**EVOLUTION OF PCSK9 MAB THERAPY FOR DYSLIPIDEMIA**

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Despite clinical trials of high intensity statin therapy showing 30-40% atherosclerotic cardiovascular disease (ASCVD) risk reductions, significant residual risk remains due to inadequate low density lipoprotein-cholesterol (LDL-C) lowering and/or intolerability of statin therapy. It has been less than 15 years since discovery of proprotein convertase subtilisin-like kexin type 9 (PCSK9) loss of function mutations, providing proof-of-concept for clinical development and marketing of PCSK9 monoclonal antibody (mAb) therapy for the treatment of dyslipidemia in high risk persons with ASCVD or familial hypercholesterolemia (FH). Both alirocumab and evolocumab were FDA approved in 2015 and bococizumab is currently in clinical development. Alirocumab and evolocumab provide average 60% LDL-C lowering beyond maximally tolerated statin therapy in persons with ASCVD, FH, and other high risk conditions with targets of <100 mg/dl and <70 mg/dl reached in most persons. Many patients also experience reductions in LDL-C to <25 mg/dl. PCSK9 mAb therapy also lowers levels of non-HDL-C and apoB by approximately 50% and lipoprotein(a) by approximately 30%. Neutralizing antibodies resulting in loss of efficacy are seen in <1% of subjects. Follow-up data over 11 months for evolocumab and 18 months for alirocumab show approximate 50% reductions in ASCVD event risk (compared to placebo) on top of maximally tolerated statin therapy. Recently, the National Lipid Association and the American College of Cardiology have provided guidance for considering PCSK9 mAb therapy based on whether certain LDL-C targets (e.g., <100 mg/dl or <70 mg/dl depending on risk group) or therapeutic response (e.g., >50% LDL-C lowering) has been achieved on maximally tolerated statin therapy. Results from ongoing long-term ASCVD outcomes trials will be important to further establish the role of PCSK9 mAb therapy in addressing ASCVD residual risk beyond statin therapy.