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•SYSTEMATIC REVIEW AND META-ANALYSIS•

Meta-analysis of the Efficacy and Safety of Adjunctive Rosuvastatin for Dyslipidemia in Patients with Schizophrenia

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Background: Metabolic syndrome in patients with schizophrenia is a major health concern. The efficacy and safety of adjunctive rosuvastatin in treating dyslipidemia were controversial.

Aims: To assess the efficacy and safety of adjunctive rosuvastatin for dyslipidemia in patients with schizophrenia.

Methods: We systematically searched for relevant controlled clinical trials from the following databases: PubMed, PsycINFO, Cochrane Library, China Knowledge Network, WanFang Database and Chinese Biomedical Database up to September 28, 2017. Standardized mean difference (SMD) and risk ratio (RR) along with their 95% confidence intervals (CIs) were calculated. The quality of the included studies was assessed using the Cochrane risk of bias assessment tool. The GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system recommendation grading method was used as the reference standard.

Results: Four studies (*n*=274) comparing rosuvastatin (*n*=138) and control (*n*=136) groups were identified and analyzed. Adjunctive rosuvastatin showed greater efficacy than control group in low density lipoprotein cholesterol (LDL-C) [4 trials, *n*=272, *SMD*: -1.31 (95%*CI*: -1.93, -0.70), I^2=81%], total cholesterol (2 trials, *n*=164, *SMD*: -2.00 (95%*CI*: -2.79, -1.21); I^2=76%) and triglycerides (2 trials, *n*=164, *SMD*: -1.05 (95%*CI*: -1.38, -0.72); I^2=0%), but not in high density lipoprotein cholesterol (2 trials, *n*=164, *SMD*: 0.14 (95%*CI*: -0.16, 0.45); I^2=0%). After removing one study without randomization for LDL-C, significance remained [3 trials, *n*=172, *SMD*:-1.07 (95%*CI*: -1.60, -0.53); I^2=63%]. No significant group differences regarding body weight (3 trials, *n*=208, *SMD*: -0.40 (95%*CI*:-1.29, 0.49); I^2=89%), body mass index (2 trials, *n*=164, *SMD*: -0.34 (95%*CI*: -1.23, 0.56); I^2=87%), waist circumference (3 trials, *n*=208, *SMD*: -0.43 (95%*CI*: -1.31, 0.46); I^2=89%), and fasting glucose (4 trials, *n*=272, *SMD*: -0.25 (95%*CI*: -0.65, 0.15); I^2=62%) were observed. The adverse reactions and any cause discontinuation rate were similar between the groups. According to the GRADE approach, the evidence levels of main outcomes were rated as ''very low'' (35.3%) to ''low'' (64.7%). Of them, the primary outcome (LDL-C) was rated as "very low ".

Conclusions: The data available on the effectiveness and safety of adjunctive rosuvastatin in treating dyslipidemia for patients with schizophrenia is insufficient to come to a definitive interpretation about its efficacy and safety. Further high quality RCTs with extended treatment duration are warranted to confirm the findings.

Review registration: PROSPERO: CRD42017078230

Key words: schizophrenia; rosuvastatin; dyslipidemia; low density lipoprotein cholesterol; meta-analysis

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1. Introduction

Metabolic syndrome is an independent risk factor of cardiovascular disease (CVD) [1,2] that is associated with high treatment costs, risk of disability [3] and premature death in schizophrenia patients.[4] A recent meta-analysis found that the pooled prevalence of metabolic syndrome in patients with major psychiatric disorder was 32.6%, with higher rates in schizophrenia (33.4%) than bipolar disorder (31.7%) and major depression (31.3%).[5] Of the metabolic syndrome features, dyslipidemia, especially elevated low density lipoprotein cholesterol (LDL-C), is a major cause of CVD.[6-8] Thus, LDL-C lowering therapy could significantly reduce the risk of CVD.[9]

Pharmacological and non-pharmacological treatments have been widely used for metabolic syndrome in schizophrenia. Of the pharmacotherapies, statins appeared to be the most effective in reducing the risk of ASCVD (atherosclerotic cardiovascular disease) by decreasing the biosynthesis of cholesterol.[7] As lipid-lowering drugs, statins mainly played a role in LDL-C subfraction.[10] A cohort study[8] found statins proved effective in improving dyslipidaemia in schizophrenia patients. Of them, rosuvastatin showed a large effect size in the management of dyslipidemia.[11] Several controlled studies [6,12-14] have found that rosuvastatin is effective and safe in improving dyslipidemia in schizophrenia patients although the findings have been inconsistent.

To the best of our knowledge, no systematic review or meta-analyses of adjunctive rosuvastatin in treating dyslipidemia in patients with schizophrenia have been published. We thus conducted this meta-analysis of controlled studies to examine the efficacy and safety of adjunctive rosuvastatin for dyslipidemia in schizophrenia patients.

2. Methods

2.1 Search Strategy and Selection Criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15], English (PubMed, PsycINFO, and Cochrane Library) and Chinese (China Knowledge Network, WanFang Database and Chinese Biomedical Database) databases were systematically searched by two authors (WZ and D-BC) independently from their inception up to September 28, 2017 using the following search terms: (crestor OR rosuvastatin) AND (schizophrenic disorder OR disorder, schizophrenic OR schizophrenic disorders OR schizophrenia OR dementia praecox). Moreover, the references of the included studies and relevant reviews were also hand-searched for identifying any omitted trials.

Two authors (WZ and D-BC) independently assessed the eligibility of studies following the criteria of the *PICOS* acronym. *P*articipants: adult patients with schizophrenia according to any diagnostic criteria. *I*ntervention: rosuvastatin plus antipsychotics. *C*omparison: antipsychotics plus placebo or antipsychotics monotherapy. *O*utcomes: The primary outcome measure was LDL-C (mg/dL). Secondary outcomes were total cholesterol (mg/dL), high density lipoprotein cholesterol (HDL-C, mg/dL), triglycerides (mg/dL), fasting glucose (mg/dL), body weight (kg), body mass index (BMI, kg/m^2), waist circumference (cm), improvement of psychotic symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS) [16] or Brief Psychiatric Rating Scale (BPRS) [17], discontinuation due to any reasons and adverse drug reactions (ADRs). *S*tudy design: controlled studies with meta-analyzable data on the efficacy and safety of adjunctive rosuvastatin in improving dyslipidemia or other metabolic symptoms. Furthermore, the title of this meta-analysis are slightly different from the registered protocol; i.e., the registered title "rosuvastatin for dyslipidemia in schizophrenia: a metaanalysis" was revised to "meta-analysis of the efficacy and safety of adjunctive rosuvastatin for dyslipidemia in patients with schizophrenia".

2.2 Data extraction

Data from the included studies were independently extracted and checked by two reviewers (X-HY and D-BC). When intention-to-treat (ITT) or modified ITT and observed cases data were reported concurrently, ITT or modified ITT data were preferred following the methodology of the previous meta-analysis.[18] The corresponding or first authors of the relevant studies were contacted for any unpublished data if needed.

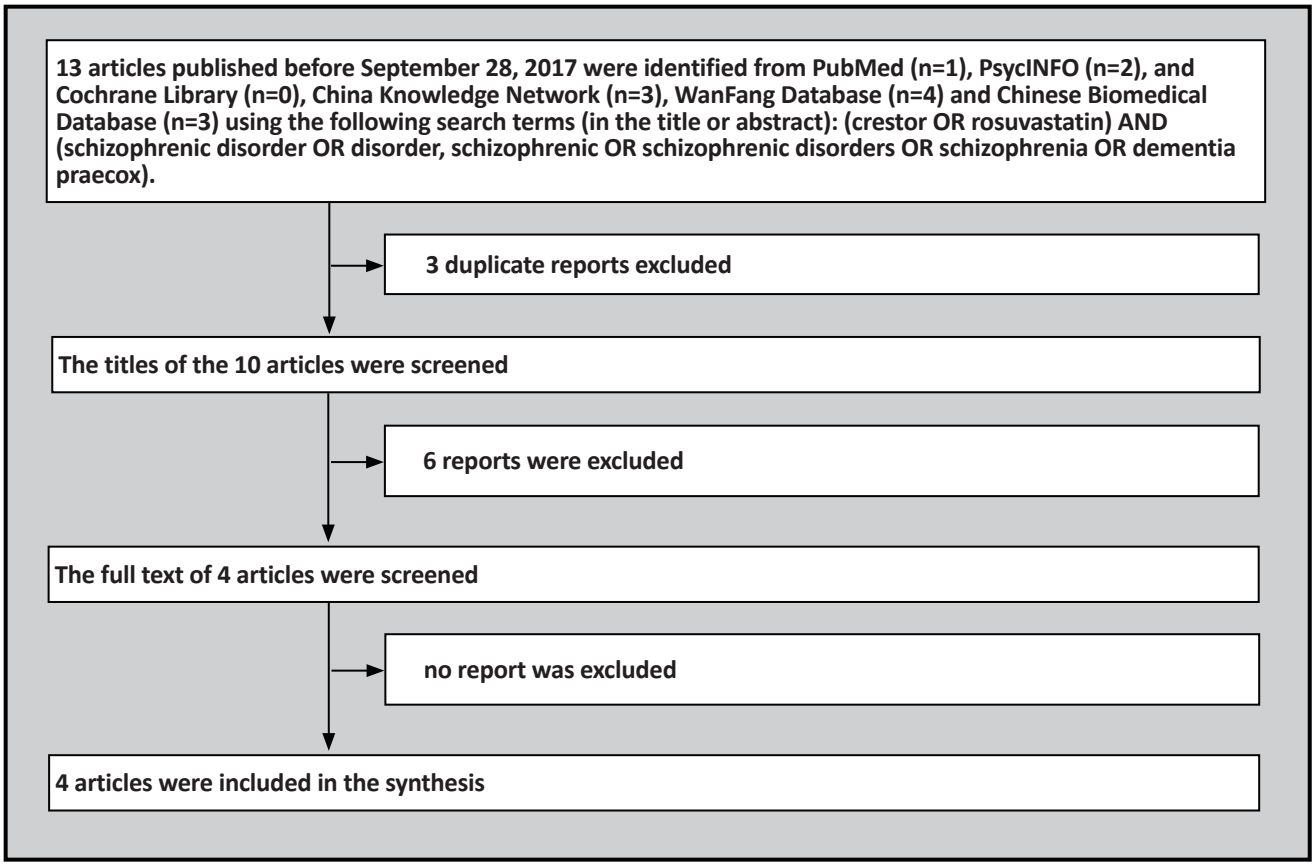
2.3 Statistical methods

This meta-analysis was conducted using the random effects model of Review Manager software (version 5.3 for Windows) (http://tech.cochrane.org/revman/) due to potential heterogeneity across studies.[19] For continuous outcomes, standardized mean differences (SMDs) with the estimated effect size (Hedges' g) were calculated. For dichotomous outcomes, risk ratio (RR) with its 95% confidence intervals (CIs) was computed. The heterogeneity between studies was investigated by considering the I^2 method alongside the chi-squared statistics, with I-squared ≥ 50% or Chi-squared p value < 0.1 as heterogeneity.[20] Moreover, a subgroup analysis (Chinese versus non-Chinese participants) was conducted. Finally, funnel plots and Egger's test [21] were used to explore potential publication bias. All analyses were two tailed, with significance level set at 0.05.

2.4 Assessment of reporting biases

The methodological quality of included studies were assessed using the Cochrane risk of bias [22] and Jadad scale.[23] The grading of recommendations assessment,

Figure 1. Flowchart of identification of studies



development, and evaluation (GRADE) system ranged from "very low", "low", "moderate", to "high" was used to interpret the overall quality level of the main outcomes of meta-analysis.[24,25]

3. Results

3.1 Results of the search

The initial literature search in English and Chinese databases yielded 13 electronic records (Figure 1). Duplication excluded 3 trials. Of the remaining 10 trials, 6 were determined to be irrelevant after review of the titles and abstracts, and zero were removed on the basis of full text review. In the end, 4 eligible studies [6,12-14] were included in this meta-analysis.

3.2 Characteristics of included studies

The 4 studies (*n*=274, Table 1) included 3 randomized controlled trials (RCTs) (*n*=174) and one controlled study without randomization (n=100) that compared adjunctive rosuvastatin (*n*=138) and control groups (*n* = 136). The weighted mean age was 39.3 years (range = 34.1 - 43.5 years), weighted mean percentage of males was 65.7% (range= 56.5% - 78.0%), and weighted mean illness duration was 12.0 years (range= 5.8 - 15.5 years). The weighted mean of treatment duration was 10.4 weeks (range= 8 -12 weeks) (Table 1). Three RCTs were conducted in China (*n*=174), and one in Belgium (*n*=100). The dosage of rosuvastatin ranged from 5 to 10 mg/day. The baseline antipsychotics included clozapine (1 trial), olazapine or risperidone (1 trial), and mixed antipsychotics (2 trials). For example, De Hert et al's study [6] included first-generation and second-generation antipsychotics (amisulpride, clozapine, risperidone, olanzapine, and quetiapine).

3.3 Study quality and GRADE assessment

In one study [6] subjects were not randomized; the remaining 3 RCTs [12-14] included two RCTs with double blinded design and one RCT [12] with open label design. One RCT [13] described randomization methods (i.e. the random number table), while selective reporting and other sources of bias were rated as having unclear risk in all RCTs (Supplemental Figure 1). In 3 RCTs, the weighted mean Jadad scores were 3.4 (range=2-5, Table 1). The quality of evidence for primary and secondary outcomes as assessed by the GRADE approach ranged from ''very low'' (35.3%) to ''low'' (64.7%) (Supplemental Table 1). Of them, the primary outcome (LDL-C) was rated as "very low".

Table 1. Study and patient characteristics of the included trials

Study (country)	Number of patients[a]	Randomized controlled trial	Trial Duration (wks)	Diagnosis Setting	Diagnostic criteria	Illness severity[a]/duration[a]	Age[a]: yrs (range)	Sex[a]: Male (%)	ROS: Dose (mg/d): mean (range)	Jadad score
De Hert 2006 (Belgium)	C: 48 I: 52	No	12	SCZ (80), SzA (20); Both	DSM-IV	-ND -13.1 yrs	38.5 (ND)	78.0	Ø=10 (FD)	NA
Gao 2014 (China)	C: 33 I: 31	Yes	8	SCZ (64); Inpatients	ICD-10	-57.7 (PANSS) -11.2 yrs	34.1 (18-40)	56.5	Ø=ND (5-10)	2
Jiang 2017 (China)	C: 32 I: 32	Yes	12	SCZ (64); Inpatients	ICD-10	-52.5 (PANSS) -15.5 yrs	43.5 (18-60)	62.5	Ø=5 (FD)	5
Qu 2015 (China)	C: 23 I: 23	Yes	8	SCZ (46); Inpatients	ND	-66.1 (PANSS) -5.8 yrs	42.5 (31-64)	56.5	Ø=ND (5-10)	3

[a]**Available data were extracted based on mean baseline value of each included trials.**

Abbreviations: Both=inpatients and outpatients; C=control; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders 4th edition; FD=fixed dosage; I=intervention; ICD-10=the 10th revision of the International Statistical Classification of Diseases and Related Health Problems; NA=not applicable; ND=not description; PANSS=Positive and Negative Syndrome Scale; ROS=rosuvastatin; SCZ=schizophrenia; SzA=schizoaffective disorder; wks=weeks; yrs=years; Ø=mean.

3.4 Efficacy and safety

3.4.1 Primary outcome

Rosuvastatin group was superior to the control group regarding the effects on LDL-C [4 trials, *n*=272, *SMD*: -1.31 (95%*CI*: -1.93, -0.70), $p < 0.001$; $I^2 = 81\%$, Figure 2]. The significance remained after excluding one study without randomization [6] [3 trials, *n*=172, *SMD*:-1.07 (95% *CI* : -1.60, -0.53), $p < 0.001$; $I^2 = 63\%$]. The subgroup analysis found more positive effects of rosuvastatin in non-Chinese than Chinese studies ($p = 0.01$). As only 4 trials were analyzed for primary outcomes, publication bias of LDL-C could not be examined using funnel plot or Egger's test.[26]

3.4.2 Secondary outcomes

Rosuvastatin group was also superior to the control group in terms of the effects on total cholesterol (2 trials, *n*=164, *SMD*: -2.00 (95%*CI* : -2.79, -1.21), $P < 0.001$; $I^2 = 76\%$) and triglycerides (2 trials, *n* = 164, *SMD*: -1.05 (95%*CI* :-1.38, -0.72), $p < 0.001$; $I^2 = 0\%$), but not in HDL-C (2 trials, *n* = 164, *SMD*: 0.14 (95%*CI*: -0.16, 0.45), $p = 0.36$; $I^2 = 0\%$) (Table 2).

No significant differences in body weight (3 trials, *n* = 208, *SMD*: -0.40 (95%*CI*: -1.29, 0.49), $p = 0.38$; $I^2 = 89\%$), BMI (2 trials, *n*=164, *SMD*: -0.34 (95%*CI* : -1.23, 0.56), $p = 0.46$; $I^2 = 87\%$), waist circumference (3 trials, *n* = 208, *SMD*: -0.43 (95%*CI*: -1.31, 0.46), $p = 0.34$; $I^2 = 89\%$), and fasting glucose (4 trials, *n* = 272, *SMD*: -0.25 (95%*CI*: -0.65, 0.15), $p = 0.23$; $I^2 = 62\%$) were found between rosuvastatin and the control group (Table 2).

Three studies measured the improvement of psychotic symptoms as assessed by the PANSS, but did not find any group difference (3 trials, *n* = 172, *SMD*: 0.05 (95%*CI*: -0.25, 0.34), $p = 0.77$; $I^2 = 0\%$, Table 2).

Meta-analyses of ADRs including dizziness, dry mouth, insomnia, tachycardia, constipation, nausea/vomiting and extrapyramidal symptoms (Table 2) showed no significant differences between groups (p = 0.29 to 0.92). Discontinuation rates due to any reasons (2 trials, *n* = 128, *RR*: 1.99 (95%*CI*: 0.36, 11.08), $p = 0.43$; $I^2 = 0\%$) were also similar between groups (Table 2).

4. Discussion

4.1 Main findings

To our knowledge, this is the first meta-analysis to examine the efficacy and safety of rosuvastatin as an adjunctive treatment for dyslipidemia in patients with schizophrenia. We found that adjunctive rosuvastatin could significantly improve LDL-C with "very low" evidence level based on GRADE assessment, total cholesterol, and triglycerides in schizophrenia patients treated with antipsychotics, which is consistent with previous findings.[27,28]

4.2 Limitations

The following limitations should be acknowledged. First, a heterogeneous result regarding the primary outcome was found. Second, 4 trials with 274 patients were included, which limits more comprehensive analyses (i.e. meta-regression analysis). Third, the dose-response effect of rosuvastatin for dyslipidemia was not evaluated since the dosage of rosuvastatin varied across all studies (5 to 10 mg/day). Fourth, the data on categorical metabolic syndrome was only reported in one trial.[6] Fifth, this meta-analysis did not focus on RCTs only, which could decrease the validity of the findings. Sixth, long-term effects of adjunctive rosuvastatin beyond 12 weeks were not examined. The quality of the studies included in this meta-analysis was relatively low (such

Table 2. Secondary outcomes

Variables	Study (subjects)	SMD/RR (95%CI)	I^2 (%)	*P*-value
Total cholesterol (mg/dL)	2 (164)	-2.00 (-2.79, -1.21)	76	**<0.001**
Triglycerides (mg/dL)	2 (164)	-1.05 (-1.38, -0.72)	0	**<0.001**
HDL-C (mg/dL)	2 (164)	0.14 (-0.16, 0.45)	0	0.36
Body weight (kg)	3 (208)	-0.40 (-1.29, 0.49)	89	0.38
Waist circumference (cm)	3 (208)	-0.43 (-1.31, 0.46)	89	0.34
BMI (kg/m^2)	2 (164)	-0.34 (-1.23, 0.56)	87	0.46
Fasting glucose (mg/dL)	4 (272)	-0.25 (-0.65, 0.15)	62	0.23
Discontinuation due to any reason	2 (128)	1.99 (0.36, 11.08)	0	0.43
Total psychopathology	3 (172)	0.05 (-0.25, 0.34)	0	0.77
ADRs: Dizziness	2 (108)	0.54 (0.10, 2.97)	0	0.48
Dry mouth	2 (126)	0.87 (0.31, 2.43)	0	0.79
Insomnia	3 (172)	1.52 (0.44, 5.23)	0	0.51
Tachycardia	2 (108)	2.41 (0.37, 15.83)	0	0.36
Constipation	3 (172)	1.06 (0.33, 3.40)	0	0.92
Nausea/vomiting	3 (172)	1.23 (0.37, 4.06)	0	0.73
Extrapyramidal symptoms	2 (126)	0.37 (0.06, 2.33)	0	0.29

Abbreviations: ADRs=adverse drug reactions; BMI= body mass index; CI=confidence intervals; HDL-C= high density lipoprotein cholesterol; RR=risk ratio; SMD=Standard mean difference.

as one study without randomization) and the quality of evidence for primary outcome was rated as ''low''. Finally, the efficacy and safety of other statins for dyslipidemia in patients with schizophrenia need to be examined.

4.3 Implications

Due to the unhealthy lifestyle, irregular diet and need for long-term antipsychotics use in schizophrenia patients, the prevention and treatment of metabolic syndrome is a major challenge in clinical practice.[1] Other medications, such as metformin [29] and topiramate [30,31], have been shown to improve weight gain or BMI, however, such effects were not observed with rosuvastatin in this study.

Hanssens et al found statin treatment for schizophrenia patients was well tolerated except from one patient who suffered from abnormal liver enzymes and high CK levels.[8] Similarly, rosuvastatin appeared to be relatively safe and well-tolerated for schizophrenia patients in this meta-analysis. Previous studies have found that rosuvastatin is associated with increased risk of myotoxicity, ranging from muscle pain without CK elevation to renal failure [32], and hepatotoxicity, ranging from asymptomatic transient elevations to liver failure.[33] However, none of these side effects were reported in the included studies with the exception of one study [6] where a subject had abnormal liver enzyme.

5. Conclusion

The data available on the effectiveness and safety of adjunctive rosuvastatin in treating dyslipidemia for patients with schizophrenia is insufficient to obtain a definitive interpretation about its efficacy and safety. Further high quality RCTs with extended treatment duration are warranted to confirm the findings.

Funding statement

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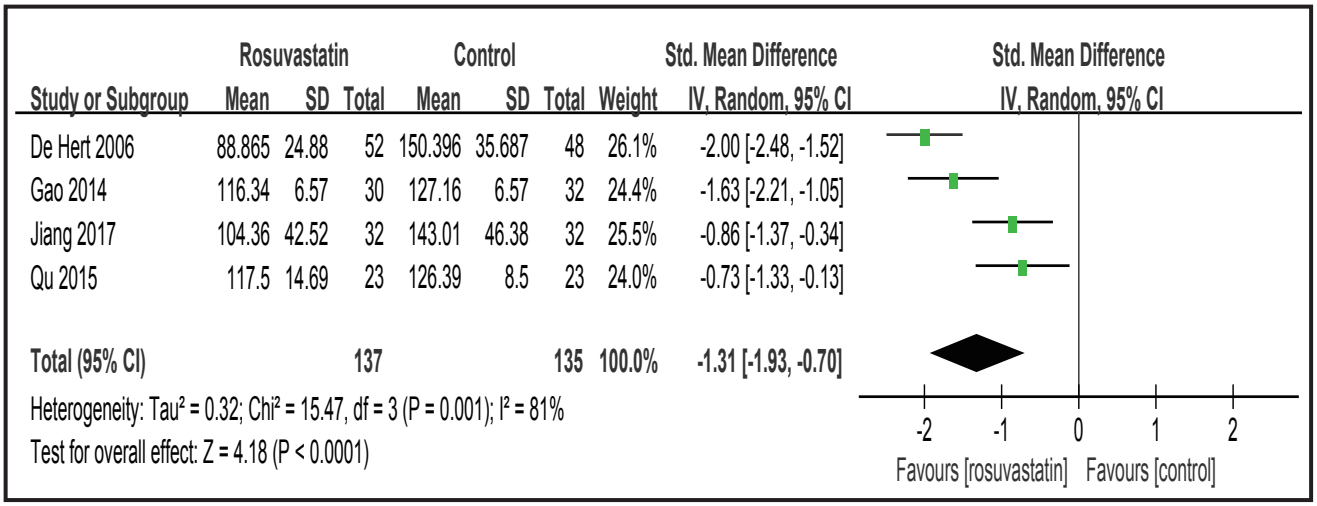
Figure 2. Adjunctive rosuvastatin for dyslipidemia in schizophrenia patients: forest plot for low density lipoprotein cholesterol (mg/dL)



De Hert for providing unpublished data for this meta-analysis. We contacted the authors of the Jiang et al study but did not receive a response.

Conflict of Interests statement

The authors declare no conflicts of interest concerning this article.

Authors' contributions

ZW and XYT designed the study and was assisted by CDB and YXH in the search for papers, data extraction, and analysis. ZW and YW drafted the manuscript. ZQE, HJQ, US, NCH, DHM and NYP made critical revisions to the manuscript. All authors approved the final version for publication.

对精神分裂症患者血脂异常的瑞舒伐他汀辅助治疗的疗效与安全性的的 Meta 分析

郑伟，杨威，张庆娥，杨欣湖，蔡东滨，胡晋卿，Ungvari.GS，HN Chee，Hert MD，宁玉萍，项玉涛

背景：精神分裂症患者的代谢综合征是一个重要的健康问题。瑞舒伐他汀对血脂异常的辅助性治疗的有效性和安全性存在争议。

目的：评价瑞舒伐他汀对精神分裂症患者血脂异常的辅助性治疗的有效性和安全性。

方法：我们从以下数据库中系统地检索了 2017 年 9 月 28 日以前相关的临床对照试验：PubMed、PsycINFO、Cochrane 图书馆、中国知网、万方数据库、中国生物医学文献数据库。我们计算了标准平均差（SMD）、风险比（RR）及其 95% 的可信区间（CIs）。使用偏移评估工具中的 Cochrane 风险评估来评价所纳入研究的质量。并采用 GRADE 系统推荐的等级方法（推荐、评估、发展、评价的等级）作为参照标准。

结果：确认和分析了 4 项比较瑞舒伐他汀组（n= 138）和对照组（n = 136）的研究（n = 274）。瑞舒伐他汀辅助治疗显示对低密度脂蛋白胆固醇（LDL-C）[4 项试验，n = 272，SMD：-1.31（95%CI：-1.93，- 0.70），I^2 = 81%]、总胆固醇（2 项试验，n = 164，SMD：-2.00（95%CI：-2.79，- 1.21）；I^2 = 76%）、和甘油三酯（2 项试验，n = 164，SMD：-1.05（95%CI：-1.38，- 0.72）；I^2 = 0%）的疗效比对照组更有效，但对高密度脂蛋白胆固醇（2 项试验，n = 164，SMD：0.14（95%CI：-0.16，0.45）；I^2 = 0%）的疗效没有显著差异。去除一项没有随机试验的 LDL-C 研究之后，显著差异仍然存在 [3 项试验，n = 172，SMD：-1.07（95%CI：-1.60，-0.53）；I^2 = 63%]。体重（3 项试验，n = 208，SMD：-0.40（95%CI：-1.29，0.49）；I^2 = 89%）、身体质量指数（2 项试验，n = 164，SMD: -0.34（95%CI: -1.23，0.56）；I^2 = 87%）、腰围（3 项试验，n = 208，SMD：-0.43（95%CI：-1.31，0.46）；I^2 = 89%）、空腹血糖（4 项试验，n = 272，SMD：-0.25（95%CI：-0.65，0.15）；I^2 = 62%）方面组间没有显著的差异。两组之间的不良反应及停药率相近。根据 GRADE 分级方法，主要结果的证据水平低被评为“非常低”（35.3%）到“低”（64.7%）。其中，主要结果（LDL-C）被评为“非常低”。

结论：对精神分裂症患者血脂异常的瑞舒伐他汀辅助性治疗的现有数据尚不足以对其有效性和安全性做出明确的解释。需进一步针对高质量的延长治疗时间的随机对照试验来验证该结论。

关键词：精神分裂症；瑞舒伐他汀；血脂异常；低密度脂蛋白胆固醇；Meta 分析；

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