viduals are those with certain risk factors that increase their likelihood of adverse ASCVD outcomes, including:

- progressive ASCVD, including unstable angina, that persists after achieving an LDL-C <70 mg/dL
- established clinical cardiovascular disease in individuals with diabetes, stage 3 or 4 CKD, and/or HeFH, and/or
- a history of premature ASCVD (<55 years of age for males, <65 for females)

Individuals at extreme risk are recommended to receive intensive high-dose statin therapy or statins in combination with ezetimibe or PCSK9 inhibitors to achieve further LDL-C reduction and reach the goal of <55 mg/dL.

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) clarified the benefits of extremely tight lipid control for individuals at very high or extreme risk. This trial investigated the effects of intensified lipid treatment (statins plus ezetimibe) versus statin use alone on a composite cardiovascular outcome (cardiovascular death, MI, hospitalization for unstable angina, coronary revascularization ≥30 days, and CVA) in individuals recently hospitalized for ACS and who had baseline LDL-C levels 50 to 100 mg/dL (individuals receiving lipid-lowering therapy) or 50 to 125 mg/dL (individuals not receiving lipid-lowering therapy). Mean LDL-C at baseline for both groups was 93.8 mg/dL; at 1 year of treatment, mean LDL-C in individuals receiving intensive treatment was 53.2 mg/dL, while individuals receiving statins alone had a mean LDL-C of 69.9 mg/dL (35 [EL 1; RCT]). A 7-year Kaplan-Meier estimate for the primary endpoint showed that 32.7% of individuals in the simvastatin–ezetimibe group experienced an event, compared with 34.7% of individuals who received simvastatin alone; this translated into a 6.4% relative risk reduction (HR: 0.936, 95% CI: 0.89 to 0.99; $P = .016$) and a 2.0% absolute risk reduction.

Individuals with diabetes (diabetes type not specified) comprised 27% of those enrolled in the IMPROVE-IT trial (35 [EL 1; RCT]). Those who received intensified lipid treatment for 1 year experienced a mean LDL-C decrease of 43 mg/dL, compared with a 23 mg/dL decrease in individuals who received statin treatment alone (487 [EL 4; NE]). The Kaplan-Meier estimate of prespecified subgroups showed that the use of intensive treatment resulted in a 14.4% risk reduction for individuals with diabetes (HR: 0.856, 95% CI: 0.779, 0.939) for the cardiovascular endpoint, whereas individuals without diabetes experienced a 2.3% risk reduction (HR: 0.977, 95% CI: 0.915, 1.044; $P = .023$) (35 [EL 1; RCT]; 487 [EL 4; NE]). This represents a 14% decreased risk for cardiovascular events with tight LDL-C control in individuals with diabetes. No other prespecified risk group (current smoker, hypertension, prior percutaneous coronary intervention, prior CVA, or elevated creatinine clearance) showed a significant interaction in subanalyses (35 [EL 1; RCT]; 488[EL 1; RCT]).

Outcomes from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial support extremely tight lipid control for individuals at very high or extreme cardiovascular risk (488 [EL 1; RCT]). This randomized, double-blind, placebo-controlled trial investigated the effects of adding evolocumab to high-intensity statin therapy compared with high-intensity statins alone on a composite cardiovascular outcome that included MI, cardiovascular death, stroke, coronary revascularization, or hospitalization for unstable angina. Median patient follow-up was 2.2 years. Study results included data for over 27,500 individuals (representing 59,865 patient-years) with clinically evident atherosclerotic disease and baseline LDL-C levels ≥70 mg/dL and HDL-C levels ≥100 mg/dL. All study participants were receiving statin therapy with or without ezetimibe, and the evolocumab and placebo groups had the same baseline LDL-C (92 mg/dL).

Patients in the evolocumab group achieved a mean LDL-C of 30 mg/dL, representing a reduction of 59% (95% CI: 58 to 60; $P<.001$) compared with the placebo group (mean LDL-C 69.9 mg/dL). At 26 months, primary composite endpoint events were experienced by 9.8% of individuals in the evolocumab group compared with 11.3% in the placebo group, representing a 15% risk decrease (HR: 0.85, 95% CI: 0.79 to 0.92; $P <.001$). Beyond the second year of the study, this risk reduction increased to 20% (95% CI: 0.73-0.89). A secondary composite endpoint, consisting of cardiovascular death, MI, or stroke, was also significantly decreased in the evolocumab group. This endpoint was experienced by 5.9% of individuals receiving evolocumab compared with 7.4% in the placebo group, for a 20% risk reduction (HR: 0.80, 95% CI: 0.73 to 0.88; $P <.001$). Beyond the second year, this risk reduction increased to 25% (95% CI: 0.66-0.85, $P <.001$). For singular endpoints, evolocumab use significantly reduced the risk of MI (HR: 0.73, 95% CI: 0.65 to 0.82; $P <.001$), stroke (HR: 0.79, 95% CI 0.66 to 0.95, $P <.01$), and coronary revascularization (HR: 0.78, 95% CI: 0.71 to 0.86; $P <.001$). However, cardiovascular death outcomes showed no significant differences at a median follow-up of 26 months.

The additional ASCVD benefit in very high-risk individuals with further lowering of LDL-C to <55 mg/dL utilizing statin therapy in combination with ezetimibe or a PCSK9 inhibitor forms the basis of the AACE recommendation for a new category of risk, extreme risk, with an LDL-C goal of <55 mg/dL.

Additionally, a 2010 Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis (N = 169,138, 26 clinical trials) investigated the benefits of statin therapy for LDL-C reduction in a large population that included individuals with ACS or stable ASCVD; the population also included individuals with diabetes (T1DM [n = 337] and T2DM [n = 5,414]) and/or heart failure. Investigators found that at 1 year of treatment, individuals who received statin