MAYO CLINIC

Mitigating Risk Patients With Dyslipidemia: A Statin a Day Does Not Always Keep the Doctor Away in Those With Elevated Triglycerides

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Coronary atherosclerosis risk is strongly associated with elevated levels of low-density lipoprotein cholesterol (LDL-C).[1] Elevated serum triglycerides are also associated with increased coronary risk, but controversy exists over whether triglycerides (TGs) themselves are atherogenic or merely reflect a surrogate marker for other cardiometabolic disorders including low high-density lipoprotein cholesterol (HDL-C), diabetes mellitus, and obesity.[2-5] An important clinical question is whether patients at high atherogenic risk, currently on statin medication, need additional specific treatment for hypertriglyceridemia if it is present.

The paper in the current issue of the *Mayo Clinic Proceedings* by Toth et al seeks to answer this question.[6] This paper highlights the additional risk posed by elevated TGs in patients with cardiovascular disease and dyslipidemia who are currently treated with statin agents. The patients studied by Toth et al[6] included a retrospective analysis from more than 80 million medical records included in the Optum database. Toth et al[6] found 23,181 patients with elevated TGs (fasting TG $>$ 150 mg/dL) who were on treatment with statin drugs for dyslipidemia. The authors matched an equal number of patients without elevated TGs (TG $<$ 150 mg/dL and HDL $>$ 40 mg/dL) who were on statin treatment using propensity score matching. Both groups had been treated with statin agents for at least 6 months and had pretreatment measurement of lipid values. Toth et al[6] demonstrated a 26% increase in major adverse cardiovascular events in patients with elevated TGs despite treatment with statin agents. These risks persisted even after adjustment with non-HDL cholesterol, which accounts for the TG-rich components of atherogenic apolipoprotein B (ApoB) lipoproteins. Patients on statin therapy with elevated TGs had increased risks for coronary revascularization and hospitalization and increased rates of nonfatal myocardial infarction.

There is an emerging body of evidence demonstrating that plasma TGs are independent risk factors for cardiovascular disease.[2-5] Several years ago, Miller et al demonstrated increases in fatal and nonfatal events in patients with elevated TGs on statin therapy who had suffered recent acute coronary syndromes.[7]

Why might these risks persist despite use of statin therapy for dyslipidemia? Several explanations come to mind. Elevated TGs are often associated with elevated cardiometabolic risks,[1,3-5,7] including metabolic syndrome and dysglycemia. It is likely that elevated TGs pose some risks for inflammatory activation, especially in atherogenic tissue. Elevated TGs promote the formation of smaller, more dense LDL: a very atherogenic ApoB- containing lipoprotein.[8,9] Recent speculation by Toth[8] and Rosenson[9] suggests that TG-rich lipoproteins likely alter atherosclerotic plaque in ways that favor plaque destabilization and progression of disease (Figure).[9]

The recent REDUCE-IT trial (Cardiovascular Event Risk reduction with icosapent ethyl trial) evaluated whether treatment with fish oil in addition to statin therapy might reduce cardiovascular risk. The results were strongly in favor of TG reduction from the use of marine oils. The REDUCE-IT trial examined 8179 patients on statin therapy,

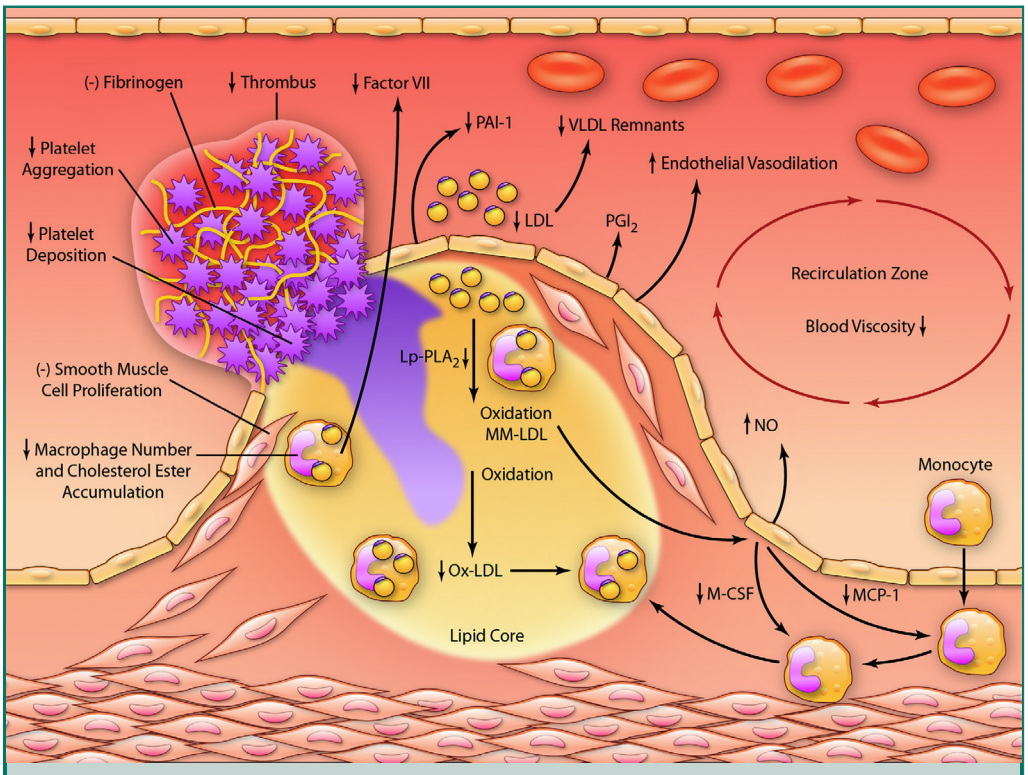

FIGURE. Anti-atherothrombotic properties of statins and potential relevance in patients with acute coronary syndromes. LDL = low-density lipoprotein; $Lp\text{-}PLA_2$ = lipoprotein-associated phospholipase A_2; M-CSF = monocyte colony stimulating factor; MCP-1 = monocyte chemoattractant protein-1; MM-LDL = minimally modified LDL; Ox-LDL = oxidized LDL; PAI-1 = plasminogen activator inhibitor-1; PGI2 = prostacyclin; VLDL = very low-density lipoprotein. (Illustration credit: Ben Smith.) From *Circ Res.*,[9] with permission.

with nearly 90% having prerandomization TGs above 150 mg/dL. Patients were randomized to 2 gm twice daily of icosapent ethyl or placebo. Those randomized to the marine-oil supplementation had a 25% reduction in major adverse cardiac events, a 20% reduction in mortality, and a 31% reduction in fatal or nonfatal myocardial infarction.[10] The subgroup analysis from REDUCE-IT suggested that the benefit was most evident in those with TGs above 150 mg/dL.

TG metabolism is complex, involving TGs derived directly from the diet that are transported in the blood as chylomicrons generated in the gut wall; chylomicrons are considered to have low atherogenic potential because of their large size and inability to cross the endothelium of the arterial wall easily. A second source of TGs is as part of the very low-density lipoprotein particles (VLDL) that transports TG generated from hepatic metabolism and are likely much more atherogenic.[9-12]

An elegant study by Ference et al reported in *Journal of the American Medical Association*, and an accompanying editorial by Navar, highlight the current speculation about the role of TGs and the impact of REDUCE-IT on reductions in cardiovascular risk.[11,12]

Ference et al evaluated genetic mutations in lipoprotein lipase (LPL), a key enzyme in metabolism of TG. Genetic LPL mutations that decrease enzyme activity led to an increase in plasma TGs and cardiovascular risk. The authors concluded that, for every 50-mg/dL TG lowering, there was an associated 18% lower risk of cardiovascular disease. Importantly, after adjusting for differences in ApoB levels, TGs were not independently related to

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cardiovascular risk. Thus, differences in ApoB, not TG levels, may directly account for the observed lower risk of cardiovascular disease. To achieve a 10-mg/dL reduction in ApoB, the TG level must be reduced by 70 mg/dL. In comparison, the same ApoB reduction could be achieved with only a 14-mg/dL reduction in LDL-C level. This may explain the previous inconsistent cardiovascular benefits seen with fibrates, agents that reduce plasma triglycerides. In other words, in the presence of statin medication, there needs to be a very large reduction of TGs to move the cardiovascular risk-reduction needle. Navar controversially argued that the ApoB decrease seen in the REDUCE-IT trial was minimal (decreased by 2 mg/dL in the treatment group vs a 4-mg/dL increase in the placebo group) and that the benefit of eicosapentaenoic acid seen in the REDUCE-IT trial was likely due to non−TG-, non−ApoB-related, off-target effects.

The data from Toth et al contribute to our understanding of the risks of elevated TGs by demonstrating in a large, real-world database that the observations from recent randomized clinical trials about the risks of elevated TGs in statin-treated patients remain a real and present danger for the cardiovascular well being of our patients with dyslipidemia. Furthermore, the data from Toth et al[6] confirm observations from epidemiological datasets and the REDUCE-IT trial that treatment with statins alone is insufficient for optimal reduction of cardiovascular risk. It is important to evaluate elevated TGs in patients on statin therapy. Might there be contributions from cardiometabolic risk? Might these patients in our own practices warrant more intensive lipid-lowering therapy with either icosapent ethyl or a fibrate to further mitigate their cardiovascular dyslipidemia? Are TGs one of the "check engine lights" that necessitate further evaluation by clinicians treating dyslipidemia with statin therapy? We believe so and find the Toth data compelling enough that we need to re-evaluate our practice patterns in those patients with elevations of plasma triglycerides.

R. Scott Wright, MD, FACC, FESC, FAHA
Department of Cardiology
Division of Preventive Cardiology
Mayo Clinic
Rochester, MN

Joseph G. Murphy, MD, FACC, FESC
Department of Cardiology
Division of Cardiac Intensive Care
Mayo Clinic
Rochester, MN

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Correspondence: Address to R. Scott Wright, MD, FACC, FESC, FAHA, Mayo Clinic, Gonda 5-477, 200 First Street SW, Rochester, MN 55905 (wright.scott@mayo.edu).

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