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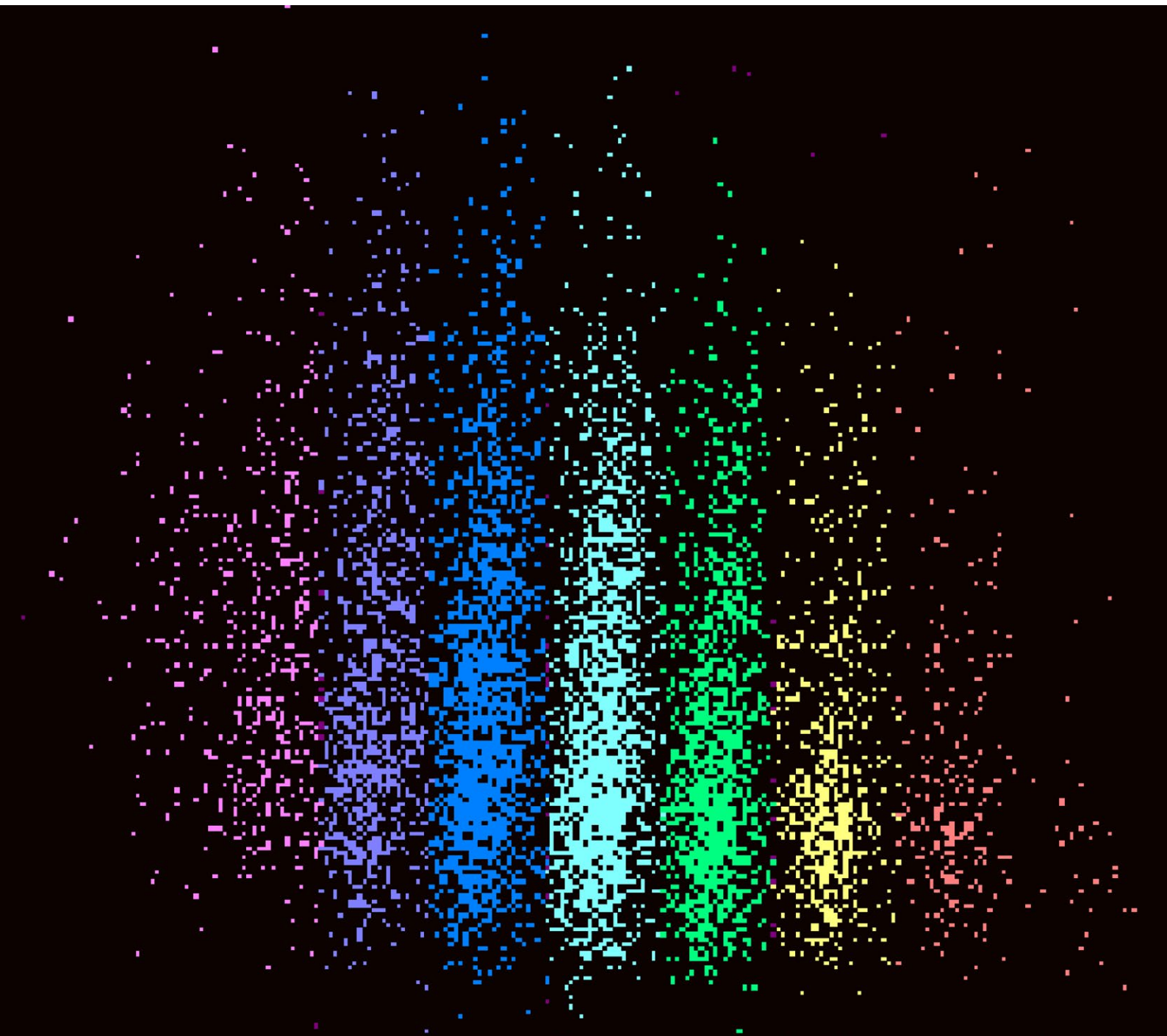

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Contents

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European Atherosclerosis Journal

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

Michel Farnier[1], Michal Vrablik[2], Alberico Luigi Catapano[3,4]

[1]*Physiopathology and Epidemiology Cerebro-Cardiovascular (PEC2), University of Burgundy and Franche Comté, Dijon, France*

[2]*Third Department of Medicine-Department of Endocrinology and Metabolism of the First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic*

[3]*IRCCS MultiMedica, Sesto S. Giovanni, Milan, Italy*

[4]*Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy*

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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.

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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-

Corresponding Author
Alberico L. Catapano: alberico.catapano@multimedica.it | alberico.catapano@gmail.com

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.

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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;

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The XVII National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITeCS)

Sining Xie[1], Manuela Casula[1,2], Federica Galimberti[2], Alberto Corsini[3], Alberico L. Catapano[1,2]

[1]*Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy*

[2]*IRCCS MultiMedica, Sesto San Giovanni (MI), Italy*

[3]*Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy*

CONFERENCE REPORT

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The XVII National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITeCS) was held in Milan on October 12-14, 2023. As is now customary, the Congress was organised in collaboration with the Italian Society for the Study of Atherosclerosis (SISA) Lombardy Region. The Congress included a discussion of the most recent evidence or the most topical issues in clinical and pharmacological research as well as presentations of scientific work by young researchers.

The first session focused on novel lipid-lowering therapies (LLTs) for the prevention of atherosclerotic cardiovascular diseases (ASCVD). Previous evidence has confirmed that the key initiating event in atherogenesis is the retention of low-density lipoprotein cholesterol (LDL-C) and other cholesterol-rich apolipoprotein-B (apoB)-containing lipoproteins within the arterial wall. Professor Giulia Chiesa emphasized the importance of LDL-C and thoroughly discussed the genetic disorders associated with abnormally elevated LDL-C levels, such as homozygous familial hypercholesterolaemia (HoFH). From a genetic perspective, she outlined the traits of mutations in HoFH patients and the status of treatments. Professor Alberto Corsini then presented the existing and novel LLTs and re-emphasized the importance of aggressive LDL-C lowering. Elevated levels of LDL-C remain one of the most closely related markers of ASCVD and a major modifiable risk factor. The combination of statins or bempedoic acid with ezetimibe could result in a greater reduction in LDL-C levels. Clinical trials for the following new lipid-lowering agents are currently underway: inclisiran [small interfering RNA (siRNA)] and MK-0616 (oral agent) as new inhibitors of the proprotein convertase subtilisin/kexin type 9 (PCSK9), obicetrapib as a new inhibitor of cholesterol ester transfer protein (CETP), pelacarsen and olpasiran as new treatments to lower lipoprotein(a) [Lp(a)] levels.

In the session dedicated to genetic dyslipidaemias, Professor Manuela Casula presented the pathology of familial hypercholesterolemia (FH) and described the virtuous example of LIPIGEN. LIPIGEN (LIpid transPort disorder Italian GEnetic Network) was established in 2009 by the Italian Atherosclerosis Society (*Società Italiana per lo Studio dell'Aterosclerosi - SISA*) through its Foundation (*Fondazione SISA*) to promote and facilitate the clinical and genetic diagnosis of familial dyslipidaemias. To date, the network involves more than 50 Italian centres specialized in the management of patients affected by primary dyslipidaemias throughout the national territory, including paediatric clinics and LDL apheresis centres. The LIPIGEN Network structure is based on close interaction between clinical centres, general practitioners and patient organisations. The main objectives are to create a structured nationwide network to identify patients with genetic dyslipidaemias, facilitate molecular genetic testing and promote research in this field. This initiative also aims to raise awareness and culture of the medical community, patients and regulatory authorities in our country in the area of genetic dyslipidaemias and encourage the exchange of information and knowledge in accordance with the recommendations of scientific societies. The clinical activity of the centres is complemented by the work of specialized genetic laboratories. Based on the European Atherosclerosis Society (EAS) consensus statement on HoFH, Dr Maria Grazia Zenti explained the genetic complexity, prevalence and global registries of HoFH, presented the updated criteria for clinical diagnosis and recom-

Corresponding Author
Sining Xie: sining.xie@unimi.it

mended giving priority to phenotypic features over genotype. Dr Laura D'Erasmo then gave an overview of the evidence on hypertriglyceridaemia. She pointed out that severe hypertriglyceridemia is primarily multigenetic (familial chylomicronaemia syndrome [FCS]) and multifactorial (multifactorial chylomicronaemia syndrome [MCS]) and underlined the importance of genetic testing for the diagnosis, prognosis and the development of new therapies for FCS. Finally, Dr Federica Galimberti presented the current results and future perspectives of the LIPIGEN paediatric group. This group focuses on improving the detection, diagnosis and management of paediatric FH patients. To date, 1602 children and adolescents have participated in this study and 93.3% of them have undergone genetic testing. More than 200 different heterozygous LDLR variants have been identified, with a more severe phenotype in individuals with receptor-negative compared to those with receptor-detective, and large variability in LDL-C levels even among subjects with the same causative variant. Compared to adults, paediatric FH patients are less characterized in terms of physical examination (tendon xanthoma and/or arcus cornealis) and the personal history of premature coronary artery disease (CAD), whereas they could be detected by checking LDL-C levels and physical examination of their first-degree relatives. The study is still ongoing, with a focus on comparing the efficacy of nutraceuticals and LLTs and improving the screening and diagnosis of paediatric FH patients.

An increased focus on residual risk factors in the session dedicated to content beyond the guidelines. In this lecture, Professor Giovanna Liuzzo presented the contribution of inflammation in the development of ASCVD and specific groups of patients characterised by increasing systemic inflammation. She reviewed the clinical attempt to use anti-inflammatory therapies in cardiovascular (CV) prevention and discussed the recent approval of colchicine in patients with CAD and the innovative therapies related to inflammation. Professor Alberico Luigi Catapano then emphasized the fundamental tenets of LDL-lowering therapy, which should be based on the risk rather than the causes of risk, and the future challenges in reducing CV risk. Except for the principle "lower is better" in controlling LDL-C concentration, he suggested starting treatment as early as possible to reduce the lifetime CV risk and mentioned some possible improvements in future therapeutic strategies (such as controlling the levels of apoB and Lp(a)).

The congress traditionally hosts a joint symposium of the Lombardy sections of the AMD (Association of Diabetes Physicians), the SID (Italian Society of Diabetology), and SISA. This year, the presentations have focused on the management of other residual risk factors (triglycerides [TG]) and the use of polytherapy in patients with diabetes. In this session, Professor Paolo Magni discussed the epidemiological and genetic evidence for the association between TG or remnant cholesterol and CVD, and the status of TG-lowering treatments, including fibrates, omega-3 fatty acids, the antisense oligonucleotide (ASO) targeting apoC-III (volanesorsen), and the monoclonal antibody targeting angiopoietin-like protein 3 (ANGPTL3) (evinacumab). Dr Marco Mirani discussed the metabolic processes in diabetic patients and the therapies currently available for this condition. He also mentioned that tirzepatide, a dual agonist of glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), may be considered for metabolic control and weight loss. In addition, a case study was presented by Dr Laura Molteni to discuss the possibility of polytherapy for people with diabetes and other conditions.

During the last day, several hot topics related to LLTs were discussed.

Professor Alberto Zambon discussed the safety and efficacy of PCSK9 inhibitors (PCSK9i), reviewing data from clinical trials conducted in Europe and Italy, as well as data from real-life settings. Previous studies have clearly shown that PCSK9i, whether in patients with or without FH, can significantly lower LDL-C levels. Patients receiving PCSK9i treatment had higher adherence and persistence and a remarkable reduction in major adverse cardiovascular events (MACE). According to real-world data from Italy, ~79% of very-high risk patients with ASCVD did not achieve LDL-C goal according to current guidelines. Thus, the 'high-intensity statin treatment' and 'the wait and see paradigm' should be abandoned in favour of treating all very high- and extremely high-risk patients with combination therapy as the basic standard of care. Dr Andrea Baragetti gave an overview of the properties of Lp(a). Lp(a) is an LDL-like particle in which apo(a) is bound to apo(B). Epidemiological studies, meta-analyses, Mendelian randomization and genome-wide association studies have clearly shown that Lp(a) is an independent and causal risk factor for ASCVD. It has been hypothesized that there may be a linear relationship between elevated Lp(a) levels and an increased risk of developing CV events. Therefore, including Lp(a) levels in risk estimation and clinical measurement may contribute to treatment decisions, especially in patients with co-morbidities and genetic forms associated with elevated CVD risk. Currently, lipoprotein apheresis is the only option to significantly reduce Lp(a) levels, which can be considered in patients with very high Lp(a) levels and progressive CVD despite optimal management of other risk factors. Randomized clinical trials of PCSK9i and CETP inhibitors, which reduce Lp(a) levels by 20% to 25%, have consistently failed to demonstrate that lowering Lp(a) levels reduces the risk of cardiovascular events beyond what would be expected from the equivalent reduction in LDL-C and other apo B–containing lipoproteins alone. Clinical trials of novel Lp(a)-lowering therapies (antisense oligonucleotide- pelacarsen, siRNA- olpasiran and SLN360, and oral small molecule - muvalaplin) are ongoing. In the absence of specific Lp(a)-lowering therapies, early 'traditional' risk factor management is recommended for individuals with elevated Lp(a), taking into account their absolute CV risk and Lp(a) level. Dr Aldo Pietro Maggioni then briefly discussed the residual risk associated with TG and the clinical benefits of treatment with omega-3 fatty acids, particularly icosapent ethyl (a highly purified form of eicosapentaenoic acid), according to the results of the REDUCE-IT trial. Compared to placebo, icosapent ethyl 4 g/day significantly reduced first and total CV events by 25% and 30%, respectively. This treatment is safe and well tolerated but may associated with a slight increase in the incidence of atrial fibrillation.

In the last part, Professor Alberico Luigi Catapano critically evaluated the latest data on bempedoic acid. Bempedoic acid is a novel, once-daily oral lipid-lowering agent that is activated in the liver to bempedoyl-CoA, which subsequently inhibits ATP citrate lyase, an enzyme upstream of enzyme 3–hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the target of statins, in the cholesterol biosynthesis pathway. Bempedoic acid lowered plasma LDL-C and TG levels, and attenuated atherosclerosis in mice and miniature pigs. In phase 2 and 3 clinical trials, bempedoic acid treatment effectively lowers LDL-C levels as monotherapy, combined with statin or ezetimibe, and in statin-intolerant patients. This treatment provides an additional therapeutic option to lower LDL-C in high CV-risk patients. Next, Professor Stefano Carugo underlined that prescribed combination therapy has a greater and more favourable impact on prognosis, adherence and persistence. It is recommended to use combination therapy as the first-line strategy in patients with high CV risk. Finally, Professor Giuseppe Danilo Norata presented the clinical trials evaluating the safety and efficacy of a PCSK9 gene silencing approach – inclisiran. Inclisiran is an siRNA that inhibits the translation of the PCSK9 protein, leading to a reduction in LDL-C levels. Clinical trials have shown that inclisiran significantly reduces LDL-C levels, also in FH patients, but its long-term safety and clinical benefit remain to be established. He also described the use of anti-ANGPTL3 treatments (evinacumab and vupanorsen) in patients with HoFH.

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Circulating plasma exosomes reflect the severity of myocardial damage in STEMI patients

Marta Zarà[1], Andrea Baggiano[1,2], Patrizia Amadio[1], Jeness Campodonico[1], Sebastiano Gili[1], Andrea Annoni[1], Gianluca De Dona[1], Maria Ludovica Carerj[1], Francesco Cilia[1], Alberto Formenti[1], Laura Fusini[1,3], Cristina Banfi[1], Paola Gripari[1], Calogero Claudio Tedesco[1], Maria Elisabetta Mancini[1], Mattia Chiesa[1], Riccardo Maragna[1], Francesca Marchetti[1], Marco Penso[1], Luigi Tassetti[1], Alessandra Volpe[1], Alice Bonomi[1], Giancarlo Marenzi[1], Gianluca Pontone[1,4] and Silvia Stella Barbieri[1]

[1]Centro Cardiologico Monzino IRCCS, Milan, Italy
[2]Department of Clinical Sciences and Community Health, University of Milan, Italy
[3]Department of Electronics, Information and Bioengineering, Politecnico di Milano, Italy
[4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Italy
https://doi.org/10.56095/eaj.v2i3.54
Marta Zarà: marta.zara@cardiologicomonzino.it

Exosomes are small extracellular vesicles involved in intercellular communication and they contribute to inflammation, coagulation and vascular injury. Exosomes have demonstrated a great potential as diagnostic markers of disease, however their ability to reflect myocardial damage assessed by Cardiac Magnetic Resonance (CMR) in ST-segment elevation myocardial infarction (STEMI) is still unknown. To fill this gap, plasma exosomes were isolated from 42 STEMI patients treated by primary percutaneous coronary intervention (pPCI) and evaluated by CMR between days 3 and 6. Exosome concentration and size were measured by Nanoparticle Tracking Analysis, surface epitopes by flow cytometry, and platelet marker expression by ELISA kit.
Exosome levels were greater in patients with anterior STEMI (p=0.0001), with the culprit lesion located in LAD (p=0.045), and in those who underwent late revascularization (p=0.038). A smaller exosome size was observed in patients with a low myocardial salvage index (MSI, p=0.014). Exosomes of patients with microvascular obstruction (MVO) had smaller dimension (p<0.002) and lower expression of the platelet marker CD41–CD61 (p=0.039). Exosome size and CD41–CD61 expression were independent predictors of MVO/MSI (OR [95% CI]: 0.93 [0.87–0.98] and 0.04 [0–0.61], respectively).
In conclusion, we reported for the first time the ability of exosomes isolated a few days after STEMI to reflect myocardial damage. In particular, the exosome size and expression of the platelet marker CD41–CD61, likely reflecting the level of circulating platelet-derived exosome, were independent predictors of MVO and low MSI that are both predictors of short-term prognosis of acute STEMI after pPCI treatment and are key variables for risk-stratification of patients after STEMI. This finding paves the way for the development of a new strategy for the timely identification of high-risk patients and their treatment optimization.

Plasma and cerebrospinal fluid cholesterol esterification is hampered in Alzheimer's disease

Marta Turri[1], Elisa Conti[2], Chiara Pavanello[1], Francesco Gastoldi[1], Marcella Palumbo[3], Franco Bernini[3], Vittoria Aprea[2], Francesca Re[4], Alberto Barbiroli[5], Davide Emide[5], Daniela Galimberti[6,7], Lucio Tremolizzo[2]*, Francesca Zimetti[3]*, Laura Calabresi[1]*

[1]Centro E. Grossi Paoletti, Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Italy
[2]Neurology Unit, IRCCS "San Gerardo dei Tintori", Monza and University of Milano-Bicocca, Italy;
[3]Department of Food and Drug, University of Parma, Italy;
[4]School of Medicine and Surgery, University of Milano-Bicocca, Italy;
[5]Dipartimento di Scienze per gli Alimenti, la Nutrizione e l'Ambiente, Università degli Studi di Milano, Italy;
[6]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Italy; 7Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy
https://doi.org/10.56095/eaj.v2i3.53
Marta Turri: marta.turri@unimi.it

Introduction: Several epidemiological studies indicate a strong inverse association between the risk of developing Alzheimer's disease (AD) and plasma HDL-C levels. The mechanism by which plasma HDL influence the pathogenesis and progression of AD is still un-

solved and since cholesterol esterification is a crucial step in HDL metabolism it could be involved. The purpose of this study was to evaluate cholesterol esterification and HDL subclasses in plasma and cerebrospinal fluid (CSF) of Alzheimer's Disease (AD) patients.
Materials and Methods: The study enrolled 70 AD patients and 74 cognitively-normal controls comparable for age and sex. Lipids and lipoprotein profile, cholesterol esterification, and cholesterol efflux capacity (CEC) were evaluated in plasma and CSF using assays set for measurement in plasma, which were appropriately modified for CSF.
Results and Discussion: AD patients have normal plasma lipids, but significantly reduced unesterified cholesterol and unesterified/total cholesterol ratio. Lecithin:cholesterol acyltransferase (LCAT) activity and cholesterol esterification rate (CER), two measures of the efficiency of the esterification process, were reduced by 29% and 16%, respectively, in plasma of AD patients. Plasma HDL subclass distribution in AD patients was comparable to that of controls, but the content of small discoidal preβ-HDL particles was significantly reduced. In agreement with the reduced preβ-HDL particles, cholesterol efflux capacity mediated by the transporters ABCA1 and ABCG1 was reduced in AD patients' plasma. The CSF unesterified to total cholesterol ratio was increased in AD patients, and CSF CER and CEC from astrocytes were significantly reduced in AD patients. In the AD group, a significant positive correlation was observed between plasma unesterified cholesterol and unesterified/total cholesterol ratio with Aβ1-42 CSF content.
Conclusion: Taken together data indicate that cholesterol esterification is hampered in plasma and CSF of AD patients, and that plasma cholesterol esterification biomarkers (unesterified cholesterol and unesterified/total cholesterol ratio) are significantly associated to disease biomarkers (i.e., CSF Aβ1-42).

Different operational definitions of polypharmacy and their association with the risk of all-cause hospitalization: A conceptual framework using administrative databases

Stefano Scotti[1], Elena Olmastroni[1,2], Federica Galimberti[1], Lorenza Scotti[3], Manuela Casula[1,2]

[1]IRCCS MultiMedica, Laboratory of Cardiovascular Research, Sesto San Giovanni, Milan, Italy
[2]Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy
[3]Department of Translational Medicine, Università del Piemonte Orientale UPO, Novara, Italy
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Stefano Scotti: stefano.scottiultimedica.it

Background: As in all pharmacoepidemiology studies, also in the cardiovascular field it is essential to take into account the clinical complexity of patients, which is very frequently estimated with polypharmacy. We aimed at describing the current heterogeneity of polypharmacy definition, and assessing the association of polypharmacy with clinical outcomes.
Methods: Using administrative databases of the local health unit of Bergamo (Lombardy), all subjects aged ≥40 years with at least one reimbursed drug prescription during the year 2017 were identified. We selected from literature relevant operational definitions of polypharmacy. First, we applied World Health Organization (WHO) definition (at least ≥5 different medications, ATC 4th level code). Second, we excluded drug prescriptions associated with short-term treatment. Third, we considered only the prescriptions of drugs with a total annual defined daily doses (DDDs) ≥60. All the approaches were evaluated within one year, one quarter, and one month. A multivariate logistic regression model was performed to estimate odds ratios (OR) and 95% confidence intervals [95% CI] for the association between polypharmacy and the risk of hospitalization for all-causes.
Results: Overall, 431,620 subjects were included in our cohort. The DDD-based definition led to estimates with little variability depending on the time windows (range 20.47%-21.16%), while the WHO definition determined the greatest variability (range 39.98%-31.24%). The DDD-based definition identified an older (mean age [SD], 72.6 [10.9]) and more complex cohort of patients (average number [SD] of previous hospitalizations 1.2 [1.7], average number of dispensed drugs 9.7 [3.5]). A dose-dependent increase in risk was observed as the number of the dispensed drugs increases regardless of definitions.
Conclusions: Different definitions of polypharmacy led to different prevalence estimates. All definitions showed a dose-dependent association with hospitalization risk, with the definition based on DDDs being the least heterogeneous. However, only a patient-by-patient approach can determine whether or not polypharmacy is appropriate.

VLDL cholesterol associates with higher plasmatic expression of inflammatory proteins and atherosclerotic pathways compared to LDL cholesterol

Elisa Mattavelli[1,2], Elena Olmastroni[1,2], Nick Nurmohamed[3], Liliana Grigore[2], Fabio Pellegatta[2], Erik S.G. Stroes[3], Alberico L. Catapano[1,2], Andrea Baragetti[1,2]

[1]Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy
[2]IRCCS MultiMedica Hospital, Milano, Italy
[3]Department of Vascular Medicine, Amsterdam University Medical Centers, University of Amsterdam
https://doi.org/10.56095/eaj.v2i3.51
Elisa Mattavelli: elisa.mattavelli@unimi.it

Background and Aim: High cholesterol in Low-Density Lipoproteins (LDL-C) is the key target of current pharmacological treatments aimed at reducing atherosclerotic cardiovascular disease (ACVD) risk. Increased cholesterol in Very low-density lipoproteins ("VLDL-C") is an independent predictor of ACVD. VLDL-C was previously associated with markers of inflammation (for instance C-reactive protein). We now tested the relationship between either VLDL-C or LDL-C with a large spectrum of inflammatory proteins in plasma collected from subjects at different ACVD risks.
Methods: We measured 276 proteins (Olink™) in plasma from a primary ACVD risk prevention cohort ("PLIC" in Milan; n=656 (8.2% on statins)) and a secondary ACVD risk prevention cohort (the Second Manifestations of ARTerial disease, "SMART", the Netherlands, n=630 (50.8% on statins)). Cohorts were divided into three

groups for VLDL-C ("Normal" VLDL-C<15 mg/dL, "High" VLDL-C 15-30 mg/dL, "Very high" VLDL-C >30 mg/dL) and LDL-C ("Normal" LDL-C <115 mg/dL, "High" LDL-C 115-155 mg/dL, "Very high" LDL-C>155 mg/dL). The expression (Normalized Protein eXpression, NPX) of each protein was compared among these groups by artificial intelligence. The performance to discriminate subjects with higher VLDL-C or LDL-C was evaluated by comparing the Areas Under the Curve (AUCs) of the Receiver Operating Characteristics curve (ROC) considering proteomics on top of ACVD risk factors ("CVRFs": age, body mass index, systolic blood pressure, glycemia, therapies), versus the AUC of the ROCs with CVRFs alone.

Results: The number of plasma proteins differentially expressed increased, as a function of higher VLDL-C in PLIC, as the NPXs of 84 were higher in "High" and the NPXs of 136 were higher in "Very high" vs "Normal" VLDL-C respectively. A similar trend was found in SMART, where the NPXs of 30 proteins were higher in "High" and the NPXs of 64 were higher in "Very high" vs "Normal" VLDL-C respectively. 26 proteins were shared between the two populations and recapitulated key atherosclerotic pathways (including chemotaxis of immune cells). The relationship between LDL-C was less marked; in PLIC, 14 proteins were more expressed in "High" and 33 in "Very high" vs "Normal" LDL-C respectively, while in SMART, the NPXs of 11 proteins were higher in "High" and the NPXs of 36 were higher in "Very high" vs "Normal" LDL-C respectively. Only 4 proteins were shared between high and very high LDL-C in the two populations. Finally, none of the proteins were shared between the groups of "High"/"Very high" VLDL-C and "High"/"Very high" LDL-C in the two cohorts.

Canonical CVRFs alone slightly improved the ability to identify subjects with increased VLDL-C both in PLIC and SMART (AUCs between 0.6 on average), but adding plasma proteomics markedly improved the performance to identify subjects with "High" VLDL-C, in PLIC (AUC=0.767 (0.709-0.837)) and in SMART (AUC=0.781 (0.681-0.873)), and with "Very high" VLDL-C (AUC=0.950 (0.899-0.976) in PLIC, and AUC=0.938 (0.894-0.971) in SMART).

The ROC of plasma proteomics with CVRFs was also superior to the ROC of the CVRFs alone to identify subjects with "High" and "Very high" LDL-C, but, as compared to the ROCs that discriminated subjects with "High" and "Very-high" VLDL-C, the AUCs were attenuated in both cohort (for "High" LDL-C: AUC=0.665 (0.558-0.774) in PLIC and AUC=0.775 (0.704-0.842) in SMART; for "Very high" LDL-C: AUC =0.776 (0.694-0.854) in PLIC and AUC=0.882 (0.825-0.931) in SMART).

Conclusion: High VLDL-C associates with a higher number of differentially expressed plasma proteins versus high LDL-C and none of the proteins were in common. Our data do not underestimate the value of LDL-C in ACVD but reinforce the concept that VLDL-C may also promote different atherosclerotic pathways involved in determining ACVD.

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