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META-ANALYSIS

Systematic review and meta-analysis of Statins-Fibrates therapy in diabetic dyslipidemia patients

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Abstract

AIM: To evaluate the efficacy, effect of preventing cardiovascular diseases and safety of statins-fibrates combination therapy in diabetic dyslipidemia patients.

METHODS: We searched the databases of MEDLINE, EMBASE, web of knowledge and Cochrane central register of Controlled Trials for literatures about the coadministration of statins and fibrates as the treatment of patients with dyslipidemia and type 2 diabetes mellitus. We included related randomized controlled trials, controlled clinical trials and cross-sectional studies and excluded animal trials and clinical observations. The primary endpoints outcomes were the concentration of plasma total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C). The secondary outcomes were cardiovascular diseases (CVD) and adverse events.

RESULTS: Ten studies were included in this meta-analysis. For lipid modifying efficacy, the combination of statins and fibrates therapy had more significant effect on reducing TC [P = 0.004, weighted mean difference (WMD) = -8.19, 95%CI: -13.82--2.56] and TG concentration (P < 0.001, WMD = -47.29, 95%CI: -68.66--25.92) and increasing HDL-C concentration (P < 0.00001, WMD = 3.79, 95%CI: 2.25-5.33) when compared with statins monotherapy, while the effect of reducing LDL-C concentration (P = 0.50, WMD = -2.52, 95%CI: -9.76-4.72) was insignificant. To fibrates monotherapy, the combination therapy was more effective on reducing TC (P < 0.00001, WMD = -48.51, 95%CI: -57.14--39.89), TG (P < 0.00001, WMD = -26.07, 95%CI: -30.96--21.18), LDL-C concentration (P < 0.00001, WMD = -45.74, 95%CI: -53.35--38.13) and increasing HDL-C concentration (P = 0.04, WMD = 1.38, 95%CI: 0.04-2.73). For cardiovascular diseases, the coadministration therapy had no significant effect on reducing the incidence of these events when compared with monotherapy (For primary clinical endpoints, P = 0.12, OR = 0.61, 95%CI: 0.33-1.14); for secondary clinical endpoints, P = 0.13, OR = 0.66, 95%CI: 0.38-1.14). For adverse events happened during the follow-up, both the incidence of hepatic-related (alanine aminotransferase and/or aspartate aminotransferase of patients were $\geqslant$ 3 times of upper limit of normal) (P = 0.38, OR = 0.55, 95%CI: 0.15-2.06) and muscular-related (myopathy and/or creatine phosphokinase $\geqslant$ 3 times of upper limit of normal) adverse events (P = 0.10, OR = 1.62, 95%CI: 0.91-2.86) had no significant difference between these two therapies.

CONCLUSION: The results showed statins-fibrates combination therapy was more effective on lipid modification and well tolerated but there was no significant effect on preventing cardiovascular diseases.

Key words: Statin; Fibrate; Dyslipidemia; Type 2 diabetes; Combination therapy

Core tip: Both dyslipidemia and type 2 diabetes were established risk factors of cardiovascular diseases. Statins therapy was highly effective at lowering low density lipo-

protein cholesterol (LDL-C). However, despite the increasing use of statins as monotherapy for LDL-C reduction, a significant residual cardiovascular risk was still presented in patients with diabetic dyslipidemia. At the same time, Fenofibrate failed to alter the primary clinical endpoints significantly. How about the efficacy of statins-fibrates combination therapy in patients with diabetic dyslipidemia? The results of this meta-analysis showed the combination therapy was more effective on lipid modification and well tolerated but there was no significant effect on preventing cardiovascular diseases.

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INTRODUCTION

Cardiovascular diseases (CVD) represent the leading cause of mortality worldwide. Many researches have confirmed that both dyslipidemia and type 2 diabetes have tight relationship with CVD[1,2]. The combination of dyslipidemia and diabetes could be called diabetic dyslipidemia, which is a well-recognized reason for atherosclerotic cardiovascular diseases[3]. Elevated low density lipoprotein cholesterol (LDL-C) is a major risk factor for CVD[4]. As a result, current guidelines recommend management of LDL-C as the primary goal of therapy for diabetic dyslipidemia[5]. Statins are the drug of first choice for aggressive lipid lowering actions and reducing risk of CVD in these patients[6]. However, current therapeutic use of statins as monotherapy is still leaving many patients with diabetic dyslipidemia at high risk for CVD[7]. Some studies have come up with the conclusion that the coadministration of statins and fibrates may be more effective with no more adverse events as the treatment to patients with mixed dyslipidemia than statins or fibrates monotherapy[8-12], which may reduce the incidence of CVD at the same time. So we are curious about the efficacy and safety of the combined statins-fibrates therapy and their benefits in reducing CVD incidence in patients with dyslipidemia and type 2 diabetes.

MATERIALS AND METHODS

Search strategy and selection criteria

The search was performed using database of MEDLINE from 1980 to March 2014, EMBASE from 1980 to March 2014, the forth quarter 2014 Cochrane central register of controlled trials and web of knowledge from 1980 to March 2014. We conducted a comprehensive and systematic search of the published literature for trials of coadministration of statins and fibrtaes as the treatment of dyslipidemia with type 2 diabetes. The initial search terms were "statin", "fibrate", "dyslipidemia", "diabetes" and their combination [statin AND fibrate /"combination therapy" AND dyslipidemia/dyslipidemia AND diabetes/(statin AND fibrate) AND dyslipidemia/(statin AND fibrate) AND diabetes/"diabetic dyslipidemia" /(statin AND fibrate) AND "diabetic dyslipidemia" /"combination therapy" AND "diabetic dyslipidemia"].

We included randomized controlled trials, controlled clinical trials and cross-sectional studies those investigated the efficacy and safety of coadministration of statins and fibrates in patients with diabetic dyslipidemia and excluded animal trials and clinical observations. The treatment group involved the coadministration of statins and fibrates. The control group used statins or fibrates monotherapy. The statins included Simvastatin, Fluvastatin, Atorvastatin, Pravastatin, Rosuvastatin and Cerivastatin. The fibrates included Fenofibrate, Bezafibrate and Fenofibric acid.

Two reviewers independently evaluated the articles and any disagreement was resolved by consensus.

Statistical analysis

Study design data including design synopsis, duration of treatment and basic characteristics of patients. The primary endpoints outcomes were the concentration of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and LDL-C. The secondary outcomes were cardiovascular diseases and adverse events. For cardiovascular diseases, the primary clinical endpoints included death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. The secondary clinical endpoints included the combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (termed the "expanded macrovascular outcome"); a combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina (termed "major coronary disease events"); nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure. For adverse events, if the alanine aminotransferase and/or aspartate aminotransferase of patients were $\geqslant$ 3 times of upper limit of normal during follow-up, it would be counted as hepatic-related adverse events. While the muscular-related adverse events included myopathy and CK (creatine phosphokinase) $\geqslant$ 3 times of upper limit of normal during follow-up.

We combined the results and expressed them as odds radio (OR) or weighted mean difference (WMD) with corresponding 95%CIs, using a fixed effect (FE) or randomized effect (RE) model for the studies with sufficient data (in this article, if the homogeneity was no more than 50%, FE model was used, else RE model was used). The homogeneity was assessed with I^2 and χ^2 test. The above statistical calculations were performed on Revman Manager 5.0 Software (Copenhagen, Denmark) for meta-analysis.

RESULTS

We searched 107 potentially relevant studies and retrieved 62 full-text articles. 52 of the full-text articles were exclud-

Table 1 Basic characteristics of included studies

Ref.	Type	Number (T/C1/C2)	Age (mean) (T/C1/C2)	Men (%)	Treatment	Contral 1	Contral 2	Duration (mo)
Athyros *et al*[19] 2002	RCT	40/40/40	58/57/58	56.7	A + Fe	A	Fe	6
Durrington *et al*[22] 2004	RCT	115/53/48	60/60/60	53.0	R + Fe	R	Fe	6
Rosenson *et al*[21] 2011	RCT	177/173/123	60/58/58	41.4	R + FA	R	FA	3
Derosa *et al*[18] 2004	RCT	25/23/0	61/59/0	50.0	F + Fe	F		6
Farnier *et al*[16] 2011	RCT	145/146/0	56/57/0	48.1	P + Fe	S		3
Hamilton *et al*[17] 2010	RCT	15/0/15	63/0/63	86.7	A/S/P/R + Fe		Fe	3
Ginsberg *et al*[20] 2010	RCT	2765/2753/0	62/62/0	69.3	S + Fe	S		56.4
Gavish *et al*[13] 2000	CCT	146/100/48	59/58/60	57.4	S + B	S	B	21
Constantinides *et al*[15] 2012	CCT	14/14/14	> 18/> 18/> 18	100	S + B	S	B	2
Klempfner *et al*[14] 2014	CSS	225/2838/0	60/65/0	71.0	A/S/P/C/F + B		B	12

RCT: Randomized controlled trial; CCT: Controlled clinical trial; CSS: Cross-sectional study; T/C1/C2: Treatment/Control 1/Control 2; S: Simvastatin; B: Bezafibrate; F: Fluvastatin; Fe: Fenofibrate; A: Atorvastatin; P: Pravastatin; R: Rosuvastatin; C: Cerivastatin; FA: Fenofibric acid.

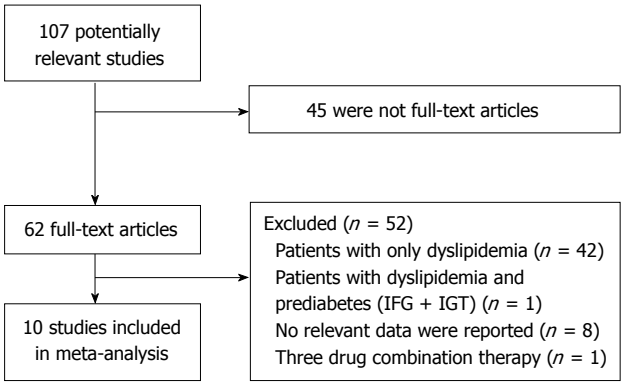

Figure 1 Flow diagram of study screening process. IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance.

ed because the patients were not having both dyslipidemia and diabetes or the data were not complete (Figure 1). Finally only 10 studies[13-22] were included in our research and their basic characteristics were shown in Table 1.

Comparisons of lipid modifying efficacy between coadministration and monotherapy

Figure 2 showed the comparisons of lipid modifying efficacy between coadministration of statins and fibrates and statins monotherapy. Figure 2A presented the results of plasma TC concentration in two different therapies; six trials investigated it with a total of 721 patients. From this figure we observed that compared with statins monotherapy, the coadministration of statins and fibrates had more strong function on reducing the concentration of plasma TC in patients with diabetic dyslipidemia (P = 0.004, WMD = -8.19, 95%CI: -13.82--2.56). Figure 2B presented the results of plasma TG concentration in two different therapies, four trials with 663 patients were included, which had the similar results with TC (P < 0.001, WMD = -47.29, 95%CI: -68.66--25.92). Both of them showed a beneficial and statistically significant effect of coadministration on diabetic dyslipidemia. Figure 2C presented the results of plasma HDL-C concentration with six trials and 721 patients. From this figure we observed the concentration of HDL-C was lower in statins monotherapy group (P < 0.00001, WMD = 3.79, 95%CI: 2.25-5.33). Figure 2D presented the results of plasma LDL-C concentration with four trials and 691 patients, which showed the modification of LDL-C was not significant between coadministration and statins monotherapy (P = 0.50, WMD = -2.52, 95%CI: -9.76-4.72). In conclusion, for lipid modifying efficacy, the combination of statins and fibrates therapy had more significant effect on reducing plasma TC and TG concentration and increasing HDL-C concentration when compared with statins monotherapy, while the effect of reducing LDL-C concentration was insignificant.

Figure 3 showed the comparisons of lipid modifying efficacy between coadministration of statins and fibrates and fibrates monotherapy. Figure 3A, B and D presented the results of plasma TC, TG and LDL-C concentration respectively. All of them showed a beneficial and statistically significant effect on reducing TC, TG and LDL-C with combination therapy (P < 0.00001). Figure 3C presented the results of plasma HDL-C concentration with three trials and 302 patients. From this figure we observed the concentration of HDL-C was lower in fibrates monotherapy group (P = 0.04, WMD = 1.38, 95%CI: 0.04-2.73). In conclusion, the combination therapy was more effective on reducing TC, TG, LDL-C concentration and increasing HDL-C concentration than fibrates monotherapy.

Comparisons of cardiovascular diseases between coadministration and monotherapy

Figure 4 showed the incidence of cardiovascular diseases between coadministration and statins or fibrates monotherapy. Three identified studies were included in this analysis with 8875 patients. Figure 4A showed the primary clinical endpoints, Figure 4B showed the secondary clinical endpoints. From Figure 4 we observed that in patients with diabetic dyslipidemia, the coadministration therapy had insignificant effect on reducing the incidence of cardiovascular diseases when compared with statins or fibrates monotherapy. For primary clinical endpoints, P = 0.12, OR = 0.61, 95%CI: 0.33-1.14); for secondary clinical endpoints, P = 0.13, OR = 0.66, 95%CI: 0.38-1.14).

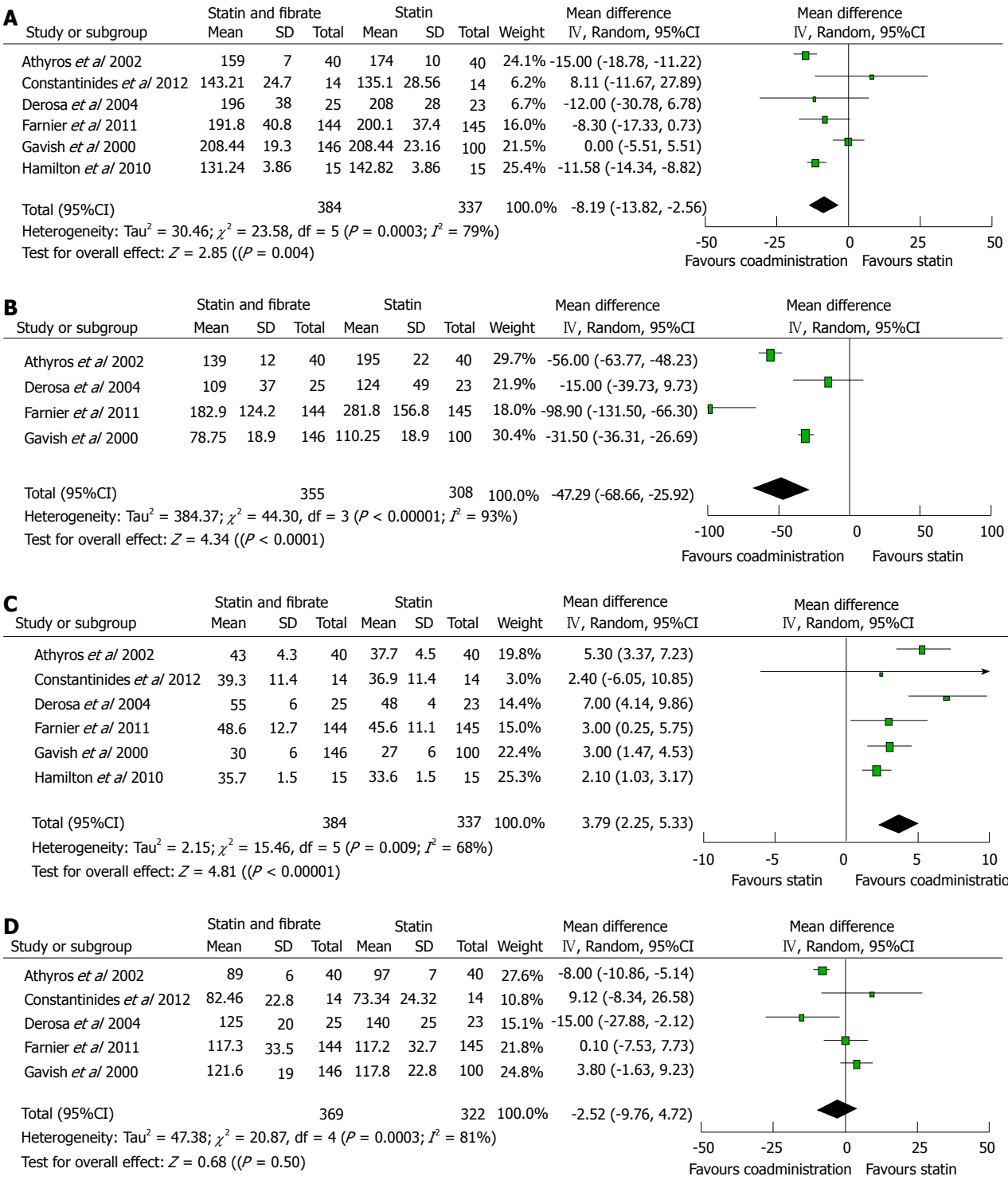

Figure 2 Summary of results of meta-analysis on the lipid modifying function between coadministration of statins and fibrates and statins monotherapy. A: Comparison of plasma TC concentration between coadministration and statins monotherapy; B: Comparison of plasma TG concentration between coadministration and statins monotherapy; C: Comparison of plasma HDL-C concentration between coadministration and statins monotherapy; D: Comparison of plasma LDL-C concentration between coadministration and statins monotherapy. LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride.

In conclusion, the coadministration therapy had no significant effect on reducing the incidence of these events when compared with monotherapy.

Comparisons of adverse events between coadministration and monotherapy

Figure 5 showed the adverse events happened in the period of two different therapies. Four related trials were included in meta-analysis with a total of 1274 patients. Figure 5A presented the hepatic-related adverse events. Figure 5B presented the muscular-related adverse events. There was no significant difference between the two therapies ($P = 0.38$ and 0.10 respectively). In conclusion, statins-fibrates combination therapy was tolerated as well

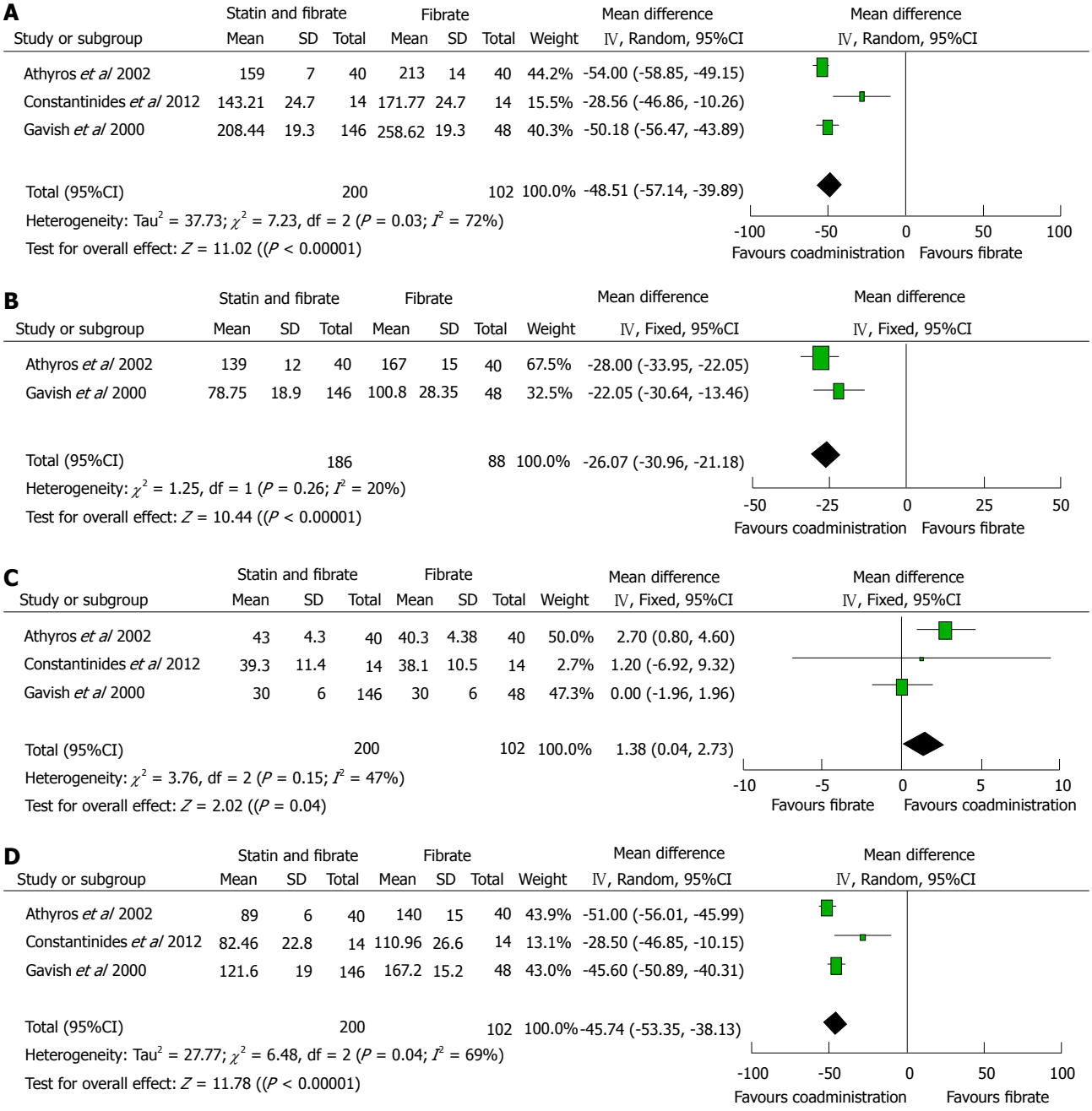

Figure 3 Summary of results of meta-analysis on the lipid modifying function between coadministration of statins and fibrates and fibrates monotherapy. A: Comparison of plasma TC concentration between coadministration and fibrates monotherapy; B: Comparison of plasma TG concentration between coadministration and fibrates monotherapy; C: Comparison of plasma HDL-C concentration between coadministration and fibrates monotherapy; D: Comparison of plasma LDL-C concentration between coadministration and fibrates monotherapy. LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride.

as statins or fibrates monotherapy.

DISCUSSION

CVD continues the leading cause of death worldwide. Both dyslipidemia and type 2 diabetes were established risk factors for CVD[1,2]. Moreover, dyslipidemia was strikingly common in patients with type 2 diabetes, affecting almost 50% of this population[2]. So it was easy to understand that CVD was more common in patients with diabetic dyslipidemia than in the general populations[23]. Several researches had come out with the idea that elevated LDL-C was a major risk factor for CVD[4,24,25]. As a result, management of LDL-C was the primary goal of therapy for patients with dyslipidemia and type 2 diabetes[5,26].

Statins therapy was highly effective at lowering LDL-C. Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) have emerged as the cornerstone for LDL-C lowering since the first agent, lovastatin, was approved in 1987[27]. However, despite the increasing use of statins as monotherapy for LDL-C reduction, a

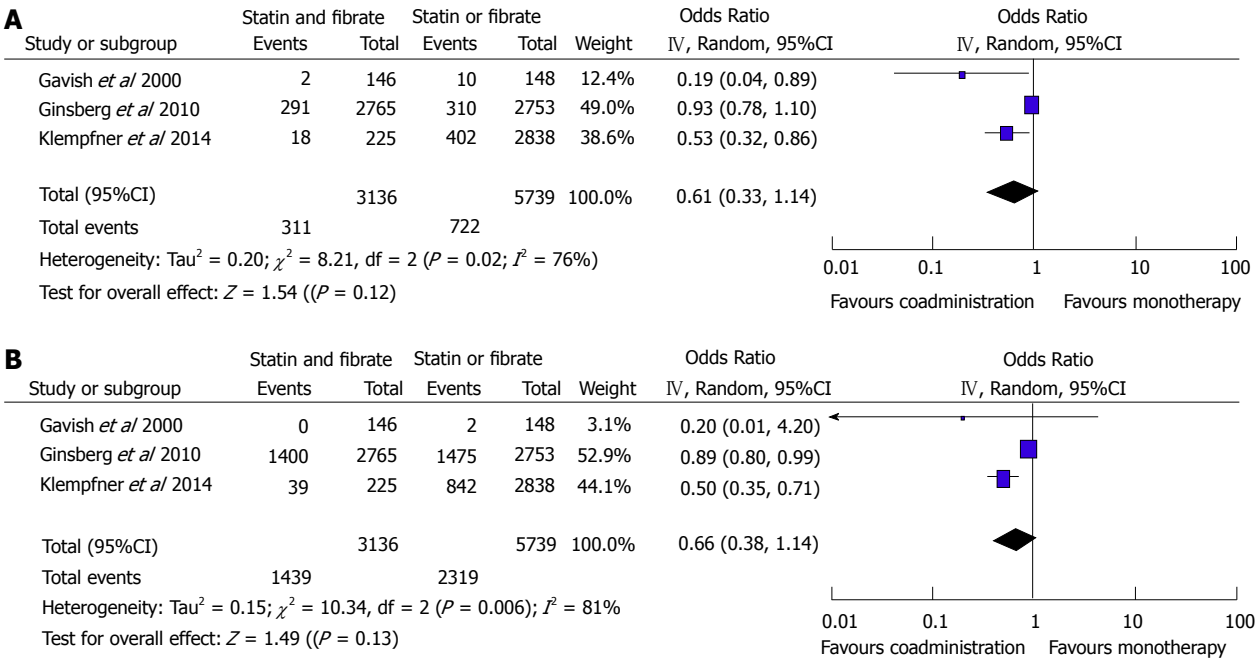

Figure 4 Summary of results of meta-analysis on cardiovascular diseases. A: Primary clinical endpoints events; B: Secondary clinical endpoints events.

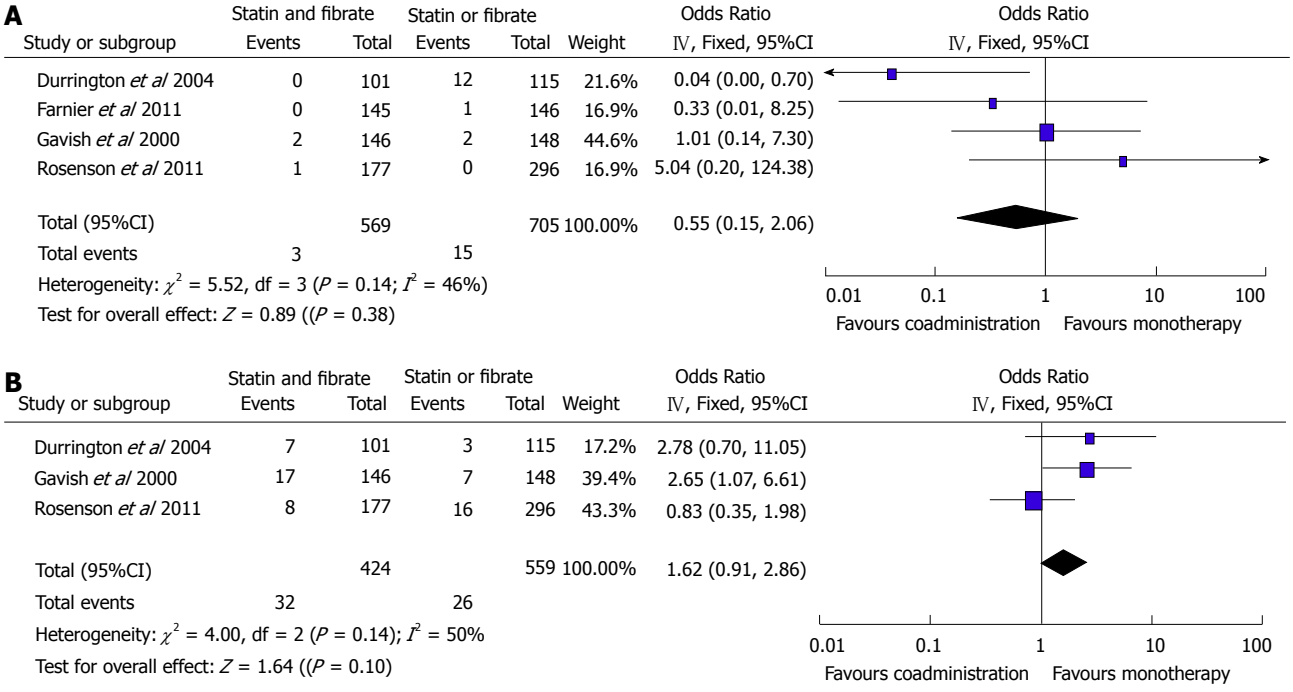

Figure 5 Summary of results of meta-analysis on adverse events. A: Hepatic-related adverse events; B: Muscular-related adverse events.

significant residual cardiovascular risk was still presented in patients with diabetic dyslipidemia[7]. The reason was that LDL-C could not reflect the classic "diabetic dyslipidemia", which consisted of hypertriglyceridemia and low levels of HDL-C[28,29]. In patients with type 2 diabetes, LDL particles were small and dense, carrying less cholesterol per particle; therefore, at any given LDL-C concentration, there were more LDL particles present in an individual with type 2 diabetes relative to an individual without the disease, which might make the LDL-C level a misleading measure of risk in patients with type 2 diabetes[5]. It was increasingly recognized that insulin resistance contributed to the characteristic dyslipidemia associated with type 2 diabetes[30]; and this dyslipidemia associated with insulin resistance was also referred to as atherogenic dyslipidemia.

Since diabetic dyslipidemia was characterized by moderately increased TG levels and reduced HDL-C, fibrates therapy should be considered as the option. Several large clinical and angiographic trials had evaluated the efficacy

of fibrates as monotherapy in halting the progression of atherosclerotic diseases[31-33]. The Fenofibrate Intervention and Event Lowering in Diabetes study was a 5-year, randomized, placebo-controlled trial testing the safety and efficacy of fenofibrate 200 mg in 9795 type 2 diabetic patients[34]. In this trial Fenofibrate failed to alter the primary clinical endpoints significantly.

Although LDL-C levels didn't differ substantially from individuals with or without type 2 diabetes, data had demonstrated that lowering LDL-C levels reduced the risk for major CVD in patients with type 2 diabetes[5]. It was well accepted that statins were the primary and more efficient method of reducing LDL-C levels even at low doses[35]. However, statins manifested minimal effects on raising HDL-C levels (5%-15%) and on decreasing TG levels (7%-30%)[36]. Fibrates had small or minimal effects on LDL-C levels, which depended on baseline TG levels[35]. These data implied that a combination of statins and fibrates may have additional benefits, especially in patients with dyslipidemia and type 2 diabetes.

Some researches have shown the efficacy of statins-fibrates combination therapy in patients with mixed dyslipidemia. Research by Goldberg *et al*[8] focused on the efficacy of fenofibric acid plus statins on multiple lipid parameters in women with mixed dyslipidemia and the results showed the coadministration could increase the HDL-C level and decrease TG level more effecctive than statin monotherapy. Similar results could observed from Research by Pepine *et al*[9] showed that in elderly patients with mixed dyslipidemia, rosuvastatin 5, 10, or 20 mg in combination with fenofibric acid 135 mg improved the overall lipid profile. Farnier *et al*[10] also found in high-risk patients with mixed hyperlipidemia not controlled by pravastatin 40 mg monotherapy, the fenofibrate 160 mg/pravastatin 40 mg fixed-dose combination therapy significantly improved the global atherogenic lipid profile. So it was easy for us to suppose that combination therapy was more effective on patients with mixed dyslipidemia than statins or fibrates monotherapy. How about patients with diabetic dyslipidemia?

From our meta-analysis, we observed that in patients with both dyslipidemia and type 2 diabetes, compared with statins or fibrates monotherapy, the coadministration of statins and fibrates had more significant effect on lowering TG concentration. For plasma LDL-C concentration, combination therapy had statistically significant effect on lowering it than fibrates monotherapy. These data gave us the implication that the coadministration may be more effective on lipid modification than statins or fibrates monotherapy in diabetic dyslipidemia patients.

Since the combination therapy had additional benefit than monotherapy on lipid modifying efficacy in diabetic dyslipidemia patients, it was reasonable for us to give the hypothesis that the combination therapy would result in an additional cardiovascular benefit, as compared with statins therapy alone. One study focused on cardiovascular events in patients received combined fibrates/statins treatment versus statin monotherapy had showed that a significantly lower risk of 30-d major adverse cardiovascular events rate was observed in patients receiving combined fibrates/statins treatment following acute coronary syndrome compared with statins monotherapy[37]. However, from the results of our meta-analysis, there was no significant difference on the incidence of cardiovascular diseases, no matter the primary or the secondary clinical endpoints, between the coadministration therapy and monotherapy in diabetic dyslipidemia patients. So our analysis did not support the use of combination therapy to reduce cardiovascular risk in the majority of patients with type 2 diabetes who were at high risk for cardiovascular diseases. But this evidence was not so robust since only three identified studies were included in this part of meta-analysis. Further studies should continue focus on the rate of CVD and maybe we could find different answers to this kind of questions.

In addition to lipid modifying efficacy, safety was an important issue influencing the selection of combination therapy or monotherapy. Common adverse events associated with statins use included gastrointestinal upset and muscle aches, although dose related hepatoxicity and myotoxicity were the most clinically significant adverse events[38]. Common adverse events associated with fibrates included gastrointestinal disturbance, rash, headache, pancreatitis, myalgia, and myotoxicity (in rare instances-and possibly more likely with gemfibrozil than with fenofibrate)[23]. Combination therapy with statins and gemfibrozil was more likely to be accompanied by severe myopathy[39,40]. This might due to the fact that gemfibrozil had significant pharmacokinetic interactions with statins that lead to increased plasma levels of statins[41]. This limitation was not observed with fenofibrate, bezafibrate, or ciprofibrate and no significant side effects had been observed with combination treatment with statins and fibrates[23]. Same conclusions could be driven from our meta-analysis, both incidence of hepatic-related adverse events and muscular-related adverse events had no obvious difference between coadministration and monotherapy. So the combination therapy could be well tolerated in diabetic dyslipidemia patients.

In conclusion, diabetic dyslipidemia was associated with elevated serum TG, low serum HDL-C levels, and a preponderance of small, dense LDL particles. Disturbance of lipid metabolism linked to insulin resistance may be the primary event in the development of type 2 diabetes, which had the tight relationship with CVD. The present meta-analysis had shown that the coadministration was more effective on lipid modification than monotherapy and it was well tolerated, though the rate of CVD had no significant difference when combination therapy was given.

However, our meta-analysis had several potential limitations. Firstly, most studies included in this mate-analysis were of small sample size and didn't describe withdrawals or dropouts. Secondly, few studies were included in the analysis of the incidence of CVD, for few related published articles were found, so our meta-analysis may

be affected by publication bias. Thus, more high quality studies were needed to evaluate the efficacy of coadministration therapy on reducing the rate of CVD in patients with diabetic dyslipidemia. Finally, our results showed there was no significant difference between combination therapy and statins monotherapy for reducing the incidence of CVD in patients with diabetic dyslipidemia. However, considering the limited literatures and most of the researches were not focus on dyslipidemia patients who need the combination therapy to prevent CVD and residual atherogenic risk after statins monotherapy, there may be some potential bias. As a result, further study aiming at these patients in need for combination therapy was necessary for a more precise and reliable comparison.

COMMENTS

Background

Statins-fibrates combination therapy has been suggested to be more effective with no more adverse events as the treatment to patients with mixed dyslipidemia than statins or fibrates monotherapy, which may reduce the incidence of cardiovascular diseases (CVD) at the same time. However, it is still unclear of the efficacy and safety of the combined statins-fibrates therapy and their benefits on reducing CVD incidence in patients with dyslipidemia and type 2 diabetes.

Research frontiers

Statins therapy was highly effective at lowering low density lipoprotein cholesterol (LDL-C). However, despite the increasing use of statins as monotherapy for LDL-C reduction, a significant residual cardiovascular risk was still presented in patients with diabetic dyslipidemia. The Fenofibrate Intervention and Event Lowering in Diabetes study was a 5-year, randomized, placebo-controlled trial testing the safety and efficacy of fenofibrate 200 mg in 9795 type 2 diabetic patients. In this trial Fenofibrate failed to alter the primary clinical endpoints significantly. Some researches have shown the efficacy and safety of statins-fibrates combination therapy in patients with mixed dyslipidemia. But no consensus was reached among patients with diabetic dyslipidemia of using the combination therapy.

Innovations and breakthroughs

This meta-analysis included 10 articles and more than 10 thousand patients were contained. Most of the included studies were randomized controlled trials. The authors found that the combination therapy was more effective on lipid modification and well tolerated but there was no significant effect on preventing cardiovascular diseases.

Applications

Statins-fibrates combination therapy may potentially be used for the therapy of diabetic dyslipidemia; however, more high quality studies are required for further estimate of the efficacy of combination therapy on reducing the rate of CVD.

Terminology

Statins are Hydroxymethylglutaryl-coenzyme A reductase inhibitors, which may inhibit HMG-CoA reductase, a precursor to the formation of cholesterol, and up-regulate the LDL-C-receptor. What's more, statins could reduce the hepatic cholesterol synthesis. Fibrates exert their primary effects on lipid metabolism *via* the activation of peroxisome proliferator activated receptor-alpha. It is able to reduce plasma triglyceride levels by inhibiting their synthesis and stimulating their clearance.

Peer review

In this article, Zheng *et al* present evidence that the coadministration of statins and fibrates in the treatment of patients with dyslipidemia and type 2 diabetes was more effective on lipid modification than statins or fibrates monotherapy. They also present evidence that statins-fibrates combination therapy was tolerated as well as statins or fibrates monotherapy. This is an interesting report for the clinical practice. Overall the report appears to be carefully examined and data adequately discussed.

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