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Head-to-head comparison of statins versus fibrates in reducing plasma fibrinogen concentrations: A systematic review and meta-analysis

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ABSTRACT

Background: Several studies suggest differences between fibrates and statins in lowering plasma fibrinogen (Fib) concentrations, but the evidence is not definitive. Therefore, the aim of this meta-analysis of head-to-head randomized trials was to compare the efficacy of statins and fibrates on plasma Fib concentrations.

Methods: The literature search included Medline, Scopus, and Web of Science up to February 1st, 2015, to identify head-to-head comparative randomized trials investigating the efficacy of fibrates vs statins on plasma Fib concentrations.

Results: In total 22 trials with 2762 participants were included to the meta-analysis. Random-effect meta-analysis suggested a significantly greater effect of fibrates vs statins in lowering plasma Fib concentrations (weighted mean difference [WMD]: −40.7 mg/dL, 95% confidence interval [CI]: −55.2, −26.3, $p < 0.001$). When the analysis was stratified according to the type of fibrate administered, there were significant Fib-lowering effects with both bezafibrate ($n = 8$ treatment arms; WMD: −23.7 mg/dL, 95% CI: −41.8, −5.7, $p = 0.01$) and fenofibrate ($n = 15$ treatment arms; WMD: −43.7 mg/dL, 95% CI: −61.3, −26.2, $p < 0.001$).

Abbreviations: ACS, acute coronary syndrome; ACC, American College of Cardiology; AHA, American Heart Association; BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; CRP, C-reactive protein; Fib, fibrinogen; HDL-C, high-density lipoprotein cholesterol; ICAM−1, intercellular adhesion molecule 1; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MCP-1, monocyte chemoattractant protein-1; NICE, National Institute for Health and Clinical Excellence; PAI-1, plasminogen activator inhibitor-1; PPAR-α, peroxisome proliferator-activated receptor-α; SD, standard deviation; SEM, standard error of the mean; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor alpha; VCAM−1, vascular cell adhesion molecule 1; WMD, weighed mean difference.

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Overall, there was a numerically greater effect in the subgroup of trials with ≥12 weeks duration ($n = 17$ treatment arms; WMD: −42.7 mg/dL, 95% CI: −60.3, −25.1, $p < 0.001$) compared with the subgroup of trials lasting <12 weeks ($n = 7$ treatment arms; WMD: −36.7 mg/dL, 95% CI: −52.0, −21.4, $p < 0.001$).
Conclusions: Monotherapy with either fibrates or statins suggested a significantly greater effect of fibrates in lowering plasma Fib concentrations. According to these findings, mechanisms associated with fibrinogen metabolism might be responsible for the distinct effects of statins and fibrates in reducing cardiovascular endpoints.

1. Introduction

Statins are potent lipid lowering agents [1]. Their therapeutic benefits in reducing cardiovascular (CV) risk may be, at least in part, due to effects, which are independent of their effect on cholesterol metabolism [2,3]. Thus, statins increase nitric oxide bioavailability, stabilize atherosclerotic plaques, regulate angiogenesis, decrease the inflammatory response and decrease prothrombotic processes [4,5]. Experimental studies and clinical trials have also reported that statins decrease the activity of the blood coagulation cascade at various levels, as a consequence of reduced tissue factor expression with consequently decreased thrombin release, increased endothelial thrombomodulin expression with successive inactivation of factor Va and activation of protein C, and attenuation of pro-coagulant reactions catalysed by thrombin like activation of factors V and XIII and fibrinogen cleavage [6]. In contrast, in the Multi-Ethnic Study of Atherosclerosis (MESA) study, healthy statin users without clinical cardiovascular disease (CVD), had marginally higher (2%) fibrinogen (Fib) and plasminogen activator inhibitor-1 (PAI-1) (22%) concentrations compared with non-users [7]. An antiplatelet effect has also been reported with statin use [8].

Fibrates are lipid-lowering drugs and peroxisome proliferator-activated receptor-α (PPAR-α) agonists, which induce expression and catabolism of apolipoproteins and lipoproteins and transcription of genes linked to peroxisomal β-oxidation of fatty acids [9]. Fibrates have also been shown to improve blood coagulation and fibrinolytic function by lowering PAI-1 and Fib levels [10]. In addition, fibrates exhibit effects on vascular inflammation, decreasing vascular cell adhesion molecule 1 (VCAM^{-}1), intercellular adhesion molecule 1 (ICAM^{-}1), C-reactive protein (CRP), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor alpha(TNF-α) levels [11,12].

There is an ongoing debate as to whether the pleiotropic effects of statins are lipid lowering independent or are associated with the significant fall in low density lipoprotein cholesterol (LDL-C) levels and in consequence, decrease inflammation and oxidative stress, as well as stabilizing plaques [13,14]. Another widely discussed issue is the role of fibrates in high-risk patients (e.g., with diabetes), especially after publication of the American College of Cardiology (ACC)/American Heart Association (AHA) lipid guidelines (2013) and the National Institute for Health and Clinical Excellence (NICE) (2014) recommendation which do not suggest fibrate therapy in these patients [15–17]. Taking into account these debates as well as the evidence indicating differences between fibrates and statins, we carried out a meta-analysis of randomized head-to-head trials to compare the effect of fibrates vs statins on plasma Fib concentrations.

2. Methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [18]. SCOPUS (http://www.scopus.com), Medline (http://www.ncbi.nlm.nih.gov/pubmed), and Web of Science (http://apps.webofknowledge.com) databases were searched using the following search terms in titles and abstracts: (fenofibrate OR bezafibrate OR ciprofibrate OR clofibrate OR gemfibrozil OR fibrates OR "fibrate therapy") AND (atorvastatin OR simvastatin OR fluvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR lovastatin OR cerivastatin OR statins OR "statin therapy") AND fibrinogen. The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in humans. The literature was searched from inception to February 1st, 2015. Two reviewers (AS and CS) evaluated each article separately. Disagreements were resolved by discussion with a third party (MB).

2.2. Study selection

Original studies were included if they met the following criteria: (i) a clinical trial with either parallel or cross-over design, (ii) investigating the impact of a statin vs a fibrate, or either of these agents, vs combination therapy on plasma/serum concentrations of Fib, (iii) presentation of sufficient information on Fib concentrations at baseline and at the end of follow-up in each group or providing the net change values.

Exclusion criteria were: (i) non-interventional studies, (ii) trials in which the combination therapy arm included a different statin or fibrate component than that in the monotherapy arm, (iii) trials in which the combination therapy arm included a statin or fibrate component with a dose different from that used in the monotherapy arm, and, (iv) lack of sufficient information on baseline or follow-up Fib concentrations.

2.3. Data extraction

Eligible studies were reviewed and the following data were abstracted: (1) first author's name, (2) year of publication, (3) study location, (4) study design, (5) number of participants in the statin, statin with fibrates, fibrates and control (in case of randomized design) groups, (5) age, gender and body mass index (BMI) of study participants, (6) baseline levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, high-sensitivity CRP (hsCRP) and glucose, (7) systolic and diastolic blood pressures, and, (8) data regarding baseline and follow-up concentrations of Fib.

2.4. Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [19]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding of subjects and personnel, blinding of outcome assessment, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the