Residual vascular risk in diabetes – will the SPPARM alpha concept hold the key?

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Blood pressure, low-density lipoprotein cholesterol (LDL-C), and glycemia (for microvascular disease) represent the triumvirate of targets for managing vascular risk in type 2 diabetes.[1] Novel treatments that substantially lower LDL-C levels,[2,3] or that improve glucose control,[4–6] can provide additional vascular risk reduction. Despite these advances in best care, however, an unacceptably high residual cardiovascular risk persists. Therefore, therapeutic interventions aimed at additional targets are needed.

A key contender to address the enigma of residual vascular risk is the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα). PPARα, which is predominantly expressed in metabolically active tissues, pivotally regulates key metabolic and inflammatory pathways.[7,8] Critical to this role is the ability of PPARα to exert either positive or negative control over the expression of genes involved in fatty acid oxidation, lipoprotein metabolism, and inflammation.

Like other nuclear receptors, activation of PPARα requires binding of an agonist, either endogenous (such as fatty acids) or synthetic, to the ligand binding domain of the receptor. This ligation allows the activated PPARα to form a heterodimer with a partner nuclear receptor, retinoid X receptor (RXR), triggering a conformational change which stabilizes the ligand binding domain. This PPARα-RXR complex then binds to specific DNA sequences in the promoter region (the PPAR receptor response element) of target genes, promoting their expression. The PPARα-RXR complex can also bind to repressor proteins which inhibit the expression of other genes.[9,10] The recruitment of a number of cofactors facilitates both processes, ensuring a ‘transcriptionally active’ PPAR complex. These cofactors can either activate transcription of target genes (coactivators) or mediate repression of other genes (corepressors).[11] To date, 38 cofactors that bind to PPAR have been identified, including those involved in the activation of genes encoding lipoprotein lipase and apolipoprotein (apo) C-III, which regulate triglyceride-rich lipoprotein metabolism, and apo A-I, A-II, and the adenosine triphosphate-binding cassette transporters A1 and G1, involved in high-density lipoprotein (HDL) metabolism. Other cofactors mediate the repression of pro-inflammatory genes, or genes influencing intracellular metabolism and oxidative stress.[8,11]

This mode of action of PPARα exerts pleiotropic biological actions likely to benefit the milieu of risk factors in type 2 diabetes.[12] Increases in HDL production, very-low-density lipoprotein (VLDL) clearance and LDL particle size, together with downstream decreases in VLDL production, and LDL particle concentration, illustrate a key role for PPARα agonism in managing atherogenic dyslipidemia (high plasma triglycerides, low HDL cholesterol, small, dense LDL particles, and elevated apo B and C-III), characteristic of type 2 diabetes. Anti-inflammatory effects limit local cellular inflammation and thrombogenesis, pathways linked to cardiovascular complications.[12] Promotion of beta-oxidation and the mitochondrial tricarboxylic acid cycle ameliorate adverse intracellular metabolic changes, including effects on glucose homeostasis.[12] This multimodal pharmacological profile implies that PPARα agonism has the potential to reduce atherosclerotic cardiovascular disease (ASCVD) risk in type 2 diabetes.

Clinicians are, however, well aware that current PPARα agonists – fibrates – have proven underwhelming in cardiovascular outcome studies. Their administration has failed to show definitive clinical benefit against a background of best evidence-based treatment including statin therapy.[13] Moreover, classical fibrates can have safety issues such as elevation in serum creatinine, which although reversible,[14] raise concerns among practitioners. Certain currently available fibrates interact with other drugs, for example gemfibrozil can cause hazard when combined with statins.[15] Understanding the mode of action of PPARα, however, suggests avenues for the development of novel selective PPARα agonists that might overcome the deficiencies of the fibrates, and also benefit metabolic diseases with an underlying inflammatory component.

Such thinking underlies the SPPARMα (Selective Peroxisome Proliferator-Activated Receptor Alpha Modulator) concept, which aims to maximize favourable effects associated with PPARα activation while simultaneously limiting the propensity for unwanted effects.[16] To this end, the large lipid-binding pocket of PPARα provides numerous potential contact points capable of triggering different conformational changes, each potentially associated with a unique cofactor recruitment pattern, and a specific profile of biological effects.[17] Thus, modulating the cofactor recruitment pattern provides the opportunity to improve the benefit versus risk profile of the agonist, in particular overcome issues with renal and hepatic safety (Figure), key deterrents of previous selective PPARα prototypes.[18]

The SPPARMα concept provides a highly attractive basis for the development of novel agents that act at multiple targets relevant to vascular risk in cardiometabolic disease. Insights into the role of PPARα in the hepatic inflammatory process may also offer therapeutic potential in non-alcoholic fatty liver disease,[19] not only implicated in the development of type 2 diabetes, but also a marker of ASCVD risk. The ultimate question is whether SPPARMα agonism provides a multifaceted solution to the enigma of residual vascular risk in type 2 diabetes; for this we await results from the cardiovascular outcomes study, PROMINENT.[20]

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Declaration of interests

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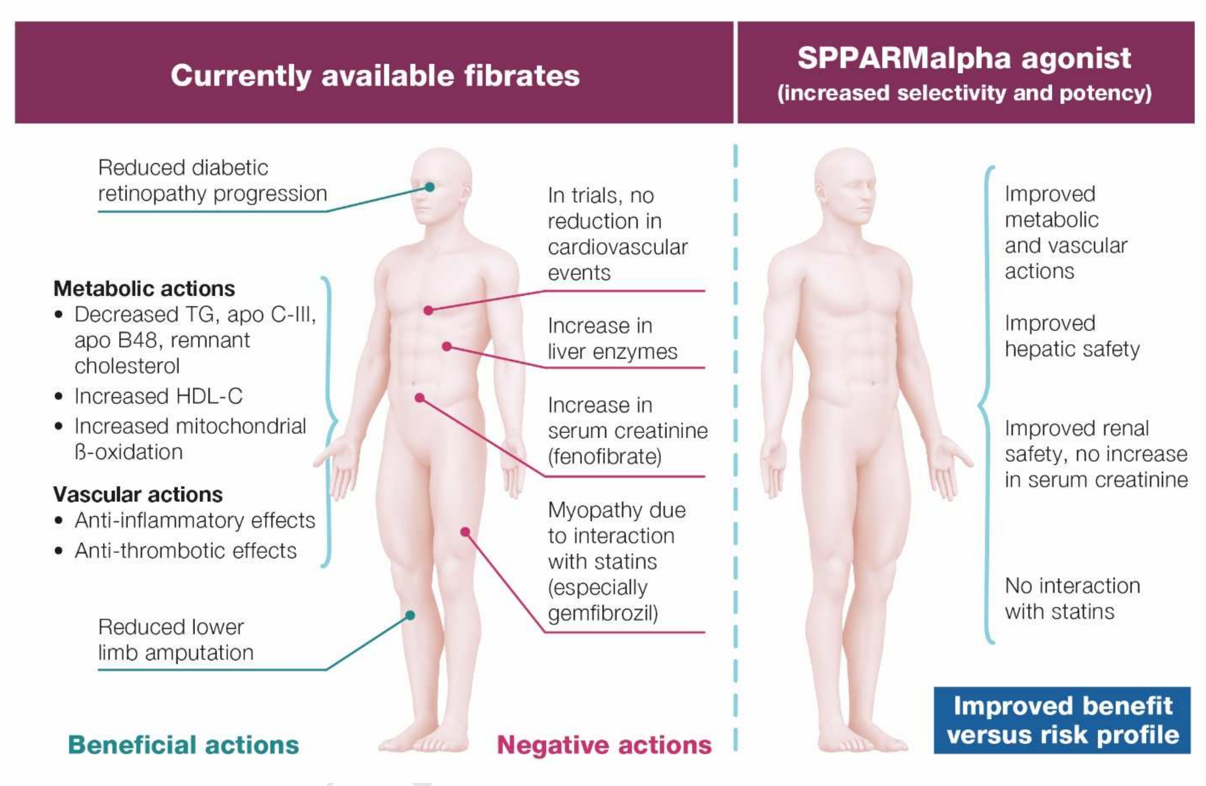
Figure. **Schematic illustrating the SPPARMα (Selective Peroxisome Proliferator-Activated Receptor Alpha Modulator) concept.**

Modulating the unique cofactor recruitment pattern associated with binding of the selective agonist to PPARα provides the opportunity to improve the benefit versus risk profile compared with currently available fibrates.

Abbreviations: apo apolipoprotein; HDL-C high-density lipoprotein cholesterol; TG triglycerides

Figure design by J-C Fruchart.



Online Appendix: Members of the International Atherosclerosis Society/ Residual Risk Reduction Initiative (R3i) Consensus Panel

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