only modest LDL-C lowering efficacy, and use of niacin in combination with a statin is not recommended for patients whose LDL-C is <70 mg/dL, based on RCT evidence for no benefit and possible harm in this group.

Special cases for statin combination and other combination therapies

In addition to further lowering atherogenic cholesterol in a patient not at treatment goal, other clinical situations can occur that require consideration of additional statin combination therapies. These include:

(1) Patients who require multiple LDL-C-lowering therapies (e.g., the patient who is intolerant to statin therapy or the FH patient who is unable to achieve optimal non-HDL-C and LDL-C levels with a high intensity statin and 1 other therapy): In these cases, combining statin and therapies with different mechanisms of action and in the order above is recommended, with careful consideration of the added cost and the potential for issues related to polypharmacy.

(2) Patients who have atherogenic dyslipidemia in which there are elevations in TG and VLDL-C (VLDL-C correlates closely with the TG level) plus low HDL-C (e.g., the patient with diabetes or metabolic syndrome, often with elevated non-HDL-C): These patients may benefit from evaluation of apo B or LDL particle concentration measurement because discordance may be present. Treatment options include additional atherogenic cholesterol lowering with statin combination therapies as described above, and/or other statin combination therapies that mainly lower TG and VLDL-C, such as fibrates and/or omega-3 fatty acids (prescription omega-3 fatty acids are currently only indicated for patients with TG ≥500 mg/dL). As stated previously, colesevelam may worsen TG, especially in those with levels ≥200 mg/dL at baseline, but it should also be noted that it might improve glucose control in patients with type 2 diabetes. Niacin may be used in patients with stable type 2 diabetes for lipid management, but monitoring of glucose control is advised.

Fibrate drugs

Of the currently available fibrates, gemfibrozil has been shown to reduce ASCVD events as monotherapy in primary prevention high risk males with elevated non-HDL-C[390] and for secondary prevention in males with below average HDL-C.[756] This class of drugs can reduce TG and non-HDL-C in patients with mixed dyslipidemia, and is considered a first-line choice for patients with severe hypertriglyceridemia (TG ≥500 mg/dL). The only outcomes trial of a fibrate (fenofibrate) added to a statin was the ACCORD Lipid study, which failed to demonstrate a benefit in the full study sample on ASCVD events compared to statin monotherapy in type 2 diabetes patients.[394] A predefined patient subgroup in this trial included those with TG in the top tertile (≥204 mg/dL) and HDL-C in the bottom tertile (≤34 mg/dL); these patients had a significantly lower ASCVD event rate with fenofibrate compared to placebo (−29%). Because of a drug-drug interaction with most statins that increases the risk for myositis, gemfibrozil should not be used with statins. Fenofibrate and fenofibric acid have not been found to have this adverse event when combined with statins. Fenofibrate has also been shown to reduce the progression of diabetic retinopathy and nephropathy, independent of ASCVD outcomes,[394,757] and has not been associated with incident diabetes. Fibrates should not be used in patients with stage 3B CKD or worse. Based on the limited available outcomes data, the main clinical situation in which fenofibrate or fenofibric acid could be considered as a statin combination therapy would be in type 2 diabetes patients with a non-HDL-C not at goal, who also have retinopathy and/or microalbuminuria, and do not have stage 3B or worse CKD.[757,758]

Omega-3 fatty acid preparations (EPA only or EPA + DHA)

These agents are effective for reducing TG, and are indicated for patients with very high TG (≥500 mg/dL). One outcomes trial, JELIS,[134] did show a significant reduction in ASCVD events (19% reduction) in 18,645 high risk Japanese patients who were treated with statins and were randomized to receive 1.8 g/day EPA or statin without EPA (placebo treatments are not allowed in Japan). The greatest benefit was found in those patients with TG ≥150 mg/dL and HDL-C <40 mg/dL. Until specific outcomes trials with this class of statin combination therapy in patients with elevated non-HDL-C levels are completed (the REDUCE IT[166] and STRENGTH studies[167] are ongoing), the NLA Expert Panel will not provide specific recommendations for their routine use except in patients with TG ≥ 500 mg/dL.

A new class for statin combination therapy: PCSK9 inhibitors

Monoclonal antibodies that inhibit PCSK9 (alirocumab and evolocumab) comprise a new class of statin combination therapy and have been approved by the FDA for use in addition to diet and maximally tolerated statin therapy in adults with heterozygous FH or with clinical ASCVD who require additional lowering of LDL-C. Two large, RCTs of PCSK9 inhibitors, including the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) and the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM), study have demonstrated their effectiveness for reducing LDL-C and non-HDL-C levels by ~60% among patients at high cardiovascular risk and receiving maximum tolerated dosages of statins[371] and among patients at various degrees of cardiovascular risk receiving standard therapy.[372] Both these studies provided data over approximately 1 year. Both drugs lower Lp(a) by