Summary of Educational Need & Gap Analysis

Executive Summary

Cardiovascular disease (CVD) is the leading cause of death worldwide, killing approximately 17.3 million individuals per year.[1] Atherosclerosis often gives rise to CVD through the buildup of plaques containing cholesterol and fatty acids in the arterial walls.[2] Increased plasma concentration of low-density lipoprotein (LDL) cholesterol is a major risk factor for atherosclerotic CVD,[3] and high cholesterol levels alone account for 4.5% of total deaths worldwide.[1] In adults over the age of 20, serum cholesterol concentrations over 190 mg/dL are considered abnormal, and an LDL concentration over 130 mg/dL is considered high.[3] In 2012, 54% of Europeans and 48% of Americans had elevated cholesterol levels over 130 mg/dL.[1] Blood LDL cholesterol concentration is a modifiable CVD risk factor, and randomized control trials have shown that reducing LDL cholesterol levels decreases the risk of CVD.[4] In fact, decreasing population serum cholesterol levels by 1 mmol/L (equivalent to 38.67 mg/dL) leads to a 19% decrease in CVD-related mortality and a 21% decrease in other major vascular events.[5]

For the past 3 decades, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been the drugs of choice for lowering plasma LDL cholesterol levels.[6] Statins have been consistently proven to decrease atherosclerotic CVD in proportion to the level of LDL reduction.[4,7] While statins have excellent safety profiles, a subset of patients is unable to tolerate statins due to muscle pains in addition to other adverse events.[8] Furthermore, a meta-analysis of statin trials found that 40% of patients failed to reach target LDL cholesterol levels of <70 mg/dL.[9] Recently, a variety of therapies have been developed as alternatives to statins, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and very low density lipoprotein (VLDL) lowering agents. These therapies are useful for treating patients who are refractory to statin treatment as well as those with familial hypercholesterolemia (FH), a genetic disease in which mutations occur in proteins involved in LDL cholesterol metabolism, making the pathway defective and leading to a buildup of LDL cholesterol.[10]

The American Heart Association has recently expanded its guidelines regarding administration of LDL cholesterol-lowering medications to encompass 4 at-risk patient groups.[3] These groups include patients with 1) any form of clinical atherosclerotic CVD, 2) primary LDL cholesterol levels >90 mg/dL, 3) diabetes mellitus who are 40-75 years and have LDL cholesterol levels >70 mg/dL, or 4) an estimated 10-year atherosclerotic CVD risk >7.5% aged 40-75 years.[3] As more patients are categorized as requiring LDL cholesterol-lowering interventions, clinicians must familiarize themselves with new and emerging research regarding LDL cholesterol treatments and atherogenic CVD screening. In the planned initiative described here, XYZ Company will develop ABC program to address the potential gaps in clinician knowledge of cascade screening methods and new cholesterol-lowering drugs as well as the guidelines for using them in a variety of populations.

Identified Gaps in Practice

Gap 1: Clinicians may not be familiar with new treatment options for refractory hypercholesterolemia and familial hypercholesterolemia.	
Current Practice	The molecular causes of atherosclerosis involve complex genetic and environmental interactions and are still under investigation,[1] but lowering LDL cholesterol with statins has been unequivocally proven to reduce the incidence of atherosclerotic CVD.[9] Until recently,

	there were few alternative options to statin therapy, but in the last five years, many new drugs have been FDA-approved for cholesterol reduction with more in phase 3 trials.[11] Since statins have been shown to cause muscle symptoms in 7% to 29% of patients and can in rare cases cause rhabdomylosis,[8] clinicians must familiarize themselves with non-statin treatment options. Furthermore, patients with homozygous FH rarely respond to statin treatment and usually require LDL apheresis with bile acid sequestrants, which are not well tolerated.[12] Clinicians may not be offering all available options to patients with refractory hypercholesterolemia or those with FH.
Best Practice	Clinicians must be familiar with the recent advances in LDL cholesterol lowering medications, especially for patients with heterozygous or homozygous FH. PCSK9 monoclonal antibodies evolocumab and alirocumab were approved by the FDA in the summer of 2015 and have been shown to decrease LDL cholesterol levels both alone and in combination with statins.[13,14] Ezetimibe is a cholesterol absorption inhibitor that was approved in 2003, but its positive effect on cardiovascular outcomes was only recently shown in a randomized clinical trial.[15] The microsomal triglyceride transfer protein (MTP) inhibitor, lomitapide, and the apolipoprotein B-100 antisense oligonucleotide, mipomersen, both decrease LDL cholesterol levels in patients with homozygous FH.[16,17] Clinicians should be up-to-date on the new and emerging therapies in order to adequately treat individuals with uncontrolled high cholesterol levels.
Learning Objective	Describe the new and emerging non-statin treatments for elevated LDL cholesterol levels.

Gap 2: Clinicians may not be familiar with new recommendations for familial hypercholesterolemia diagnostic screening methods.	
Current Practice	A recent analysis of survey data indicates that 1 in 250 adults in the United States have FH based on the Dutch diagnostic criteria.[18] Despite this high prevalence, only 15% to 20% of FH adults are diagnosed, and the United States still lacks national standards for the most effective screening method, cascade screening.[19] A recent survey of accredited medical schools, pharmacy schools, and osteopathic medicine schools indicated that only one-third of universities teach students about the importance of cascade screening,[20] and a survey of physicians found that only 47% comprehended the autosomal dominant inheritance pattern of FH in first-degree relatives.[21] Furthermore, when cascade screening is implemented, it is often through indirect contact with family members instead of direct contact through physicians, which is the most effective method of conveying genetic risk factors.[22]
Best Practice	When an index case of FH is identified, physicians should employ stepwise cascade screening of relatives in order to diagnose family members with FH.[19] Research indicates that the most effective method of cascade screening for FH occurs through direct contact from the clinic, and this can be done while maintaining the patient's autonomy and privacy.[23] Cascade screening methods should be based on Dutch or Simon Broome criteria, which incorporate lipid profiles in addition to genetic and familial factors, giving clinicians more information about potential conditions.[19]
Learning Objective	Describe the most effective methods for FH screening and the best criteria for accurate diagnoses.

Appendix: Literature Review Supporting the Educational Need

CVD currently accounts for more than 17 million deaths worldwide, and high cholesterol causes 15% of those deaths despite the fact that elevated cholesterol is a modifiable risk factor.[1] Since statins were discovered in the late 1970s, mean total cholesterol levels have decreased by 0.2 mmol/L (approximately 8 mg/dL) in North America, Australasia, and most regions of Europe.[24] This trend is tied to pharmacological intervention[11], not lifestyle changes, as in the same time span mean body mass index has increased.[25] In order to enhance the benefits seen thus far through LDL cholesterol reduction, clinicians must embrace new screening methodologies and the emerging therapies designed to benefit those who exhibit suboptimal responses to statin therapies.[19]

Gap 1: Clinicians may not be familiar with new treatment options for refractory hypercholesterolemia and familial hypercholesterolemia.

The first line therapy for hypercholesterolemia is usually monotherapy with a statin.[3] In most individuals, statins are well tolerated and have an excellent risk-benefit profile, but a subset of patients experience statin intolerance, usually due to muscle pain.[8] Additionally, even among patients for whome statins are well-tolerated, a cross-sectional trial recently found that less than 50% reached their goal LDL cholesterol level, and only 22.8% of patients at high risk for CVD reached their goal LDL cholesterol level.[26]

Patients with heterozygous and homozygous FH comprise another population of individuals who are usually not responsive to statin treatment.[11] FH is an autosomal dominant disorder caused by mutations in the LDL receptor, leading to high LDL cholesterol levels and an increase in mortality from CVD before the age of 60.[29] Despite the fact that 96% of patients diagnosed with FH are on lipid-lowering therapies,[30] FH patients still have a higher risk of CVD than the general population.[29]

While some patients may benefit from an increased statin dosage, many may be unresponsive to statins at the highest recommended doses and may benefit from combination therapy with another drug class.[3] Since 2013, 4 new treatments have been approved for LDL cholesterol reduction, and a fifth compound was shown to significantly decrease CVD when administered in combination with statins.[16,27,28]

PCSK9 Inhibitors

PCSK9 binds the LDL receptor and accelerates the lysosomal degradation of the receptor, depleting the LDL receptor from the cell membrane and disrupting cholesterol metabolism.[31] Monoclonal antibodies targeting PCSK9 (alirocumab, evolocumab, and bococizumab) decrease LDL cholesterol levels in serum and have been shown to reduce the incidence of CVD. PCSK9 antibodies are all parenteral agents.

Evolocumab

When evaluated in 614 patients with uncontrolled hypercholesterolemia, biweekly evolocumab alone was shown to significantly reduce LDL cholesterol by 56.5% when compared to placebo after 12 weeks (95% CI 53% to 60%; $P < .001$) and 39.4% when compared with the cholesterol absorption inhibitor ezetimibe (35.9% to 42.9%; $P<.001$).[32] Evolocumab was also evaluated in statin intolerant patients in the GAUSS-2 trial, and the treatment group had a 53% to 56% decrease in LDL cholesterol from baseline when compared with placebo and a 37% to 39% decrease from baseline when compared to ezetimibe.[13]

In the phase 3 LAPLACE 2 trial, evolocumab was added to moderate- and high-intensity statin therapy in order to evaluate the efficacy of evolocumab as a combination therapy.[33] In moderate-intensity statin groups, biweekly evolocumab reduced mean LDL cholesterol levels from baselines of 123 to 126 mg/dL to 43 to 48 mg/dL (66%; 95% CI 58% to 73%), and in high-intensity statin groups, biweekly evolocumab reduced LDL cholesterol from a baseline mean of 89 to 94 mg/dL to 35 to 38 mg/dL (63%; 95% CI, 54% to 71%).[33] These results indicate that evolocumab can be utilized alone or in combination with statin therapy to decrease LDL cholesterol levels in patients with primary hypercholesterolemia.

Evolocumab was evaluated in patients with heterozygous FH in the phase 3 RUTHERFORD-2 trial. In this study, 331 heterozygous FH patients with suboptimal LDL cholesterol levels received 140 mg evolocumab biweekly, 420 mg monthly, or placebo in addition to statin treatment. Both treatment groups had significantly reduced cholesterol levels after 12 weeks ($P < .0001$ for both groups). In the phase 3 TESLA trial, evolocumab was administered to patients with homozygous FH. While these patients are usually thought to have no LDL receptors, some FH patients have different loss-of-function mutations in each receptor allele, making them susceptible to LDL receptor-dependent interventions such as PCSK9 inhibitors.[34] Evolocumab was tested in 49 patients with homozygous FH who were on statins but not undergoing lipoprotein apheresis. The treatment group had significantly reduced LDL cholesterol when compared to placebo at 12 weeks (30.9%; 18% to 43.9%, $P <.0001$). There were no serious adverse effects of evolocumab reported in any of the trials described.

The effect of evolocumab on cardiovascular outcomes has also been tested in the phase 2 OSLER trial. After treatment with 140 mg evolocumab biweekly or 420 mg monthly, the risk of CVD was reduced from 2.18% in the standard of care group to 0.95% in both evolocumab groups (Hazard Ratio (HR) 0.47; 95% CI 0.28 to 0.78; $P = 0.003$). No major adverse effects were described.

Alirocumab

The fully human monoclonal antibody alirocumab was evaluated in 103 patients at moderate risk for CVD (100 to 190 mg/dL LDL cholesterol) as a monotherapy in the ODYSSEY-MONO phase 3 trial. Alirocumab reduced LDL cholesterol by 47.2% compared with 15.6% in patients receiving ezetimibe (mean difference 31.6%, $P<0.0001$).[35] When evaluated as a combination therapy in patients on maximum statin doses, alirocumab significantly decreased LDL cholesterol levels compared with ezetimibe at weeks 24 and 52 ($P < 0.001$). Furthermore, patients in the alirocumab groups were more likely to reach target LDL cholesterol levels (< 70 mg/dL) than ezetimibe-treated patients ($P < 0.0001$).[36,37]

When evaluated in patients with heterozygous FH, alirocumab decreased LDL cholesterol levels both in patients without prior CVD and with prior CVD (48.8% and 48.7%, respectively), and more patients in the alirocumab group reached target LDL cholesterol levels.[38] In the phase 3 ODYSSEY LONG-TERM trial, patients were monitored for 78 weeks, and in a post-hoc analysis, researchers found that the alirocumab group was less likely to experience CVD (1.7% alirocumab group vs 3.3% placebo group, $P = 0.02$).[39] There were no major adverse events reported for alirocumab.

Bococizumab

While not yet FDA-approved, humanized monoclonal antibody bococizumab is currently in phase 3 testing for patients at high risk of CVD with expected results in June 2018 (NCT02100514, clinicaltrials.gov). In a phase 2 study, patients on statin therapy with suboptimal LDL cholesterol levels were randomized to bococizumab or placebo. Both 150 mg and 300 mg bococizumab doses were

effective and decreased LDL cholesterol levels by 53.4 mg/dL and 44.9 mg/dL, respectively.[39] Adverse events were similar between bococizumab and placebo groups.

NPC1L1 Inhibitor

Ezetimibe binds and inhibits the Niemann-Pick C1-like 1 (NPC1L1) transporter, which reduces both intestinal absorption of cholesterol as well as bile reabsorption of cholesterol.[11] While Ezetimibe was approved for hypercholesterolemia treatment in 2003, clinicians questioned its utility in preventing CVD. In a phase 3 trial comparing statin monotherapy and statins plus ezetimibe, researchers found no significant difference in intima-media thickness between the two groups despite the fact that ezetimibe decreased LDL cholesterol by 16.5% ($P < .01$).[40] Nevertheless, in 2015, the phase 3 IMPROVE-IT trial implied that ezetimibe decreased CVD risk when added to statin therapy. Researchers evaluated 18,000 patients who received either placebo or ezetimibe in addition to simvastatin after acute coronary syndromes and found that the ezetimibe group had a 6% reduction in major cardiovascular events (HR 0.93; 95%CI 0.88 to 0.98, $P = 0.007$).[41] No significant differences in adverse events were observed between patients in the simvastatin monotherapy group and patients in the simvastatin-ezetimibe group.

MTP Inhibitor

The microsomal transfer protein (MTP) is a polyprotein complex that facilitates the production of VLDL, a precursor to LDL.[42] Lomitapide is a first-in-class oral MTP inhibitor approved for use in adults with homozygous FH. In a phase 3 randomized control trial, lomitapide was added to current lipid-lowering therapies in 29 patients with homozygous FH.[16] LDL cholesterol concentrations were reduced by 50% (95%CI 39% to 62%) from baseline within 26 weeks.[16] Gastrointestinal upset, including diarrhea, nausea, and vomiting, was the most common adverse event and affected 90% of patients on treatment.[16] Additionally, transaminitis, an indicator of hepatotoxicity, was observed in 10 patients during the study.[16] A 10-year observational study (LOWER) is currently underway to asses the safety, efficacy, and utilization of lomitapide.[43]

ApoB-100 Synthesis Inhibitor

Apolipoprotein B-100 (ApoB-100) is the major apolipoprotein found in atherogenic VLDL and LDL cholesterol particles.[44] Mipomersen is a parenteral apoB-100 antisense oligonucleotide approved for patients aged 12 and over with homozygous FH. In the phase 3 trial evaluating the efficacy of mipomersen, 51 patients were randomly assigned to 200 mg mipomersen weekly or placebo. Mipomersen was shown to reduce LDL cholesterol by 24.7% (95% CI 17.7% to 31.6%), which was significantly greater than placebo ($P = 0.0003$).[17] When assessed in patients with heterozygous FH, mipomersen had similar benefits, reducing LDL cholesterol at a greater level than placebo (26.3%, $P < .001$).[45] In a recent long-term, open-label trial, researchers found that mipomersen maintained benefits over 2 years, with a mean reduction in LDL cholesterol of 28% at 76 weeks.[46]

Gap 2: Clinicians may not be familiar with new recommendations for familial hypercholesterolemia diagnostic screening methods.

Based on data from Europe, only 15 to 20% of individuals with FH are diagnosed and appropriately treated,[10] and research suggests that children with FH are at the highest risk of going undiagnosed.[47] Furthermore, heterozygous FH is believed to affect 1 in 300 to 1 in 500 individuals, making it the most common metabolic disorder worldwide.[10] Patients with FH are at an increased risk for adverse

cardiovascular events, and 20% of myocardial infarctions in patients under 45 years are attributable to FH.[48] Clinicians must be prepared to test patients for FH using appropriate cascade screening methodologies.[19]

There are currently no international FH diagnostic criteria, but the 3 criteria that are used most regularly are the Dutch, Simon Broome, and US MedPed criteria.[19] The US MedPed criteria are exclusively based on LDL cholesterol levels and stratified by age and family history of FH.[49] Both the Simon Broome and Dutch criteria incorporate personal LDL cholesterol and lipid levels, familial LDL cholesterol and lipid levels, familial history of premature CVD (<55 years in mean and <65 years in women), physical examinations, and genetic testing.[50,51] The Dutch criteria uses a scoring system, and the Simon Broome criteria classifies patients as possible, probable, or definitive FH.[50,51] In order to classify as definitive FH, patients must be identified by a positive genetic test.[51]

The National Lipid Association Expert Panel suggests that clinicians use cascade screening when presented with an index case of definitive or probable FH.[52] Cascade screening involves diagnosis and screening of relatives of FH patients, beginning with first-degree relatives before moving on to second- and third-degree relatives. When cascade screening guidelines were implemented in the United Kingdom, CVD-related mortality was reduced in patients 20 to 79 years due to improved FH diagnosis, which increased the number of FH patients on LDL cholesterol-lowering therapy.[53]

While cascade screening can be performed using either nongenetic clinical criteria or genetic testing, data from a national cascade screening program in the Netherlands suggests that genetic testing is beneficial. When genetic testing was performed, the number of FH patients on LDL cholesterol-lowering medications increased from 39% to 85%.[54] When genetic testing for common FH mutants was performed on relatives of patients with FH, 45% were found to have FH, suggesting to the researchers that less than 2.2% of FH patients have been identified.[55]

However, it is important to note that no randomized clinical trial has been performed to determine the efficacy of cascade screening in reducing population-level LDL cholesterol levels or CVD.[19] Furthermore, there have been no comparative trials to evaluate whether nongenetic clinical testing or genetic testing is better when used for FH diagnosis.[19] Nevertheless, FH is known to be underdiagnosed and undertreated, and cascade screening has been shown to be effective in post-hoc analysis of data from other national cascade screening programs. As such, the Familial Hypercholesterolemia Foundation created a multicenter registry, CASCADE-FH, to evaluate the efficacy of cascade screening programs and outcomes.[56] A cross-sectional analysis of the data in the CASCADE-FH registry already indicates that FH patients are diagnosed late in life and usually do not reach optimal LDL cholesterol levels,[57] further indicating the importance of implementing a cascade screening approach to FH diagnosis.

When communicating risk to relatives in cascade screening, clinicians must consider the best way in which to contact at-risk family members without violating the autonomy or privacy of the patient.

Communication of risk can occur through family-mediated contact without physician assistance, family-mediated contact with the assistance of a written information aide, or direct contact of relatives by the clinician.[23]

A review of the literature suggests that the most effective way to communicate risk for FH is through direct clinician contact.[22] Relatives are more likely to present for screening when contacted by clinicians and also receive more accurate information on their risks and possible disease state.[22] Furthermore, patients diagnosed with FH prefer that clinicians contact family members due to a feeling of inadequate authority to convince relatives to present for screening.[58]

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