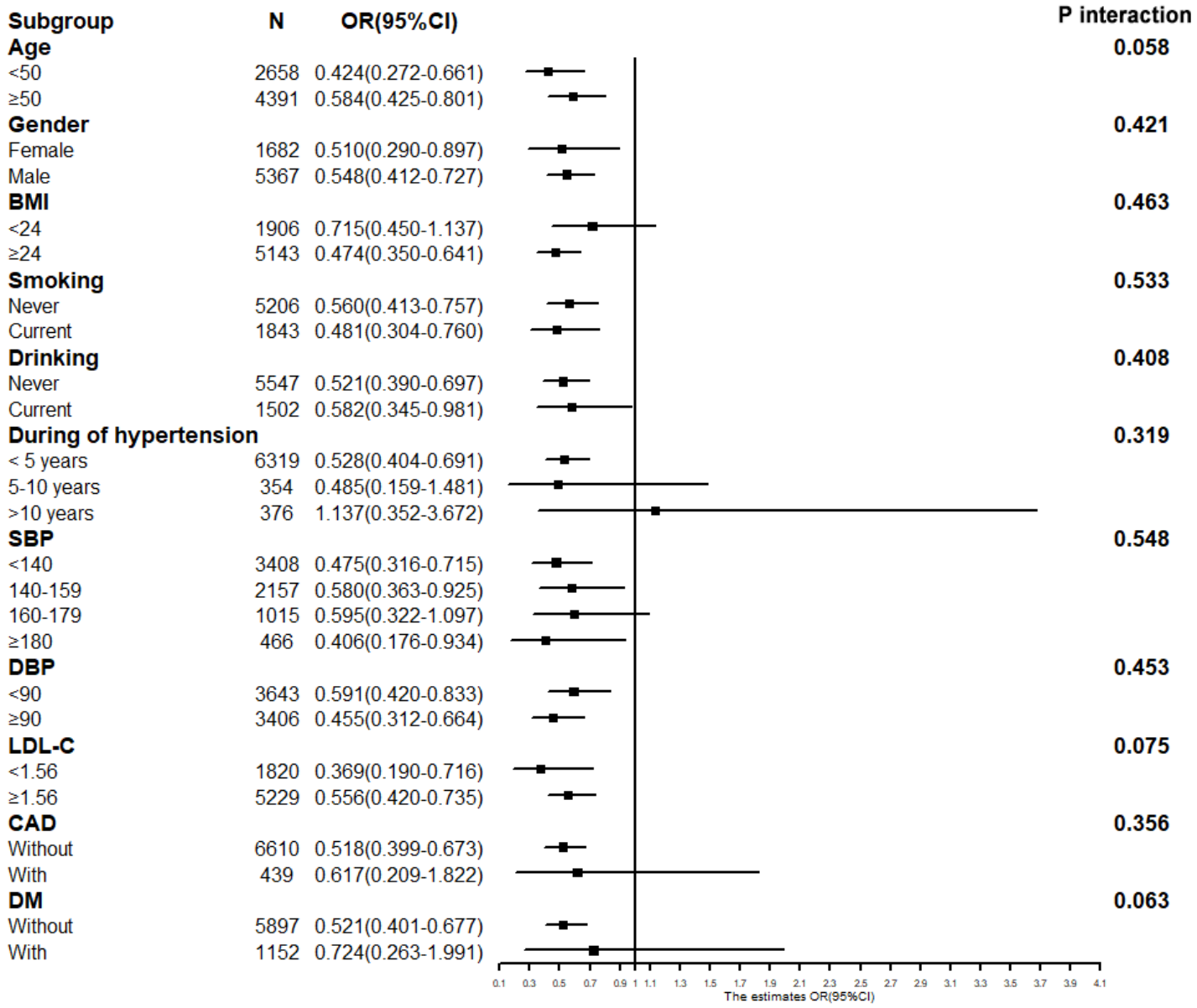

Figure 2

Association of statins with aortic dissection and aneurysm forest illustration

Adjusted age, sex, BMI, smoking, drinking, duration of hypertension, CAD, cerebral infarction, cerebral hemorrhage, diabetes, pulse, SBP, DBP, TC, TG, HDL, LDL, Cr, spironolactone, ACEI, ARB, β-block, CCB, and aspirin

Supplementary Files

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