Statins yield only modest (approximately 6%) LDL-C reductions for each dose doubling above standard dosage (28 [EL 4; NE]). Therefore, in some instances, adding a drug with a complementary mode of action may be more effective than increasing the statin dosage. For example, the combination of simvastatin and ezetimibe is highly effective in lowering LDL-C. The Study of Heart and Renal Protection (SHARP) study, in which simvastatin, 20 mg daily, plus ezetimibe, 10 mg daily, was given, showed that a reduction of LDL-C safely reduced the incidence of major atherosclerotic events in a wide range of individuals with advanced CKD (512 [EL 1; RCT]). The IMPROVE-IT study also demonstrated a significant ASCVD benefit when ezetimibe 10 mg was added to simvastatin treated to an LDL goal of 70 mg/dL in individuals with recent ACS (35 [EL 1; RCT]). The combination of statin and bile acid sequestrant has also been shown to have additive LDL-C lowering effects compared with regular-dosage monotherapy (513 [EL 1; RCT]; 514 [EL 1; RCT]; 515 [EL 1; RCT]; 516 [EL 1; RCT]). Such combinations have been shown to provide LDL-C lowering comparable to or greater than that achieved by high-dosage statin monotherapy (513 [EL 1; RCT]; 514 [EL 1; RCT]; 515 [EL 1; RCT]; 518 [EL 1; RCT]). Examples of potentially appropriate dual therapy include statin + bile acid sequestrant, statin + ezetimibe, and statin + niacin.

Lower Dosages of 2 or More Drugs May Help to Avoid or Minimize Toxicity

Some adverse effects associated with statin drugs are dosage related (e.g., myopathy/rhabdomyolysis), and with some statins, liver dysfunction may increase with increased dosage (519 [EL 4; NE]; 520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]; 523 [EL 4; NE]) and may reverse with lower doses or changing to less than daily dosing (524 [EL 2; RCCS]). Therefore, if statin tolerability is a concern, a combination of drugs at lower dosages may be effective. Moreover, if one combination causes tolerance problems, another combination may safely achieve the desired results (10 [EL 4; NE]). Examples include statin + bile acid sequestrant and statin + ezetimibe.

Mixed Dyslipidemia is Present (High TG, Low HDL-C, High LDL-C)

If high-dosage monotherapy does not achieve lipid goals, a combination regimen may be warranted to lower both cholesterol and TG levels and to raise HDL-C levels (510 [EL 4; NE]; 511 [EL 4; NE]). For example, the statin and niacin combination produces LDL-C reductions comparable to those of statin monotherapy and leads to significantly greater improvements in HDL-C and TG levels (326 [EL 1; RCT]; 352 [EL 1; RCT]; 353 [EL 1; MRCT]).

Niacin increases HDL-C and in higher doses lowers LDL-C; however, no clinical benefit has been demonstrated when niacin is added to aggressive statin regimens (483 [EL 1; RCT]; 525 [EL 4; NE]). Although the ezetimibe and fenofibrate combination moderately improves LDL-C, it also substantially improves TG and HDL-C levels (Tables 15 and 16). Examples of combination therapy include statin + fibrate, statin + niacin, statin + bile acid sequestrant, ezetimibe + fibrate, and ezetimibe + niacin. The National Institutes of Health Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides (AIM-HIGH) study failed to show a cardiovascular outcome benefit with the addition of niacin in individuals treated with statins and an average LDL-C of 71 mg/dL (525 [EL 4; NE]). The Treatment of HDL to Reduce the Incidence of Vascular Events from the HPS research unit (HPS2-THRIVE) trial found that extended-release niacin in combination with laropiprant added to effective statin-based LDL-C-lowering therapy did not significantly reduce major vascular events but did increase the risk of serious adverse events (484 [EL 1; RCT]).

Choosing Lipid-Lowering Drugs

Currently available lipid-lowering drugs include hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), fibric acid derivatives (fibrates), nicotinic acid (niacin), bile acid sequestrants, cholesterol absorption inhibitors (ezetimibe), PCSK9 inhibitors (alirocumab, evolocumab), a microsomal transfer protein (MTP) inhibitor (lomitapide), and an antisense apolipoprotein B oligonucleotide (mipomersen). The primary metabolic effects and main drawbacks of these 8 drug classes are summarized in Table 13 (410 [EL 4; NE]; 517 [EL 1; RCT]; 519 [EL 4; NE]; 520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]; 523 [EL 4; NE]; 526 [EL 2; PCS]; 527 [EL 1; RCT]; 528 [EL 2; NRCT]; 529 [EL 2; NRCT]; 530 [EL 2; NRCT]; 531 [EL 1; RCT]; 532 [EL 1; RCT]; 533 [EL 1; RCT]; 534 [EL 1; MRCT]; 535 [EL 4; NE]; 536 [EL 1; RCT]; 537 [EL 1; RCT]; 538 [EL 2; PCS]; 539 [EL 1; RCT]; 540 [EL 1; RCT]; 541 [EL 1; RCT]; 542 [EL 1; RCT]; 543 [EL 2; PCS]; 544 [EL 1; RCT]; 545 [EL 1; RCT]; 546 [EL 4; NE]; 547 [EL 1; RCT]; 548 [EL 4; NE]; 549 [EL 4; NE]; 550 [EL 4; NE]; 551 [EL 1; MRCT]; 552 [EL 4; NE]; 553 [EL 1; MRCT]; 554 [EL 4; NE]; 555 [EL 4; NE]; 556 [EL 4; NE]; 557 [EL 4; NE]; 559 [EL 4; NE]; 560 [EL 4; NE]; 561 [EL 4; NE]; 562 [EL 4; NE]; 563 [EL 4: NE]; 564 [EL 4; NE]; 565 [EL 4; NE]). The clinical efficacy of these pharmacologic agents in both primary and secondary prevention of coronary events and mortality is outlined Table 15 and Table 16. A summary of available lipid-lowering therapies and dosages is presented in Table 18 (519 [EL 4; NE]; 520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]; 523 [EL 4; NE]; 548 [EL 4; NE]; 549 [EL 4; NE]; 552 [EL 4; NE]; 554 [EL 4; NE]; 555 [EL 4; NE]; 556 [EL 4; NE]; 557 [EL 4; NE]; 558 [EL 4; NE]; 559 [EL 4; NE]; 560 [EL 4; NE]; 562 [EL 4; NE]; 563 [EL 4; NE]; 564 [EL 4; NE]; 565 [EL 4; NE]; 566 [EL 4; NE]).