RESIDUAL CARDIOVASCULAR RISK IN DIABETIC PATIENTS: THE ROLE OF FIBRATE/STATIN COMBINATION

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ABSTRACT

Patients with Type 2 diabetes mellitus (T2DM) have increased cardiovascular disease (CVD) risk. The use of statins significantly reduces the rate of CVD events but many T2DM patients, especially those with mixed dyslipidaemia (MD), have residual CVD risk. The use of fibrates, which improve triglyceride and high-density lipoprotein cholesterol levels, is beneficial for the treatment of patients with MD. Evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study showed a possible beneficial effect on CVD events of the addition of fenofibrate (FF) to statin treatment in patients with T2DM and atherogenic MD. Furthermore, FF has been associated with slowing of the progression of early diabetic retinopathy. The combination of statin with a fibrate may improve the residual CVD risk and microvascular complications of patients with T2DM. However, trials specifically designed to assess the effects of fibrate-statin combination on cardiovascular outcomes in patients with T2DM are missing.

Keywords: Fibrate, fenofibrate, fenofibric acid, statin, diabetes, cardiovascular risk, retinopathy.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with a significantly increased risk of cardiovascular disease (CVD).[1,2] The increased CVD risk is, in part, attributed to an adverse lipid profile observed in T2DM patients, which includes increased levels of low-density lipoprotein cholesterol (LDL-C), increased concentration of triglycerides (TG), and reduced levels of high-density lipoprotein cholesterol (HDL-C).[3,4] The primary target of lipid lowering therapy in T2DM patients is the reduction of LDL-C levels. The use of statins is the cornerstone of therapy in patients with T2DM, since these drugs significantly reduce the concentration of LDL-C and have been proven efficacious for the reduction of CVD risk.[5,6] In the Collaborative Atorvastatin Diabetes Study,[7] which included 2,838 patients with T2DM, atorvastatin reduced the rate of major vascular events by 37% in a period of 4 years ($p<0.001$).

Many patients with T2DM, despite receiving a statin and having a satisfactory LDL-C concentration, are characterised by the presence of atherogenic mixed dyslipidaemia (MD) (elevated TG concentration and low levels of HDL-C).[3,4,8] This adverse lipid profile is considered a main factor for the increased CVD risk of diabetic patients on statin treatment. Indeed, in the Treating to New Targets study[9] and in the Pravastatin or Atorvastatin Evaluation and Infection Therapy study,[10] it was shown that patients with LDL-C <70 mg/dl, low HDL-C levels, and/or increased TG levels had higher CVD risk compared with patients without MD. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study,[11] patients with T2DM and atherogenic dyslipidaemia (AD) had 70% greater rate of major CVD events compared with the group of T2DM patients without AD.

The 'residual' CVD risk in T2DM patients on statin treatment has also been attributed to many other variables that affect the atherosclerotic

progression in patients with T2DM, including the presence of the atherogenic small-dense LDL particles, alterations in the distribution of HDL-C subclasses, and increased levels of inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP) and lipoprotein-associated phospholipase A_2.[12-27] The residual CVD risk in diabetic patients could be targeted with the combination of statins with other hypolipidaemic drugs that improve MD, such as fibrates.

FIBRATES

Fibrates are a class of drugs that activate peroxisome proliferator-activated receptor α. Bezafibrate (BF), gemfibrozil (GF), and the newer agents, fenofibrate (FF) and fenofibric acid (FA), are members of this family. These drugs reduce TG levels by 30-50% and increase HDL-C concentration by 2-20%. Furthermore, fibrates have been associated with improvement of the distribution of LDL and HDL subclasses and other markers of the atherosclerotic process.[28-35]

The administration of BF and GF as monotherapy in patients with T2DM has been proven beneficial in terms of CVD risk reduction.[36,37] In a more recent study, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial,[38] FF 200 mg/day or placebo was given for 5 years in 9,795 patients with T2DM. FF administration did not significantly reduce major coronary heart disease (CHD) events (primary trial outcome; -11%, p=NS). However, FF administration was associated with a significant reduction of total CVD events (-11%, p=0.035) compared with placebo, which was attributed mainly to the reduction of non-fatal myocardial infarctions (NFMI) (-24%, p=0.01) and coronary revascularisations (-21%, p=0.003).[38] It should be noted that significantly more patients in the placebo group were receiving statins during the trial compared with the FF group (17% versus 8%, p<0.0001), a fact that may have obscured the possible beneficial CVD effect of FF.[38]

A meta-analysis of 18 trials with 45,058 participants showed that fibrates resulted in a 10% relative risk reduction for major CVD events (p=0.048) and a 13% risk reduction for coronary events (p<0.0001).[39] Another meta-analysis of six trials examined the effects of fibrates in patients with AD.[40] The administration of fibrates reduced the risk of vascular events by 25% (p<0.001) in 7,389 subjects with high TG levels, by 29% in 5,068 subjects with high TG and low HDL-C levels (p<0.001), and by 16% in 15,303 subjects with low HDL-C (p<0.001). Of note, fibrate therapy did not reduce the risk of vascular events in 9,872 subjects without high TG and low HDL-C (p=0.53).[40] The beneficial effects of fibrates in reducing TG levels and increasing HDL-C concentration seem promising targets for the reduction of CVD risk in patients with MD. These beneficial effects, as well the effects of fibrates on inflammatory markers and the distribution of LDL subclasses, make these drugs candidates for use in combination with a statin aiming to reduce the residual CVD risk in patients with T2DM.

STATIN-FIBRATE COMBINATION THERAPY IN PATIENTS WITH T2DM

Effects on Metabolic Variables

Several clinical trials have shown beneficial effects on the lipid profile in patients with T2DM when these individuals are treated with a statin/fibrate combination.[41-44] The larger trial examining the statin-fibrate combination is the ACCORD Lipid study,[11] which randomised 5,518 patients with T2DM in FF or placebo on top of simvastatin (SV). The combination of FF with SV led to significantly greater improvements of total cholesterol (-13.5%), TG (-22.2%), and HDL-C (+8.4%) levels compared with placebo/SV (-12.5%, -8.7%, and +6%, respectively, all p<0.05). However, the improvement in LDL-C levels did not differ between combination (-18.9%) and placebo groups (-20.9%, p=0.16).[11] The effects of SV/FF combination on postprandial lipid profile was investigated in a subgroup of 139 subjects from the ACCORD Lipid trial[45] who received an oral fat load. The combination treatment significantly reduced the TG incremental area under the curve compared with the placebo + SV group (p=0.008). Furthermore, in patients with increased fasting TG levels, a significant reduction of the atherogenic apolipoprotein B-48 (ApoB48) was observed (p=0.008).[45] Another double-blind study of 196 patients with newly onset, untreated T2DM, and MD (treatment groups: SV 40 mg/day, FF 200 mg/day, SV/FF combination, or placebo) showed that the combined therapy produced greater improvements in the levels of TG and ApoA-I compared with SV monotherapy, and in the concentration of total cholesterol, LDL-C and ApoB levels compared with FF monotherapy (all p<0.05).[46] Furthermore, the combination therapy

significantly improved inflammatory markers, such as hs-CRP, interferon-gamma, tumour necrosis factor alpha, and lymphocyte release of interleukin-2, compared with monotherapy groups.[46]

The newer FA has also shown beneficial effects in terms of lipid profile when combined with a statin.[47] A pooled subgroup analysis of three randomised, controlled, double-blind trials that included 586 patients with MD and T2DM showed that the combination of FA and moderate-dose statin significantly improved the concentration of TG (-43.4%) and HDL-C (+16.3%) compared with moderate-dose statin monotherapy (-24.2% and +8.7%, respectively), as well as LDL-C (-32.6%) compared with FA monotherapy (-5.3%, p<0.05 for all comparisons).[48] The combination of FA and low-dose statin produced similar results compared with monotherapy with low-dose statin or FA. Of note, the combination of FA with low or moderate-dose statin led to a 5-fold higher percentage of patients with simultaneously optimal levels of LDL-C, TG, non-HDL-C, and HDL-C.[48] It should be mentioned that GF should not be given combined with a statin due to the increased risk of rhabdomyolysis. The other fibrates appear safe when combined with a statin.

Effects on T2DM-Related Complications

The addition of fibrates to statin treatment results in the improvement of lipid profile and reduction of estimated cardiovascular risk.[41] The effect of statin/fibrate combination on hard CVD endpoints was investigated in the ACCORD Lipid trial.[45] As mentioned above, the addition of FF to SV resulted in significant reductions of total cholesterol, TG, and HDL-C levels (all p<0.05) compared with the placebo/SV group. However, the observed reduction in LDL-C levels was similar between groups (p=0.16).[11] The annual rate of the primary outcome (first occurrence of a major CVD event, i.e. NFMI, nonfatal stroke, or death from CVD causes) was 2.2% in the FF group and 2.4% in the placebo group (HR for the FF group 0.92, 95% CI 0.79-1.08; p=0.32). Similarly, no significant differences were seen in secondary outcomes (HRs ranged from 0.82-1.17, p≥0.10 for all comparisons).[11] Furthermore, the annual rate of death from all causes was 1.5% with the combination of FF/SV, and 1.6% with the placebo/SV (HR 0.91, 95% CI 0.75-1.10, p=0.33).[11]

These results do not support the administration of FF/SV combination therapy in patients with T2DM. However, the study has received some criticism based on the open-label administration of SV and the fact that the enrolment of patients did not achieve the predetermined power. Furthermore, in a pre-specified analysis in the subgroup of patients with high baseline TG (≥204 mg/dl) and low baseline HDL-C (≤34 mg/dl) levels, a significant reduction in CVD events was observed in the FF + SV group compared with the placebo group (-28%, p<0.05).[11] This result implies that the addition of a fibrate to statin treatment is beneficial in patients with AD. Notably, a similar analysis of patients with marked dyslipidaemia in the FIELD trial showed a significant reduction of CVD events with FF compared with placebo (-27% relative risk reduction, p=0.005).[49]

Microvascular complications are another major factor for the increased morbidity of T2DM patients. Diabetic retinopathy is one of the most devastating disabilities. The addition of FF to SV in the ACCORD Eye Study[50] (n=2,856) reduced the rate of progression of diabetic retinopathy compared with the administration of placebo/SV (-6.5% versus -10.2%, OR 0.60, p=0.006). The magnitude of this effect was greater than the benefit observed with the intensive glycaemic treatment when compared with the standard glycaemic treatment in the ACCORD study (OR 0.67). Additionally, FF in the FIELD trial[51] significantly reduced the rate of first laser treatment for retinopathy compared with the placebo group (3.4% versus 4.9%, HR 0.69, p=0.0002). These effects support the use of FF in patients with T2DM and early retinopathy. Indeed, the FF manufacturer has recently announced that it secured an indication by the Australian Therapeutic Goods Administration for the use of the drug to slow the progression of diabetic retinopathy.[52]

Patients treated with FF usually experience an increase in serum creatinine levels, which has been attributed to several mechanisms.[53-56] Generally, the increase in serum creatinine levels during FF treatment is reversible. In the ACCORD Lipid study,[11] serum creatinine levels increased from 0.93 to 1.10 mg/dl in the FF group during the first year, and from 0.93 to 1.04 mg/dl in the placebo group. Despite these increases, no significant difference in the occurrence of end-stage renal disease and the need for dialysis was observed between treatment groups. Moreover, the incidence of microalbuminuria (38.2% versus 41.6%, p=0.01) and macroalbuminuria (10.5% versus 12.3%, p=0.04) was lower in patients treated with FF/SV compared with placebo/

SV, an effect that seems promising for the prevention of diabetic nephropathy.[11] Furthermore, there is evidence that long-term FF treatment is protective against pathological changes in diabetic nephropathy, and slows the progression of renal function impairment.[57, 58]

CONCLUSION

Patients with T2DM have a high risk for CVD. The administration of statins aiming to decrease LDL-C levels is the cornerstone of therapy in patients with T2DM. However, many patients with T2DM have residual CVD risk despite treatment with statins, which is mainly attributed to the presence of MD. The addition of a fibrate to statin treatment in T2DM patients with MD seems promising in terms of lipid profile improvement and CVD risk reduction. However, aside from the prespecified analysis from the ACCORD study, there are no clinical trials yet to show that fibrate/statin combination therapy has better results on CVD risk than statin alone in patients with the atherogenic phenotype.

In conclusion, clinicians could use a fibrate combined with a statin in T2DM patients at high CVD risk and MD, since this combination leads to an overall improvement of the lipidaemic profile. However, we live in the era of evidence-based medicine and clinicians should discuss with their patients that the effects of this combination on CVD events has not been studied in specifically designed studies. Medical associations should increase pressure on drug companies to design one or more future trials focusing on the role of fibrate-statin combination in T2DM patients with MD.

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