European Atherosclerosis Journal
www.eathj.org
EAJ 2023;3:44-49
https://doi.org/10.56095/eaj.v2i3.55

Is there still a place for fenofibrate-statin combination therapy?

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Keywords
Fibrates; fenofibrate; PPARα; combination therapy; triglycerides; atherogenic dyslipidaemia

ABSTRACT

Although low-density lipoprotein cholesterol (LDL-C) is the main target for the prevention of atherosclerotic cardiovascular disease (ASCVD), hypertriglyceridaemia (HTG), a common condition characterised by elevated blood triglyceride (TG) levels, contributes to residual cardiovascular risk independently of LDL-C levels. Elevated TG levels are a feature of atherogenic dyslipidaemia, which also includes low HDL-C levels and high levels of atherogenic small, dense LDL, together with accumulation of atherogenic remnant particles.

Treatment of HTG includes lifestyle interventions, but these are not always sufficient to significantly reduce TG levels in people at high cardiovascular risk. Current guidelines for the treatment of dyslipidaemias recommend the use of statins as the first choice in people with HTG (TG >200 mg/dL) and high CV risk, and consideration of the use of specific TG-lowering drugs, such as fenofibrate, bezafibrate or icosapent ethyl if HTG persists.

Fenofibrate acts by activating the peroxisome proliferator receptor alpha (PPARα), a nuclear receptor that plays an important role in lipid and lipoprotein metabolism, glucose homeostasis and inflammation. Several clinical trials have shown that fibrates may reduce the incidence of major cardiovascular events only in patients with high TG levels and low HDL-C levels, a finding that was also observed with fenofibrate in combination with a statin compared to statin therapy alone. The recent failure of the PROMINENT trial with pemafibrate in combination with a statin highlighted the notion that treatment with fibrates provides a clinical benefit only if they lower apoB levels.

Received 1 December 2023; accepted 21 December 2023

Introduction

Low-density lipoprotein cholesterol (LDL-C) is a causal factor for atherosclerotic cardiovascular disease (ASCVD) and is the main target for ASCVD prevention [1]. Although several drugs are available that effectively lower LDL-C levels, many patients continue to experience cardiovascular events even when their LDL-C is at goal. Many factors contribute to the residual CV risk beyond LDL-C levels, including hypertriglyceridaemia (HTG) [2].

HTG is a common condition characterised by elevated levels of triglycerides (TG) in the blood. TG are energy-storage molecules made up of glycerol and fatty acids. They are stored in adipose tissue until they are needed. In the blood, TG are transported via lipoproteins, and in particular via TG-rich lipoproteins, which include very-low-density lipoproteins (VLDL), chylomicrons and their remnants. The remnants originate from partial lipolysis mediated by lipoprotein lipase, are TG-depleted and cholesterol-enriched compared to their naïve counterparts and are highly atherogenic [2]. The most important apolipoprotein of TG-rich lipoproteins is apolipoprotein B (apoB), which present in one copy per particle.

The main causes of HTG are an unbalanced diet, being overweight or obese, metabolic syndrome, excessive alcohol consumption, taking certain medications and genetics. Elevated levels of TG are a feature of the so-called atherogenic dyslipidaemia, which is also characterized by low levels of HDL-C and high levels of small dense LDL. A common feature in atherogenic dyslipidaemia is an increase of either apoB or non-HDL-cholesterol, both parameters reflecting the global number of atherogenic lipoproteins. Atherogenic dyslip-

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idaemia is associated with an increased CV risk [3] and severe HTG (TG levels >500 mg/dL) can lead to acute pancreatitis, a potentially life-threatening condition.

Treatment for HTG includes dietary changes, weight control, increasing physical activity and reducing alcohol consumption. However, these approaches are not always sufficient to significantly reduce TG, especially in people at high CV risk, who may need specific drugs to lower TG levels and reduce CV risk. The most common drugs used to control HTG are fibrates and omega-3 polyunsaturated fatty acids. However, these drugs can be ineffective for severe HTG, which requires specific treatments to massively reduce TG levels.

Fibrates include clofibrate (the first drug developed, which is no longer available due to the increased risk of adverse effects), gemfibrozil, fenofibrate, bezafibrate, ciprofibrate and the most recent pemafibrate. These molecules work by activating the peroxisome proliferator receptor alpha (PPARα). PPARα belongs to the nuclear receptor superfamily and plays an important role in physiological processes such as lipid and lipoprotein metabolism, glucose homeostasis and inflammation [4]. Activated PPARα forms a heterodimer with another nuclear receptor, the retinoid X receptor, which binds to specific peroxisome proliferator response elements, resulting in either activation or inhibition of several genes involved in lipid metabolism. This in turn leads to a decrease in TG and an increase in HDL-C levels, with the efficiency depending on the molecule and the baseline lipid levels. Activation of PPARα leads to the stimulation of fatty acid oxidation, an increase in lipoprotein lipase (LPL) synthesis and a decrease in apoC-III expression, resulting in increased lipolysis and improved clearance of TG-rich lipoproteins. Fibrates also stimulate lipolysis in adipose tissue, releasing fatty acids into the bloodstream. Finally, fibrates reduce the hepatic synthesis of TG by inhibiting the enzymatic activity of diacylglycerol acyltransferase (DGAT), a key enzyme in TG synthesis. In addition to lowering triglycerides, fibrates can also increase levels of HDL-C. The increase in HDL-C results from the PPARα-mediated stimulation of the expression of apo A-I and apo A-II and a reduction in the activity of the cholesteryl ester transfer protein (CETP), which transfers cholesterol from HDL to VLDL in exchange for TG.

Current guidelines for the treatment of dyslipidaemias recommend the use of statins as the first choice to reduce CVD risk in HTG individuals (TG >200 mg/dL) at high CV risk [5]. In high-risk or very-high-risk patients who have high TG levels (135-499 mg/dL) despite statin treatment, icosapent ethyl in combination with a statin should be considered [5]. Fenofibrate or bezafibrate may be considered in combination with a statin in patients in primary prevention or in high-risk patients with LDL-C at goal and TG >200 mg/dL [5]. Of note, in the recently released 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes the use of fibrates is no longer considered to manage elevated TG levels in these patients due to the little benefit demonstrated in RCTs, aside from sub-group analysis including subjects with very high TG levels [6].

Fenofibrate

Fenofibrate is by far the most commonly used fibrate in clinical practice. Fenofibrate is a pro-drug that is converted in the liver to the pharmacologically active metabolite fenofibric acid. Following oral administration, fenofibrate is rapidly absorbed; the extent of absorption ranges from 30-50% when the drug is taken in a fasting state to 60-90% when administered after a meal [7]. Fenofibrate does not accumulate with repeated administration, and fenofibric acid is >99% bound to plasma albumin. It is excreted mainly as fenofibric acid and its glucuronide conjugate in the urine, with smaller amounts excreted in the faeces [8].

While gemfibrozil inhibits hepatic uptake of statins through OATP1B1 and competes for the same glucuronosyltransferases that metabolise most statins, determining a clinically relevant drug -drug interaction, fenofibrate is glucuronidated by enzymes not involved in the glucuronidation of statins. Therefore, fenofibrate-statin combinations are less likely to cause myopathy than combination therapy with gemfibrozil and statins. In fact, co-administration of fenofibrate and atorvastatin, for instance, did not result in relevant clinical-pharmacokinetic drug interactions in healthy subjects [9].

Evidence from cardiovascular endpoint trials

Clinical trials with fibrates have provided conflicting results. In the Helsinki Heart Study (HHS) primary prevention trial, 4,081 asymptomatic middle-aged men (40-55 years) with primary dyslipidaemia (non-HDL-C ≥200 mg/dL) without CVD were treated with gemfibrozil or placebo [10]. Gemfibrozil lowered total cholesterol, LDL-C, non-HDL-C and TG, while it increased HDL-C. After 5 years, a 34% reduction in the primary endpoint (fatal and non-fatal myocardial infarction (MI) and cardiac death) was observed in the gemfibrozil group compared with placebo [10]. In the subgroup of patients with TG >2.3 mmol/L and LDL-C/HDL-C ≤5 the benefit was even greater (71% risk reduction) [11]. The benefit of gemfibrozil was confirmed in a secondary prevention trial in men with low HDL-C, with a 22% reduction in the primary endpoint (non-fatal MI or coronary death) [12]. However, two subsequent trials with bezafibrate, the BIP and LEADER trials, could not confirm this positive effect on the primary endpoint in the overall population [13, 14]. Of note, the Bezafibrate Infarction Prevention (BIP) trial reported a 41.8% reduction in the primary endpoint in the subgroup of patients with high TG and low HDL-C levels [13] and reduced the incidence of myocardial infarction in patients with metabolic syndrome during long-term follow-up (6.2 years for events and 8.1 years for mortality data) [15]. In addition, a 40% reduction in the secondary endpoint of non-fatal CHD events was observed in patients aged <65 years in the Lower Extremity Arterial Disease Event Reduction (LEADER) trial testing bezafibrate in patients with peripheral artery disease (PAD) [14].

The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) was the first cardiovascular outcomes trial of fenofibrate [16]. Patients with type 2 diabetes mellitus who were not taking statins at baseline were treated with fenofibrate or placebo. Fenofibrate did not reduce the risk for the primary endpoint (first occurrence of non-fatal myocardial infarction or death from coronary heart disease), but it did reduce the risk for total CVD events (HR 0.89 [0.80-0.99], P=0.035) and coronary revascularisation (HR 0.79 [0.68-0.93], P=0.003) [16]. It should be noted that in this trial, patients in the placebo group were significantly more likely to take statins than patients in the fenofibrate group (36% vs 19%), which may have reduced the expected effect of fenofibrate. The effect of fenofibrate in the subgroup of patients with marked dyslipidaemia (TG >2.3 mmol/L and lower HDL-C) was significant (HR 0.73 [95% CI 0.58-0.91], P=0.005) [17]. The subsequent outcome trial of fenofibrate, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid, investigated the effect of fenofibrate or placebo in addition to simvastatin in patients with type 2 diabetes [18]. After a mean follow-up of 4.7 years, the combination of fenofibrate and simvastatin did not reduce the rate of the primary endpoint (first occurrence of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes) compared to simvastatin alone [18]. However, in the prespecified subgroup of patients with low HDL-C (≤34 mg/dL) and high TG levels (≥204 mg/dL) fenofibrate therapy resulted in a significant 31% risk reduction [19], which is consistent with the

results of post-hoc subgroup analyses in other fibrate trials [11, 13, 17]. It is worth noting that variants in the *PPARα* gene can influence the response to fenofibrate in patients with type 2 diabetes [20].

The ACCORDION study was a post-trial follow-up of the participants (90%) of the ACCORD Lipid study. The mean overall duration of follow-up was 7.7 years for the primary outcome and 9.1 years for all-cause mortality [21, 22]. This extended follow-up confirmed the neutrality of fenofibrate in the overall study cohort, but the incidence of the primary endpoint was 27% lower in patients with atherogenic dyslipidaemia, which is consistent with the results of the original ACCORD trial [21]. A secondary analysis of trial and post-trial data in patients who had atherogenic dyslipidaemia of the ACCORDION study showed that treatment with fenofibrate during the initial trial period was associated with a legacy benefit of improved survival over the post-trial follow-up, an effect that was observed despite similar achieved lipid levels during the follow-up [22]. These findings support the use of fibrates as an add-on to statins to reduce CV risk in diabetic patients with atherogenic dyslipidaemia.

Putative explanations for the different clinical outcomes between fenofibrate and pemafibrate

The clinical efficacy of a new selective PPAR-alpha modulator, pemafibrate, has been evaluated in the PROMINENT trial conducted in patients with type 2 diabetes, mild to moderate HTG and low HDL-C [23]. More than 95% of patients were on background statin therapy at baseline. Despite significant reductions in TG (26.2%), VLDL-C (25.8%) and remnant cholesterol (25.6%), the incidence of major adverse cardiovascular events (a composite of myocardial infarction, ischemic stroke, hospitalization for unstable angina warranting unplanned coronary revascularization, or death from cardiovascular causes) was similar in patients treated with pemafibrate or placebo [23]. Both LDL-C and apoB were significantly increased after pemafibrate therapy [23].

What possible explanations are there for this difference in the effect of fenofibrate and pemafibrate? Some studies contain information that could help explain this difference, particularly with regard to the different effects on atherogenic lipid parameters, including apoB, LDL-C and sd-LDL. A phase 3 study compared the efficacy and safety of pemafibrate with fenofibrate in Japanese patients with high TG and low HDL-C levels [24]. Pemafibrate 0.4 mg/day and fenofibrate 200 mg/day -the usual doses of these two drugs- produced similar reductions in TG levels and remnant cholesterol [24]. Both drugs caused an increase in LDL-C, but this was greater with pemafibrate than with fenofibrate (+19.3% versus +6.6%, p=0.001). ApoB levels were slightly increased with pemafibrate treatment while decreasing with fenofibrate (+3.2% versus -7.3%, p<0.001) [24]. It is noteworthy that diabetic patients who received the fenofibrate/simvastatin combination therapy showed no increase in LDL-C levels in the ACCORD Lipid trial [18].

The deleterious effect of pemafibrate 0.4 mg/day was confirmed in European patients with high TG and low HDL-C on statin therapy [24]: pemafibrate 0.4 mg/day (twice daily) increased LDL-C by 20.5% (p<0.001 versus placebo) and no significant effect was observed in either apoB or non-HDL-C levels [24]. So the increase in LDL-C was largely due to an increased amount of cholesterol per particle rather than an increase in LDL particle number, as demonstrated by ion mobility analyses, which showed that pemafibrate increased the concentration of large LDL particles and decreased the concentration of small dense LDL particles [25], consistent with other observations [26].

The results of a meta-analysis of three randomised clinical trials have suggested that pemafibrate is more effective than fenofibrate in in reducing TG-rich lipoproteins [27]. Indeed, pemafibrate reduced more TG, VLDL-C, remnant cholesterol, apoB48 and apoC-III and increased more HDL-C and apoA-I compared with fenofibrate [27]. However, the dose of fenofibrate was only 100 mg daily in these trials. No significant difference in non-HDL-C and apoB levels was observed between the two groups, and a slight LDL-C-increasing effect was observed in the pemafibrate group, which is consistent with previous observations [27]. A more-in-depth analysis showed that LDL-C levels increased in patients with higher baseline TG levels and lower baseline LDL-C levels [26], which is likely explained by the effect of pemafibrate on TG-rich lipoprotein catabolism, leading to increased conversion of VLDL to LDL and a change in LDL composition. However, when calculating the levels of small dense LDL in the PROMINENT study, no difference was found between the pemafibrate and placebo groups [28], suggesting that the influence of TG on small LDL-C levels is attenuated when LDL-C is tightly controlled [29].

Overall, these observations suggest that the effect on apoB levels rather than the TG-lowering efficacy may be crucial for the potential beneficial effect of a fibrate-based therapy, together with the choice of the right type of patient to be treated, potentially with regard to PPAR-α gene polymorphisms modulating response to (feno)fibrate.

Meta-analyses of fibrate trials

A meta-analysis of 18 trials with 45,058 participants showed that fibrate therapy resulted in a 10% relative risk reduction for major CV events and a 13% relative risk reduction for coronary events, but had no effect on stroke, all-cause mortality, CV mortality, sudden death, or non-CV mortality [30]. Overall, fibrates lowered total cholesterol, LDL-C and TG levels and increased HDL-C levels, with gemfibrozil being the most effective [30]. Patients with higher baseline TG levels (≥2.0 mmol/L) appeared to benefit more from fibrate therapy [30]. The beneficial effect on CV risk in individuals with atherogenic dyslipidaemia was noted in the meta-analysis of data from 6 trials with more than 25,000 participants [31]. While fibrate therapy did not reduce the rate of vascular events in 9,872 subjects with neither high TG nor low HDL-C, a significant benefit was observed in 5,068 subjects with high TG and low HDL-C, with a relative risk reduction of 29% (RR 0.71, [0.62-0.82], P<0.001) [31]. It is worth noting that benefit was also observed in 7,389 subjects with high TG and in 15,303 subjects with low HDL-C (RR 0.84, 95% CI 0.77 to 0.91, P<0.001) [31]. Another meta-analysis of 5 trials of fibrates found similar results: a significant protective effect was observed in patients with high TG levels or atherogenic dyslipidaemia, in whom fibrates reduced CV risk by 28% (15% to 39%; P < 0.001) and 30% (19% to 40%, P <0.0001), respectively, but only by 6% (−2% to 13%, P=0.13) in patients without atherogenic dyslipidaemia [32].

Fenofibrate and statins combination therapy

The rationale for using a combination therapy is that it provides complementary mechanisms of action on lipid metabolism, leading to a better improvement in the lipid profile. Monotherapy with high intensity statins can lead to greater improvements not only in LDL-C but also in TG; however, this type of approach still does not correct all the lipoprotein abnormalities in patients with combined hyperlipidaemia. On the other hand, fibrates significantly reduce TG-rich lipoproteins, as well as the LDL fraction of small, dense particles. Fibrates and statins thus regulate serum lipids by different mechanisms, so that combination therapy could offer desirable advantages in patients with combined hyperlipidaemia, at least if this combination therapy produces a complementary reduction in the total

number of atherogenic lipoproteins, i.e. a reduction in apoB levels, compared with statin monotherapy.

As mentioned above, the ACCORD Lipid trial showed that the combination fenofibrate/simvastatin did not reduce the rate of major adverse cardiovascular events compared to simvastatin alone [18], although a positive effect was observed in the subgroup of patients with elevated TG levels and low HDL-C levels [18, 19]. The DIACOR (Diabetes and Combined Lipid Therapy Regimen) study investigated the effect of simvastatin/fenofibrate combination therapy on inflammatory biomarkers in patients with diabetes [33]. The combination was not superior to monotherapies in modulating inflammatory biomarkers, while the overall lipid profile was better [33]. Similar results were observed in the SAFARI trial, in which the combination fenofibrate/simvastatin 160/20 mg improved the lipid levels more than simvastatin 20 mg alone in patients with combined hyperlipidaemia, especially a 10% complementary decrease in apoB levels [34]. Two doses of the fixed dose combination (FDC) fenofibrate/simvastatin were compared for efficacy and safety with the monotherapies in patients at high CV risk and with mixed dyslipidaemia [35]. After 12 weeks, both FDC doses significantly reduced TG and increased HDL-C levels compared with simvastatin; LDL-C levels were not increased as instead observed with fenofibrate alone; non-HDL-C and apoB decreased with both FDC doses [35].

The effect of a FDC of fenofibrate 100 mg and atorvastatin 40 mg has been investigated in adults with mixed dyslipidaemia [36]. The FDC was more effective in lowering TG and non-HDL-C (-49.1% and -44.8%, respectively) than monotherapies with atorvastatin 40 mg (-28.9% and -40.2%, respectively) or fenofibrate 145 mg (-27.8% and -16.1%, respectively) [36]. As expected, the decrease in LDL-C was significantly greater in the FDC group than in the fenofibrate 145 mg monotherapy group (–42.3% versus –13.9%; $P < 0.001$) but was not significantly different from the decrease in the atorvastatin monotherapy group (–43.1%; n.s.). However, the decrease in apoB levels was significantly greater with the FDC than with atorvastatin 40 mg monotherapy (-40.5% versus -35.7%, respectively, p=0.046) [36]. This treatment was generally well tolerated and argued for the use of the combination to better control the lipid profile.

The co-administration of rosuvastatin 10 mg or 20 mg with fenofibric acid was more effective in reducing TG levels and increasing HDL-C levels compared to rosuvastatin monotherapy in patients with mixed dyslipidaemia, while LDL-C lowering was comparable [37]. Combination therapy with rosuvastatin 10 mg led to a greater reduction in non-HDL-C and apoB than rosuvastatin alone (non-HDL-C: -44.7% versus -39.8%, p<0.001; apoB: -39.2% versus -34.1%, p<0.001). However, no differences were observed for the same parameters between combination therapy with rosuvastatin 20mg and rosuvastatin 20 mg monotherapy groups [37]. The fixed-dose combination of rosuvastatin and fenofibric acid (20 mg/135 mg, 10 mg/135 mg, and 5 mg/135 mg) was compared with simvastatin 40 mg in 474 patients with high levels of LDL-C and TG [38]. A greater reduction in LDL-C levels was observed in patients treated with all doses of the rosuvastatin/fenofibric acid combination than with simvastatin alone [38]. All other biochemical parameters (including non-HDL-C, apoB, TG, HDL-C and hs-CRP) were improved more by the combination [38], and side effects were comparable between groups.

A study comparing the non-lipid effects of rosuvastatin-fenofibrate (160 mg/10 mg) combination with rosuvastatin monotherapy (10 mg) in high-risk Asian patients with mixed hyperlipidaemia showed that the incidence of muscle or liver enzyme elevations were similar in the two groups (2.8% and 3.9% in the combination and rosuvastatin groups, respectively, p = 1.00) over a 24-week treatment period [39]. Overall, the proportion of patients experiencing adverse events was comparable in both groups [39]. Higher elevations of homocysteine, blood urea nitrogen, and serum creatinine and a greater reduction in leukocyte and haemoglobin levels were observed in the combination group [39], which may indicate cautious use in individuals with renal dysfunction.

A fixed-dose combination of fenofibrate and pravastatin (160 mg and 40 mg) was given to high-risk patients with mixed hyperlipidaemia for 12 weeks. Compared to pravastatin alone, greater reductions in non-HDL-C, LDL-C, TG and apoB were observed, with comparable incidences of adverse events [40]. This FDC therapy was shown to be effective and safe over a 52-week period and resulted in greater reductions in lipid levels than pravastatin 40 mg in a group of high-risk hyperlipidaemic patients [41].

Altogether, the results of clinical trials suggest that the combination of fenofibrate with a statin is effective in improving atherogenic dyslipidaemia, especially in terms of complementary decrease in apoB levels, and may provide clinical benefit in patients with elevated TG levels and low HDL-C levels. The presence of a statin in the combination ensures the reduction in LDL-C essential to reduce the CV risk. Of note, the effect is similar for all statins (class effect), and thus similar benefits can be expected regardless of which statin is used in combination with fenofibrate. Since fenofibrate appears to provide significant microvascular benefits in patients with type 2 diabetes, specifically a reduction of the progression of diabetic retinopathy [42, 43], the combination of fenofibrate with a statin may be a valuable tool for these patients; despite this consideration, fibrates are no longer recommended in the recently released 2023 ESC guidelines for the management of CVD in diabetic patients [6].

Conclusions

Fibrates have been in use for many decades and have proven effective and safe treatments of atherogenic dyslipidaemia. Their current position in the management lies primarily in combination with a statin. Most data documenting efficacy and safety of statin-fibrate combinations come from fenofibrate/fenofibric acid. Beneficial anti-atherogenic effects of the combination regimens are linked with ApoB reductions [44] that have been achieved in a number of trials of fenofibrate and statin combinations. Pharmacological differences between fenofibrate and pemafibrate, the latter associated with ApoB increase in the PROMINENT trial, might explain the observed lack of clinical benefits in contrast to fenofibrate.

Funding

The authors received no financial support for the authorship and/or publication of this article.

Authorship and author contribution statement

ALC Writing - original draft, writing – review & editing; MF and MV Writing – review & editing.

Acknowledgements

The work of MV is supported in part by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, Project No. LX22NPO5104) - Funded by the European Union - Next Generation EU. The work of ALC is supported in part by Ministero della Salute Ricerca Corrente to MultiMedica.

Competing interests

MF has received consulting or lecture fees and/or honoraria from Abbott, Amarin, Amgen, AstraZeneca, Ajanta, Kowa, Merck and Co, Novartis, Organon, Pfizer, Recordati, Sanofi/Regeneron, Servier, SMB, Ultragenyx and Viatris, outside the submitted work;

MV has received honoraria, lecture fees, or research grants from Amgen, Astrazeneca, Bayer, Eli Lilly, Ionis Pharmaceutical, Krka, Merck, Novartis, Pfizer, Recordati, Regeneron, Sanofi, Viatris and Zentiva, outside the submitted work.; ALC has received honoraria, lecture fees, or research grants from Aegerion, Amgen, Amryt, Astrazeneca, Bayer, Daiichi-Sankyo, Eli Lilly, Genzyme, Ionis Pharmaceutical, Kowa, Mediolanum, Medscape, Menarini, Merck, Mylan, Novartis, PeerVoice, Pfizer, Recordati, Regeneron, Sanofi, Sigma-Tau, and The Corpus, outside the submitted work.

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