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Current Therapy of Hypercholesterolemia

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Abstract

Randomized, double-blind, placebo-controlled secondary prevention and primary prevention studies and observational studies have documented that statins reduce cardiovascular events in high-risk patients with hypercholesterolemia. The 2013 American College of Cardiology/American Heart Association guidelines on treatment of hypercholesterolemia support the use of statins in 4 major groups that will be discussed. The Expert Panel of these guidelines could find no data supporting the routine use of nonstatin drugs combined with statins to further reduce cardiovascular events. Since these guidelines were published, a double-blind, randomized trial of 18, 144 patients with an acute coronary syndrome demonstrated at 7-year follow-up that the incidence of cardiovascular events was 34.7% in patients randomized to simvastatin plus placebo versus 32.7% in patients randomized to simvastatin plus ezetimibe (hazard ratio = 0.936; p = 0.016). Proprotein convertase subtilisinkexin type 9 (PCSK9) inhibitors further lower serum low-density lipoprotein cholesterol by 50% to 70% in patients treated with statins and 4 phase 3 trials including more than 70, 000 patients are investigating whether these monoclonal antibodies to PCSK9 will lower cardiovascular events.

Keywords:

Lipids; Statins; Lipid-Lowering drugs; Hypercholesterolemia; Serum low-density Lipoprotein cholesterol; Ezetimibe; Pro protein convertase subtilisinkexin Type 9 inhibitors

Introduction

Numerous studies have shown that a high serum total cholesterol or low-density lipoprotein (LDL) cholesterol is a risk factor for cardiovascular events in men and in women [1-4]. Randomized, double-blind, placebo-controlled secondary prevention and primary prevention studies [5-32] and observational studies have also shown that statins lower the incidence of cardiovascular events in high-risk patients with hypercholesterolemia.

Lifestyle measures should be used to treat patients with hypercholesterolemia. The patient should achieve and maintain a weight between 18.5 to 24.9 kg/m2 [33]. The diet should include less than 200 mg of cholesterol daily. Less than 30% of total caloric intake should be fatty acids. Saturated fatty acids should comprise less than 7% of total calories, polyunsaturated acids up to 10% of total calories, and monounsaturated fatty acids 10% to 15% of total calories. The diet should also be high in fiber and high in fruits and vegetables. There is no good evidence to support any dietary supplements. A more liberalized diet is warranted in elderly persons who are prone to malnutrition. Moderate intensity exercise is recommended for 30 to 60 minutes daily [33]. Smoking should be stopped, and exposure to environmental smoke avoided [33]. Hypertension should be treated, and the blood pressure reduced to less than 140/90 mm Hg [33]. Diabetes mellitus should be controlled, and the hemoglobin A1c reduced to less than 7.0% [33].

Randomized, Double-Blind, Studies

At 5.4-year median follow-up of 4,444 men and women with coronary heart disease (CHD) and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin 20 mg to 40 mg lowered all-cause death 30%, CHD death 42%, nonfatal myocardial infarction 33%, major coronary events 34%, cerebrovascular events

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30%, any atherosclerosis-related endpoint 34%, coronary revascularization 37%, new or worsening angina pectoris 26%, intermittent claudication 38%, and arterial bruits 30%. [5-7]. Reductions in endpoint events were similar in men and women. The absolute risk reduction for both all-cause death and CHD death was approximately twice as great in patients 65 years of age and older as in those younger than 65 years. At 7.4-year median follow-up, simvastatin lowered all-cause death 30% and CHD death 38% [8].

In the Cholesterol and Recurrent Events study, pravastatin or placebo was given for 5 years to 4, 159 post-myocardial infarction patients with serum total cholesterol levels less than 240 mg/dL and serum LDL cholesterol levels of 115 to 174 mg/dL [9, 10]. At 5-year median follow-up, compared with placebo, pravastatin 40 mg daily lowered CHD death or nonfatal myocardial infarction 24%, stroke 31%, coronary bypass surgery 26%, and coronary angioplasty 23% [9]. For every 1,000 patients aged 65 to 75 years treated for 5 years with pravastatin, 225 cardiovascular hospitalizations would be prevented compared with prevention of 121 cardiovascular hospitalizations in 1,000 younger patients [10].

The Long-Term Intervention with Pravastatin in Ischaemic Disease study randomized 9,014 patients with a history of myocardial infarction or unstable angina pectoris who had initial serum total cholesterol levels of 155 to 271 mg/dL to pravastatin 40 mg daily or placebo [11,12]. At 6.1-year follow-up, compared with placebo, pravastatin lowered all-cause death 22%, death from CHD or nonfatal myocardial infarction 24%, nonfatal myocardial infarction 29%, stroke 19%, and coronary revascularization 20% [11]. Treatment of 1,000 patients for 6 years with pravastatin prevented 30 deaths, 28 nonfatal myocardial infarctions, 9 nonfatal strokes, 23 episodes of coronary artery bypass surgery, 20 episodes of coronary angioplasty, and 82 hospital admissions for unstable angina pectoris 11]. At 8-year follow-up, pravastatin lowered all-cause death 18%, CHD death 25%, and CHD death or nonfatal myocardial infarction 17% [12].

The Heart Protection Study randomized 20,536 men and women (5,806 aged 70 to 80 years) with prior myocardial infarction (8,510 patients), other CHD (4,876 patients), and no CHD (7,150 patients) and a serum total cholesterol level of 135 mg/dL or higher to simvastatin 40 mg daily or to placebo [13] Of 7,150 patients without CHD, 25% had cerebrovascular disease, 38% had peripheral arterial disease (PAD), 56% had diabetes mellitus, and 3% had treated hypertension without atherosclerotic vascular disease or diabetes mellitus. At 5-year follow-up, compared to placebo, simvastatin lowered all-cause death 13%, any cardiovascular death 17%, major coronary events 27%, any stroke 25%, coronary or noncoronary revascularization 24%, and any major cardiovascular event 24% [13]. The reductions in death and in cardiovascular events occurred regardless of initial levels of serum lipids, age, or gender. Five years of simvastatin therapy prevented myocardial infarction, stroke, and revascularization in 70 to 100 patients per 1,000 treated patients [13].

In the Heart Protection Study, 3,500 patients had initial serum LDL cholesterol levels below 100 mg/dL. Lowering serum LDL cholesterol from 97 mg/dL to 65 mg/dL by simvastatin in these patients caused a similar lowering in risk as did treating patients with higher serum LDL cholesterol levels [13]. The Heart Protection Study Investigators recommended treating patients at high risk for cardiovascular events with statins, regardless of their initial levels of serum lipids, age, or gender [13].

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study, 3,086 patients with an acute coronary syndrome and a mean serum LDL cholesterol level of 124 mg/dL were randomized to atorvastatin 80 mg daily or placebo 24 to 96 hours after hospitalization for 16 weeks [14]. At 16-week follow-up, compared with placebo, atorvastatin lowered death, nonfatal myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization 16% and stroke 50% [14].

Sixty-nine patients with intermittent claudication caused by PAD and hypercholesterolemia were randomized to simvastatin 40 mg daily or placebo [15]. Compared with placebo, simvastatin increased treadmill exercise time until onset of intermittent claudication 24% at 6 months after treatment and 42% at 1 year after treatment [15].

In a study of 354 patients with intermittent claudication caused by PAD and hypercholesterolemia randomized to atorvastatin 80 mg daily or placebo, at 1-year follow-up, compared with placebo, atorvastatin 80 mg daily improved pain-free treadmill walking distance 40% and community-based physical activity [16]. In another study of 86 patients with intermittent claudication caused by PAD and hypercholesterolemia, at 6-month follow-up, compared with placebo, simvastatin 40 mg daily improved pain-free walking distance and total walking distance on a treadmill, improved the mean ankle-brachial index at rest and after exercise, and improved symptoms of claudication [17].

In the Lipid Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes trial, 10, 305 patients with hypertension and 3 or more other cardiovascular risk factors with no history of CHD and a mean serum LDL cholesterol of 133 mg/dL were randomized to atorvastatin 10 mg daily or to placebo [18]. At 3.3-year follow-up, compared with placebo, atorvastatin lowered the incidence of fatal CHD and nonfatal myocardial infarction 34% in patients aged 60 years and younger and 36% in patients older than 60 years [18]. Atorvastatin also reduced fatal and nonfatal stroke 27% [18].

In 4,162 patients hospitalized for an acute coronary syndrome, the median serum LDL cholesterol was 95 mg/dL in patients randomized to pravastatin 40 mg daily versus 62 mg/dL in patients randomized to atorvastatin 80 mg daily [19]. At 2-year follow-up, the primary end point of death from any cause, myocardial infarction, documented unstable angina pectoris needing rehospitalization, coronary revascularization (performed at

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least 30 days after randomization), and stroke was 26.3% in pravastatin-treated patients versus 22.4% in atorvastatin-treated patients, a 16% reduction by atorvastatin [19].

In the Collaborative Atorvastatin Diabetes Study, 2, 838 patients with diabetes mellitus, no cardiovascular disease, and a serum LDL cholesterol less than 160 mg/dL were randomized to atorvastatin 10 mg daily or to placebo [20]. At 3.9-year median follow-up, compared with placebo, atorvastatin lowered time to first occurrence of acute CHD events, coronary revascularization, or stroke 37%, acute coronary events 36%, and stroke 48% [20].

In the Treating to New Targets (TNT) study of 10, 001 patients with stable CHD and a serum LDL cholesterol less than 130 mg/dL, the effect of atorvastatin 10 mg daily versus 80 mg daily was investigated [21]. The mean serum LDL cholesterol levels were 77 mg/dL in patients treated with atorvastatin 80 mg daily versus 101 mg/dL in patients treated with atorvastatin 10 mg daily. At 4.9-year median follow-up, the primary endpoint of a first major cardiovascular event was lowered 22% by atorvastatin 80 mg daily [21].

In the Study Assessing Goals in the Elderly (SAGE), 893 ambulatory CAD patients aged 65 to 85 years with 1 or more episodes of myocardial ischemia lasting for at least 3 minutes during 48-hour ambulatory electrocardiographic screening were randomized to atorvastatin 80 mg daily or to pravastatin 40 mg daily and followed for 12 months [22]. The total duration of myocardial ischemia detected by 48-hour ambulatory electrocardiograms at month 3 and at month 12 after randomization was reduced by both atorvastatin and pravastatin. Compared with pravastatin, atorvastatin lowered serum LDL cholesterol and lowered all-cause death 67% [22].

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study, 4,731 patients who had a stroke or transient ischemic attack within 1 to 6 months prior to study entry, a serum LDL cholesterol of 100 to 190 mg/dL and no CHD were randomized to atorvastatin 80 mg daily or to placebo [23]. At 4.9-year median follow-up, atorvastatin lowered the incidence of new stroke 16% and of major cardiovascular events 20% [23].

In the Justification for the Use of Statins in Prevention : an Intervention Trial evaluating Rosuvastatin, 17,082 apparently healthy persons with a serum LDL cholesterol less than 130 mg/dL and high-sensitivity C-reactive protein levels of 2.0 mg/L or higher were randomized to rosuvastatin 20 mg daily or placebo [24]. At 1.9-year median follow-up, rosuvastatin lowered serum LDL cholesterol 50%, high-sensitivity C-reactive protein levels 37%, and the primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina pectoris, or death from cardiovascular causes 44%. [24].

A meta-analysis was performed of 26 randomized trials of statins in 170, 000 patients [25]. The decrease in major cardiovascular events per 1.0 mmol/L reduction in serum LDL cholesterol was 22% in patients aged 65 years and younger, 22% in patients aged 66 to 75 years, and 16% in patients older than 75 years [25].

A meta-analysis was also performed of 9 randomized trials of statins for secondary prevention in 19, 569 patients aged 65 to 82 years [26]. Over 5 years, statins lowered all-cause mortality 22%, CHD mortality 30%, nonfatal myocardial infarction 26%, requirement for revascularization 30%, and stroke 25%. The estimated number needed to treat to save 1 life was 28 [26].

In 5,518 patients with type 2 diabetes mellitus treated with simvastatin, patients were randomized to receive either masked fenofibrate or placebo [27]. At 4.7-year mean follow-up, the combination of fenofibrate plus simvastatin did not lower the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin plus placebo [27].

In 9,795 patients with type 2 diabetes mellitus (2,131 with cardiovascular disease), patients were randomized to fenofibrate or placebo [28]. At 5-year follow-up, the primary outcome of coronary events was not decreased by fenofibrate [28].

A study investigated 15,067 patients at high cardiovascular risk who were randomized to atorvastatin plus the cholesteryl ester transfer protein (CETP) inhibtor torcetrapib or to atorvastatin alone [29]. Torcetrapib increased serum HDL cholesterol 72% and decreased serum LDL cholesterol 25%. At 1-year follow-up, the trial was terminated because torcetrapib increased cardiovascular events 25% and all-cause death 58% [29].

A study investigated 15,871 patients with a recent acute coronary syndrome who were randomized to the CTEP inhibitor dalcetrapib or placebo [30]. Dalcetrapib increased serum HDL cholesterol 31% to 40% and had a minimal effect on serum LDL cholesterol levels. At 31-month median follow-up, dalcetrapib insignificantly increased the primary outcome of CHD death, nonfatal myocardial infarction, ischemic stroke, unstable angina pectoris, or cardiac arrest with resuscitation by 4% [30].

Among 3,414 patients with atherosclerotic cardiovascular disease and low serum HDL cholesterol levels treated with simvastatin plus ezetimibe if needed to maintain the serum LDL cholesterol below 70 mg/dL, at 36-month follow-up, patients randomized to niacin had improvements in serum HDL cholesterol and triglyceride levels but no clinical improvement compared to patients randomized to placebo [31]. In this study, patients treated with niacin had a 67% insignificant increase in ischemic stroke or stroke of uncertain origin [31].

In the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study, 25, 673 high-risk patients with vascular disease were randomized to treatment with simvastatin or simvastatin/ezetimibe plus 2 grams of extended-release niacin plus the anti-flushing agent laropriprant or to treatment with simvastatin or simvastatin/ezetimibe plus placebo [32]. At 3.9-year follow-up, compared to treatment with simvastatin

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or simvastatin/ezetimibe, addition of niacin did not lower the primary outcome of major vascular events but increased serious adverse events with an absolute excess of 3.7% [32].

Observational Studies

In an observational prospective study of 488 men and 922 women, mean age 81 years, with prior myocardial infarction and a serum LDL cholesterol of 125 mg/dL or higher, 48% of patients were treated with statins [34-36]. At 3-year follow-up, compared to no lipid-lowering therapy, treatment with statins lowered CHD death or nonfatal myocardial infarction 50% [34], stroke 60% [35], and heart failure 48% [36]. The lower the serum LDL cholesterol in these patients treated with statins, the greater was the decrease in new coronary events [34] and in stroke [35].

In an observational prospective study of 171 men and 358 women with prior myocardial infarction, diabetes mellitus, and a serum LDL cholesterol of 125 mg/dL or higher, 53% of patients were treated with statins [37]. At 29-month follow-up, compared with no lipid-lowering therapy, treatment with statins lowered in diabetics CHD death or nonfatal myocardial infarction 37% and stroke 47% [37].

In an observational prospective study of 264 men and 396 women with symptomatic PAD and a serum LDL cholesterol of 125 mg/dL or higher, 48% of patients were treated with statins [38]. At 39-month follow-up, compared with no lipid-lowering therapy, therapy with statins lowered CHD death or nonfatal myocardial infarction 52% in patients with prior myocardial infarction and 59% in patients with no prior myocardial infarction [38].

Statins lowered death or ventricular tachycardia or ventricular fibrillation 35% in patients with an implantable cardioverter-defibrillator (ICD) in the Multicenter Automatic Defibrillator Implantation trial (MADIT)-II [39]. Use of statins in 402 of 965 patients who had an ICD was associated with a 42% lowering of all-cause death [40]. Use of statins in 121 of 209 patients with heart failure who had combined cardiac resynchronization-ICD therapy was associated with a 54% lowering of appropriate ICD shocks and with a 95% lowering of death [41]. Use of statins in 58% of 209 patients with heart failure treated with combined cardiac resynchronization- ICD therapy and in 49% of 320 patients with heart failure treated with an ICD lowered appropriate ICD shocks 65% and reduced time to mortality 82% [42]. At 1,243 days follow-up of 549 patients with heart failure treated with an ICD, use of statins lowered appropriate ICD shocks 46%, inappropriate ICD shocks 48%, and time to all-cause mortality 68% [43].

In the MADIT-Cardiac Resynchronization Therapy trial, 499 of 821 patients (61%) with nonischemic cardiomyopathy were treated with statins [44]. At 4-year follow-up, the cumulative probability of fast ventricular tachycardia/ventricular fibrillation or death was reduced from 19% in nonstatin users to 11% for patients treated with statins [44].

In 100 patients undergoing noncardiac vascular surgery, the incidence of cardiac death, nonfatal myocardial infarction, stroke, or unstable angina pectoris at 6-month follow-up was less in 50 patients treated with atorvastatin than in 50 patients treated with placebo (8% versus 26%, respectively [45]. Of 510 patients who survived abdominal aortic aneurysm ((AAA) surgery beyond 30 days and were followed for a median of 4.7 years, 154 (30%) were treated with statins [46]. In this study, statins reduced all-cause mortality 60% [46].

In 160 patients who died during hospitalization after undergoing major noncardiac vascular surgery and in 320 controls, statin therapy was less commonly administered to patients who died (8%) than to controls (25%) [47]. Perioperative cardiovascular complications of death, myocardial infarction, myocardial ischemia, congestive heart failure, or ventricular tachyarrhythmias occurring after major noncardiac vascular surgery were less in patients treated with statins (9.9% of 526 hospitalizations in patients treated with statins and in 16.5% of 637 hospitalizations in patients not treated with statins [48].

In a study of 577 patients undergoing carotid endarterectomy (300 patients), lower extremity revascularization (179 patients), or AAA repair (98 patients), stepwise Cox regression analysis demonstrated that use of statins was an independent predictor of reduced perioperative myocardial infarction or death during 2-year follow-up by 57% [49]. In a study of 408 patients with diabetes mellitus who had ischemic stroke and of 404 age-matched and gender-matched patients with diabetes mellitus without ischemic stroke, the serum LDL cholesterol level was higher in diabetics who had ischemic stroke [50].

Of 130 patients with an AAA not treated surgically, 58% of patients were treated with statins [51]. The sizes of the AAAs were 4.6 cm at baseline and 4.5 cm at 23-month follow-up in patients treated with statins and 4.5 cm at baseline and 5.3 cm at 24-month follow-up in patients not treated with statins. Four of 75 patients (5%) treated with statins died at 45-month follow-up, and 9 of 55 patients (16%) not treated with statins died at 44-month follow-up [51].

Of 449 patients with severe carotid arterial disease who did not undergo revascularization, 298 (66%) were treated with statins [52]. Follow-up was 26 months in patients taking statins and 21 months in patients not taking statins. Stepwise Cox regression analysis demonstrated that use of statins lowered the time to development of new stroke or new myocardial infarction or death by 87% [52].

In 197, 551 patients, the beneficial effect of statins in preventing the development of renal dysfunction were independent of their lipid-lowering effect [53]. Statin therapy modifies the lipid profile in chronic kidney disease patients not on dialysis therapy [54]. Data from clinical trials on the clinical potential of statins in dialyzed patients are limited [55].

In a study of 180 patients with mild valvular aortic stenosis, 62 patients (34%) were treated with statins [56]. At 33-month follow-up, use of statins was associated with a reduction in the

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progression of aortic stenosis [56]. In a study of 174 patients with mild or moderate aortic stenosis, 57 patients (33%) were taking statins [57]. At 21-month follow-up, use of statins decreased progression of aortic stenosis [57]. In a community-based study of 156 patients with aortic stenosis, 38 patients (24%) were treated with statins [58]. At 3.7-year follow-up, use of statins had slowed progression of aortic stenosis [58]. In a study of 1,046 patients with aortic sclerosis, mild aortic stenosis, and moderate aortic stenosis, 309 patients were treated with statins [59]. At 5.6-year follow-up, statins slowed progression of aortic sclerosis and of mild aortic stenosis but not of moderate aortic stenosis [59].

These observational data were confirmed by 1 prospective trial using rosuvastatin [60]. However, 2 prospective trials (1 using atorvastatin and 1 using simvastatin plus ezetimibe) did not confirm these data [61,62]. It is unlikely that statins will affect a heavily calcified valve with severe aortic stenosis. However, patients with aortic stenosis often have associated cardiovascular disease such as CHD, other atherosclerotic vascular disease, or diabetes mellitus, which will benefit from treatment with statins.

In a study of 551 patients with congestive heart failure and a reduced left ventricular ejection fraction 45% of patients were treated with statins [63]. At 1-year follow-up, treatment with statins was associated with a 59% reduction in death [63]. In 54, 960 Medicare patients hospitalized for heart failure, treatment with statins caused 20% lower 1-year mortality and an 18% lower 3-year mortality [64]. A double- blind , placebo-controlled study in 4,574 patients with heart failure and reduced or preserved left ventricular ejection fraction showed at 3.9-year median follow-up that rosuvastatin 10 mg daily did not affect clinical outcomes [65].In a study of 5,011 patients with heart failure due to ischemic heart disease and a reduced left ventricular ejection fraction randomized to treatment with rosuvastatin or placebo, if you include repeat hospitalization for heart failure events, rosuvastatin lowered the risk of heart failure hospitalization by 15% to 20% with 76 fewer hospitalizations for heart failure per 1,000 patients treated over a median of 33 months of follow-up [66].

American College of Cardiology/American Heart Association 2013 Lipid Guidelines

The American College of Cardiology (ACC)/American Heart Association (AHA) 2013 Lipid Guidelines recommend therapy of hypercholesterolemia to lower cardiovascular events in 4 major groups [67]. High-dose statin therapy (atorvastatin 40-80 mg daily or rosuvastatin 20-40 mg daily) decreases serum LDL cholesterol ≥50% and should be administered as first-line therapy to adults ≤75 years of age with atherosclerotic cardiovascular disease (ASCVD) for secondary prevention with a class I indication. Moderate-dose or high-dose statins should be considered for use in adults older than 75 years with ASCVDwith a class IIa indication [67].

Adults aged 21 years and older with a serum LDL cholesterol of ≥190 mg/dL should be treated with high-dose statin therapy for primary prevention with a class I indication [67]. For primary prevention in diabetics aged 40 to 75 years and serum LDL cholesterol between 70 to 189 mg/dL, moderate-dose statins should be given with a class I indication. For primary prevention in diabetics aged 40 to 75 years, a serum LDL cholesterol between 70 to 189 mg/dL, and a 10-year risk of ASCVD of 7.5% or higher calculated from the Pooled Heart Equation, high-dose statins should be given with a class IIa indication. For primary prevention in diabetics aged 21 to 39 years or older than 75 years and serum LDL cholesterol between 70 to 189 mg/dL, moderate-dose statins or high-dose statins should be given with a class IIa indication [67].

Adults aged 40-75 years of age with a serum LDL cholesterol of 70-189 mg/dL without ASCVD or diabetes mellitus and a 10-year risk of ASCVD of ≥7.5% should be treated with moderate-dose or high-dose statin therapy for primary prevention with a class I indication [67]. Adults aged 40-75 years of age with a serum LDL cholesterol of 70-189 mg/dL without ASCVD or diabetes mellitus and a 10-year risk of ASCVD of 5% to 7.4% should be treated with moderate-dose statin therapy for primary prevention with a class IIa indication [67]. These guidelines also state that there is no additional ASCVD reduction from adding nonstatin therapy to further decrease non-HDL cholesterol once an LDL cholesterol goal has been reached [67].

Ezetimibe Plus Statin Therapy after Acute Coronary Syndromes

After the ACC/AHA 2013 lipid guidelines were published, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was published [68]. This double-blind, randomized trial of 18, 144 patients with an acute coronary syndrome compared simvastatin plus ezetimibe with simvastatin plus placebo. The median serum LDL cholesterol level during the study was 69.5 mg/dL on simvastatin plus placebo versus 53.7 mg/dL on simvastatin plus ezetimibe. The primary endpoint was cardiovascular death, nonfatal myocardial infarction, unstable angina requiring hospitalization, coronary revascularization ≥30 days after randomization, or nonfatal stroke and was at 7 years 32.7% in the simvastatin plus ezetimibe-treated group versus 34.7% in the simvastatin plus placebo-treated group (a 6.4% reduction) with the number needed to treat=50 to prevent 1 cardiovascular event in 7 years due to a decrease in nonfatal myocardial infarction and nonfatal stroke [6]. All-cause mortality was similar in both treated groups [68]. However, Dr. Giugliano reported at the European Society of Cardiology Meeting on August 30, 2015 that the primary endpoint in 4,933 diabetics (27% of the patients) was reduced 14% from 45.5% to 40.0% by ezetimibe but was not reduced by ezetimibe in the 13,211 nondiabetics.

PCSK9 Inhibitors

Several monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9) have lowered serum LDL cholesterol levels 50% to 70% across various patient populations and background lipid-lowering therapy [69]. A meta-analysis of 24 randomized clinical trials including 10,159

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patients showed that PCSK9 inhibitors lowered serum LDL cholesterol 47.49% [70]. The Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER)-1 and OSLER-2 randomized 4465 patients in a 2:1 ratio to evolocumab given subcutaneously at a dose of 140 mg every 2 weeks or 420 mg monthly plus standard lipid-lowering therapy or to standard lipid-lowering therapy alone [71]. Compared with standard lipid-lowering therapy alone, evolocumab plus standard lipid-lowering therapy reduced serum LDL cholesterol 61% from 120 mg/dL to 48 mg/dL. The incidence of cardiovascular events at 1 year was lowered 53% from 2.18% in the standard lipid-lowering therapy group alone to 0.95% in the group treated with evolocumab plus standard lipid-lowering therapy [71].

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 randomized 2, 341 patients at high risk for cardiovascular events who had serum LDL cholesterol levels of 70 mg/dL or higher despite treatment with statins at the maximum tolerated dose in 2:1 ratio to receive alirocumab 150 mg or placebo subcutaneously every 2 weeks for 78 weeks [72]. Compared to placebo, alirocumab reduced serum LDL 62%. At week 78, a post hoc analysis found that the incidence of death from CHD, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization was 1.7% on alirocumab versus 3.3% on placebo (a 48% reduction by use of alirocumab) [72].

At this time, there are 4 ongoing placebo-controlled phase 3 trials in more than 70,000 patients investigating whether PCSK9 inhibitors on a background of statin therapy lower cardiovascular events [69]. These trials are investigating the PCSK9 inhibitors alirocumab, evolocumab, and bococizumab (2 trials) [69]. The completion of these cardiovascular endpoint trials is expected in 2018 [69].

Despite absence of long-term clinical trial data on efficacy and safety , alrocumab and evolocumab have been very recently approved by the USA Food and Drug administration for use in addition to diet and maximally-tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or clinical ASCVD who require additional lowering of serum LDL cholesterol. Alirocumab will cost about $14, 600 per year and evolocumab about $14, 100 dollars per year. The topic of statin intolerance is discussed elsewhere [73].

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