**Milwaukee Academy of Medicine**
**1361st Meeting**
**April 20, 2021**

Dr. Rita Hanson, President, opened the 1361st meeting of the Academy. Shailendra Patel, MD, PhD was introduced as the speaker by Dr. Kaup Shetty. Dr. Patel is Professor and Chief, Division of Endocrinology and Metabolism at the University of Cincinnati College of Medicine in Cincinnati, Ohio. The topic was "Newer Treatments of LDL-C lowering: PCSK9 Inhibitors and Then Some". Highlights of the April 20, 2021 Zoom presentation to the Academy are summarized by K. Shetty and L. Martin.

Cholesterol metabolism mechanisms won Goldstein and Brown the Nobel Prize in 1985. LDL receptors on the liver cell membrane bind extra-cellular LDL-C, bring it into the cell to be metabolized, and then are recycled back to the cell membrane. PCSK9 (Proprotein Convertase Subtilsin- Kexin type 9) enzymatically decreases LDL receptor activity, causing serum LDL-C to rise. A PCSK9 inhibitor therefore causes serum LDL-C to decrease. LDL receptor mutations (which can be autosomal dominant) can cause LDL-C to rise to high levels in the serum, with greatly increased cardiovascular risk, frequent arthralgias, and sometimes xanthomata. (Interestingly, these mutations may in the past have provided survival benefit because they help protect against sepsis.)

PCSK9 inhibitors, alirocumab and evolocumab, were found to decrease LDL-C by about 70% in 2 weeks, and they were approved for q 2 week injection in 2015. They have been found very useful for uncontrolled Familial Hyperlipidemia, but, disappointingly, they have not been shown to significantly decrease the all-cause mortality of people with general hyperlipidemia (for which studies may have been too short and under-powered). Therefore, statins continue to be the mainstay for treatment of less high-risk hyperlipidemia. But statins may be poorly tolerated, causing weakness and myalgia, etc. Statins do increase insulin resistance, HgbA1c, and new-onset DM, however, cardiovascular benefits are greater than the increased DM risk.

Understanding of lipid metabolism genetics and gene expression pathways is rapidly increasing. We now know of many different mutations of ApoB, PCSK9, and LDL receptors that can cause hyper or hypo cholesterolemia. There are many new targets for tailored prevention and treatment. Serum concentration of LDL containing lipid particles (each of which contains one Apo-B protein), is a better predictor of development of atheromatous plaque than is LDL level. Therefore, Apo-B levels predict cardiovascular risk better than do lipid levels. (Apo-B should be less than 80mg/dL.)

Mipomersen, an antisense to Apo-B mRNA, decreases the Apo-B that is essential to creation of lipid particles, thus lowering LDL and VLDL; but, because of risk of liver damage, it can only be used if enrolled in a Risk Evaluation and Mitigation Strategies (REMS) program approved by FDA. Bempedoic acid, inhibitor of an enzyme that is upstream of the enzyme inhibited by statins in the cholesterol synthesis pathway, was approved by the FDA in 2020, and is used in conjunction with statins to lower severely elevated LDL. Various methods to inhibit PCSK9 have been studied, including gene silencing through small interfering RNA (siRNA). A siRNA drug called inclisiran, which is administered subcutaneously every 6 months and is reported to reduce LDL by 54% from baseline, has been approved in Europe, but not yet by FDA.

Dr. Patel's presentation was followed by a lively Q & A session:

Since PCSK9 inhibitors are very expensive, can we use a combination of statins, ezetimibe (which blocks a mediator of cholesterol absorption), and bempedoic acid to lower LDL-C? Yes, we can. However, using a combination of the statins, ezetimibe and bile acid sequestrants that have been in use works well.

Should CoQ10 (depleted by statins) be supplemented when taking statins? In spite of intensive study of CoQ10, there is no clear answer to this.

A recent increase in CHF is noted. Could this be due to statin use? Statin use has not been shown to increase in the incidence of CHF. This could be related to higher incidence of DM in the population and associated diastolic dysfunction.

Is intermittent treatment with statins (like intermittent fasting) effective at decreasing cardiovascular risk? I do use intermittent (once or twice weekly) dosing of statins for people who do not tolerate daily statins, and this does improve their lipid profiles, particularly if they are also on a low dose of the cholesterol absorption inhibitor ezetimibe.