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Safety and efficacy of fibrate–statin combination therapy compared to fibrate monotherapy in patients with dyslipidemia: A meta-analysis

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ABSTRACT

Background: Dyslipidemia is a major risk factor for the development of cardiovascular disease. Treatment with fibrate, statins, or other lipid-lowering drugs prevents primary or recurrent cardiovascular events. However, all lipid-lowering drugs have side effects, which may become more severe if combination therapy is prescribed.
Methods: We performed a meta-analysis of published data to compare the safety and efficacy of fibrates alone, compared to fibrate–statin combinations, in patients with dyslipidemia. Six articles were assessed in terms of the efficacy of therapy and nine from the viewpoint of therapeutic safety.
Results: In terms of efficacy, fibrate–statin combinations afforded significantly greater reductions in the levels of total cholesterol (SE = −2.248; 95% CI 1.986–2.510), LDL cholesterol (SE = −2.274; 95% CI 2.015–2.533), and triglycerides (SE = −0.465; 95% CI 0.272–0.658) compared to fibrate alone. In terms of safety, treatment with fibrate alone was associated with a significant decrease in the number of kidney-related adverse events (RR = −0.547; 95% CI 0.368–0.812), compared to treatment with fibrate–statin combinations.
Conclusion: We suggest that treatment with a fibrate–statin combination affords clinical benefits that are superior to treatment with fibrate alone, but increases the risk of side effects (particularly renal). Therapy should thus be carefully monitored.

1. Introduction

Dyslipidemia is an important risk factor for the development of coronary heart disease. The condition should thus be controlled to prevent initial or recurrent heart conditions. Many effective lipid-lowering drugs are available. Of these, a fibric acid derivative (fibrate) is commonly used either alone or in combination with other lipid-lowering drugs. These materials effectively lower the blood levels of triglycerides and high-density lipoprotein (HDL) cholesterol [13]. Combinations of fibrate and statins (which very effectively lower the levels of both total and low-density lipoprotein [LDL] cholesterol) are more efficacious for treating patients with mixed or severe dyslipidemia, associated with extremely high levels of LDL cholesterol or other forms of serum cholesterol, than either type of drug alone [28]. However, combination therapy is associated with an increased risk of adverse events including myopathy and hepatic or renal function problems [22,23,26]. Moreover, drug-related adverse events compromise patient compliance. It is very important for patients with dyslipidemia to not stop taking medication; most such patients are recommended to remain under long-term treatment that may even extend to the entire lifespan.

Statins are chosen firstly to treat dyslipidemia in most patients, but fibrates are recommended as a drug of choice in some patients depending on their lipid levels. Thus safely adding statins to fibrates is an important clinical issue. Recently, many clinical trials have shown that fibrate alone, and statin–fibrate combinations, improve lipid profiles and prevent cardiovascular events. However, the comparative efficacy of fibrate monotherapy and statin–fibrate combination therapy has not yet been evaluated in detail. The safety of combination therapies remains controversial.

Thus, in the present meta-analysis, we reviewed changes in lipid profiles, and the numbers of adverse events, in patients on various forms of lipid-lowering therapy. We integrated efficacy and safety data. The aim of our work was to highlight the advantages and disadvantages of fibrate alone, or statin–fibrate combinations, used to treat patients with dyslipidemia.

2. Methods

2.1. Search strategy

We searched for published works comparing the lipid-lowering effects and safety of statins and fibrates in patients with dyslipidemia. We interrogated online databases, including MEDLINE (OVID and PubMed), EMBASE, and the Cochrane Library. The search terms were

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combinations of the following PubMed MeSH terms and related text terms: *fibric acids*, *fibrates*, *hydroxymethylglutaryl-CoA reductase inhibitors*, *statins*, *dyslipidemias*, and *hyperlipidemias*. The bibliographies of retrieved articles and relevant reviews were searched to identify additional eligible studies. We did not impose any publication or language limitations. The searches were completed on January 25, 2013.

2.2. Study selection

Two authors (HDC and JYL) independently reviewed and selected studies to be evaluated. The inclusion criteria were: (1) the work was a randomized clinical trial that (2) compared the efficacy and safety of fibrates and statins, (3) included measurements of lipid profiles, and (4) described a number of adverse events. Any disagreement in terms of inclusion of an article for evaluation was resolved by consensus (attained via discussion) with a third investigator (WGS). If a trial had been described in more than one report, we extracted data from the most complete account and used the other publications only to clarify those data.

2.3. Data extraction and quality assessment

Detailed reviews of full-text articles were independently conducted by two authors (HDC and BCK). The following data were extracted from each study: the first author's surname; the year of publication; the country in which the work was performed; the number of participants; patient characteristics (type of dyslipidemia, gender, and age); the treatment given (regimen and period); and changes in serum lipid concentrations. The methodological quality of each trial was evaluated by two authors (HDC and JYL) with the aid of the Jadad scale [16]. This scale evaluates randomized controlled trials using five indicators: an adequate description of how randomization was achieved, the appropriateness of the randomization method, an adequate account of how investigators were double-blinded, the appropriateness of the double-blinding method chosen, and details on patient withdrawal and dropout. A score of greater than three was considered to reflect high-quality work. Any disagreement between the two authors was resolved by consensus (attained via discussion) with a third investigator (WGS).

2.4. Efficacy analysis

In terms of evaluation of efficacy, the endpoints of analysis were changes in lipid concentrations, including those of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Each change was calculated as the difference between the baseline and final measurements performed in each study group (i.e., patients treated with fibrates alone or combination fibrate–statin therapies). Each mean change, with a 95% confidence interval (CI), was calculated to allow assessment of the lipid-lowering effects of fibrate monotherapy or combination fibrate–statin therapy.

2.5. Safety

To evaluate treatment safety, we counted the total numbers of adverse events and the numbers of muscle-, liver-, and kidney-related adverse events in each study group, and compared these values between treatments. Relative risk (RR) values and 95% CIs were calculated to compare the frequencies of adverse events associated with the use of fibrate monotherapy or combination fibrate–statin therapy.

2.6. Statistical analysis

Study heterogeneity was assessed using the χ^2 test (employing Q statistics) and quantified by calculating I^2 values [5]. A fixed-effects model (the Mantel–Haenszel method) was used in analysis [21]. The results were compared to those yielded by a random-effects model (the Der Simonian–Laird method) [8].

Sensitivity analyses were performed by excluding, in turn, the contribution of each study to the meta-analysis data. The potential existence of publication bias was examined using the tests of Begg [2] and Egger [10].

All statistical analyses were performed using Comprehensive Meta-analysis Software version 2 (CMA 26526; Biostat, Englewood, NJ). All statistical tests were two-sided and a value of $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Study quality and characteristics

A total of 385 articles were identified by a literature search. After removal of duplicates, the titles and abstracts of 356 articles were screened. Of these, 326 articles were excluded, and the full texts of the remaining 30 articles, and 1 additional article identified upon review of the bibliographies of the 30 articles, were assessed in terms of eligibility. A further 19 articles were excluded, and data from the remaining 12 articles are included in the present meta-analysis. The characteristics of six studies on treatment efficacy are shown in Table 1 and the characteristics of nine studies on safety are shown in Table 2. Three articles conducted both efficacy and safety analysis. Using the Jadad system, only 1 study was classified as of low quality (a score of 2 or less), whereas 11 studies were of high quality (scores of 3 or greater) (details available on request).

3.2. Analysis of efficacy

3.2.1. Total cholesterol

In total, six studies measured changes in total cholesterol levels in 230 patients treated with a fibrate alone and 226 treated with a fibrate–statin combination (Fig. 1A). There were no significant differences in total cholesterol levels between the two groups both at baseline (standard difference in means (SE) = 0.046; 95% CI −0.711 to 0.802). The combination treatment afforded a significantly greater reduction in total cholesterol levels than did treatment with fibrate alone. Data re-analysis using a random-effects model also revealed a significant between-treatment difference.

3.2.2. LDL cholesterol

In total, six studies assessed changes in LDL cholesterol levels in 230 patients treated with a fibrate alone and 226 treated with a fibrate–statin combination (Fig. 1B). There were no significant differences in LDL cholesterol levels between the two groups both at baseline (SE = 0.246; 95% CI −0.286 to 0.778). The combination treatment afforded a significantly greater reduction in LDL cholesterol levels than did treatment with fibrate alone. Data re-analysis using a random-effects model also revealed a significant between-treatment difference.

3.2.3. HDL cholesterol

In total, six studies assessed changes in HDL cholesterol levels in 230 patients treated with a fibrate alone and 226 treated with a fibrate–statin combination (Fig. 1C). There were no significant differences in HDL cholesterol levels between the two groups both at baseline (SE = −0.651; 95% CI −1.509 to 0.207). The combination treatment afforded a significantly greater reduction in HDL cholesterol levels than did treatment with fibrate alone. However, re-analysis using a random-effects model showed that the difference was not significant (SE = 0.393; 95% CI −0.047 to 0.834).

3.2.4. Triglycerides

In total, five studies assessed changes in triglyceride levels in 216 patients treated with a fibrate alone and 212 treated with a fibrate–statin