Trials demonstrate that ezetimibe reduces LDL-C by 10 to 25%, with significant, favorable changes in TG, apo B, and in some trials, HDL-C (534 [EL 1; MRCT]; 536 [EL 1; RCT]; 553 [EL 1; MRCT]). In combination therapy studies, ezetimibe added to ongoing statin treatment (simvastatin, atorvastatin, lovastatin, pravastatin, or fluvastatin) produced an additional LDL-C reduction of 23 to 30% (537 [EL 1; RCT]; 541 [EL 1; RCT]; 543 [EL 2; PCS]; 544 [EL 1; RCT]), and among individuals not at LDL-C goal, it significantly improved goal attainment (65-81%) compared with statin-only treatment (17-22%) (537 [EL 1; RCT]; 541 [EL 1; RCT]; 543 [EL 2; PCS]; 544 [EL 1; RCT]; 631 [EL 1; RCT]). Two multicenter, randomized, double-blind, placebo-controlled trials found that ezetimibe and simvastatin combination therapy reduced LDL-C levels by 53% (517 [EL 1; RCT]; 518 [EL 1; RCT]). The efficacy of ezetimibe and simvastatin combination has not yet been compared with that of lovastatin, pitavastatin, pravastatin, or fluvastatin monotherapy, but trials have found that this approach produces significantly greater LDL-C reductions than monotherapy with rosuvastatin (52-61% vs. 46-57%) or atorvastatin (47-59% vs. 36-53%) (632 [EL 1; RCT]; 633 [EL 1; RCT]). Ezetimibe is also effective when co-administered with fenofibrate, reducing LDL-C by an additional 20 to 22% (542 [EL 1; RCT]; 545 [EL 1; RCT]).

In 2005, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial studied the effect of the ezetimibe and simvastatin combination in individuals with HeFH using a surrogate endpoint of CIMT (634 [EL 4; NE]). Results indicated no benefit from the addition of ezetimibe to statin therapy (333 [EL 1; RCT]); however, some elements of the trial, including the study population and its baseline characteristics, suggest further study is required before definitive conclusions can be drawn (635 [EL 4; NE]). The population in this study was highly selective since HeFH affects only 2.2% of the population, this is a dyslipidemia type not typical of individuals seen in daily practice and this probably contributed to participants' high mean baseline LDL-C level of 319 mg/dL. Moreover, baseline CIMT was not at a level normally considered diseased (0.68 mm), which may have minimized results; this may have been due to the high percentage (80%) of individuals with a history of statin use (636 [EL 4; NE]).

The SHARP study, published in 2011, showed that a reduction of LDL-C with simvastatin, 20 mg daily, plus ezetimibe, 10 mg daily, safely reduced the incidence of major atherosclerotic events in a wide range of individuals with advanced CKD (512 [EL 1; RCT]). Also of interest are results from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (637 [EL 1; RCT]). This 4-year, randomized, placebo-controlled study enrolled 1,873 men and women with asymptomatic aortic stenosis and found that while the primary endpoint (a composite of cardiovascular outcomes) was not achieved, ischemic events, a secondary endpoint, were significantly reduced by 20% among individuals taking ezetimibe, 10 mg daily, and simvastatin, 40 mg daily, compared with findings in the placebo group.

Additionally, IMPROVE-IT is the only large randomized clinical trial that evaluated additional LDL-C lowering using ezetimibe in individuals with recent ACS being treated with a statin to LDL-C levels <70 mg/dL. The trial demonstrated a significant reduction in the ASCVD endpoints with an average achieved LDL-C of 53.2 mg/dL in individuals treated with ezetimibe/simvastatin versus simvastatin alone (average LDL-C 69.9 mg/dL) (35 [EL 1; RCT]).

Ezetimibe has minimal adverse effects and a strong safety profile. In several 1-year efficacy/safety studies, ezetimibe in combination with statins or fenofibrate demonstrated no significant difference in adverse event rates compared with either monotherapy (545 [EL 1; RCT]; 586 [EL 1; RCT]; 588 [EL 1; RCT]). Ezetimibe recycling via enterohepatic circulation and its elimination half-life of about 22 hours make it easy to administer in oral form (536 [EL 1; RCT]; 537 [EL 1; RCT]; 586 [EL 1; RCT]; 588 [EL 1; RCT]).

PCSK9 Inhibitors

Two monoclonal antibody inhibitors of PCSK9, a protein that regulates the recycling of LDL receptors, have recently been approved by the FDA (560 [EL 4; NE]; 564 [EL 4; NE]). Alirocumab and evolucumab are subcutaneously injectable LDL-lowering agents capable of further reducing LDL approximately 60% when added to maximum statin therapy (70 [EL 1; RCT]; 638 [EL 1; RCT]). Their strong efficacy in reducing LDL-C and possible synergistic effects with statins, combined with a favorable safety profile and tolerability, give these drugs the potential to revolutionize the treatment of the highest risk individuals, as well as those individuals unable to reach LDL-C goals with maximally tolerated statin dose (639 [EL 4; NE]). Alirocumab and evolucumab are both indicated for individuals with HeFH or as secondary prevention in individuals with clinical ASCVD who require additional LDL-lowering therapy (560 [EL 4; NE]; 564 [EL 4; NE]). Evolocumab is also indicated for treatment of individuals with HoFH (551 EL 4; NE]). This drug class meets a large unmet need for more aggressive lipid-lowering therapy beyond statins in an effort to further reduce residual risk in individuals with clinical ASCVD and diabetes, which up to now has not been possible. The recently published results of the FOURIER trial demonstrate the efficacy of evolucumab in lowering LDL-C and reducing cardiovascular risk in high-risk individuals receiving high intensity statin therapy. In this trial, evolocumab use led to 59% mean reductions in LDL-C and significantly reduced risk for the primary and secondary major cardiovascular event composite outcomes (488