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The efficacy and cost-effectiveness of evolocumab in the prevention of cardiovascular disease

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**THE EFFICACY AND COST-EFFECTIVENESS OF EVOLOCUMAB IN THE
PREVENTION OF CARDIOVASCULAR DISEASE**

by

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**THE EFFICACY AND COST-EFFECTIVENESS OF EVOLOCUMAB IN THE
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KELLY FAHEY

ABSTRACT

Heart disease is the leading cause of death in the United States. Hyperlipidemia is a predominant risk factor in the development of atherosclerotic cardiovascular disease (ASCVD). The statin drug class is the first line therapeutic for lowering atherogenic low-density lipoprotein (LDL) levels by competitively inhibiting 3-hydroxy-3methyl-glutaryl-coenzyme A (HMGCR) reductase, the rate-limiting enzyme in cholesterol biosynthesis. However, there are patients who are unable to achieve desirable LDL levels despite statin therapy, such as those with familial hypercholesterolemia or those who are statin intolerant. A new therapy was discovered in 2015 to benefit patients with uncontrolled LDL levels by inhibiting Proprotein convertase subtilisin-kexin type 9 (PCSK9), a key protein in LDL receptor metabolism. Evolocumab (Repatha, AMGEN) is a human monoclonal antibody against human PCSK9. Evolocumab is approved to lower LDL-cholesterol in adult patients who have, despite dietary and lifestyle changes and maximally tolerated statin dose continued suboptimal lipid levels with either ASCVD or Heterozygous Familial Hypercholesterolemia (HeFH). Evolocumab has been shown to significantly reduce atherogenic lipid levels and the recent FOURNIER clinical trial showed that evolocumab reduces cardiovascular events. However, the high annual cost of evolocumab has raised questions as to its cost-effectiveness and role in the prevention and treatment of ASCVD. At the present price levels, this therapy does not appear to be

cost-effective with multiple analyses suggesting significant price reduction will be necessary before this drug can be used in standard treatment for secondary prevention of cardiovascular disease in the United States.

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
Apo.....	apolipoprotein
ASCVD.....	Atherosclerotic Cardiovascular Disease
CAD	Coronary artery disease
CE	Cholesterol ester
FDA.....	Food and Drug Administration
FH	Familial hypercholesterolemia
HDL	High Density Lipoprotein
HeFH.....	Heterozygous Familial Hypercholesterolemia
HMGCR.....	3-hydroxyl-3methyl-glutaryl-coenzyme A reductase
HoFH.....	Homozygous Familial Hypercholesterolemia
ICER	Incremental cost-effectiveness ratio
IDL.....	Intermediate Density Lipoprotein
LDL-C.....	Low-Density Lipoprotein Cholesterol
LDL.....	Low-Density Lipoprotein
LPL	Lipoprotein Lipase
NICE	National Institute of Health and Clinical Excellence
PCSK9.....	Proprotein convertase subtilisin-kexin type 9
QALY	Quality-adjusted life year
Q2W	Every two weeks

Q4W Every four weeks
SREBPS Sterol regulatory element binding proteins
TAG Triacylglycerol
VLDL Very Low Density Lipoprotein
WHO World Health Organization

INTRODUCTION

Heart disease is the leading cause of death in both men and women; over 610,000 people in the United States die annually from cardiovascular disease (Doonan et al., 2018). It is calculated that every 40 seconds, an adult dies from a heart attack, stroke, or other related cardiovascular disease (CDC, 2016). The American Heart Association (AHA) in 2011 predicted that by the year 2035, more than 45% of the United States population, more than 131.2 million Americans, would have some form of heart disease due to the nation's inability to combat obesity, poor diet, high blood pressure, rise in Type 2 diabetes, and high cholesterol (AHA, 2017). In addition to a high mortality rate, heart disease and stroke can also lead to extreme morbidity including serious illness, disability, and a lower quality of life (Doonan et al., 2018).

The cost of cardiovascular disease to the United States health care system is staggering- it is currently the nation's costliest chronic disease (AHA, 2017). Currently, one out of every six health care dollars is spent on the treatment of cardiovascular disease (CDC, 2016). Additionally, more than \$193.1 billion was spent in 2016 on direct medical expenses associated with cardiovascular disease, and another \$123.5 billion in 2016 was lost due to decreased productivity from premature deaths (CDC, 2016). The cost of cardiovascular disease is only expected to increase; the AHA anticipates a price tag of more than \$1.1 trillion by the year 2035 (AHA, 2017). To help improve the nation's cardiovascular health and economic burden of this disease, it is recommended that access to quality health care be preserved and expanded, prevention with a focus on lifestyle

changes be emphasized, and continued research on treatments to reduce the morbidity and mortality associated with cardiovascular disease (AHA, 2017).

SPECIFIC AIMS

In the first section of this thesis, the importance of lowering low-density lipoprotein cholesterol (LDL-C) levels will be explored, including an overview of lipoprotein biochemistry pathways and how dysfunction of this system can lead to familial hypercholesterolemia (FH) and the development of atherosclerotic cardiovascular disease (ASCVD), which is the primary cause of morbidity and mortality in western society. Next, the American College of Cardiology (ACC) and American Heart Association (AHA) cholesterol level recommendations as well as therapies to lower LDL-C will be discussed, including the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) inhibitors, known as statins, and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, specifically evolocumab. Evolocumab (trade name Repatha) is a human monoclonal immunoglobulin G2 indicated to lower LDL-C levels in adult patients who have, in addition to improving their diet, tolerated the maximum amount of statins available and are diagnosed with either ASCVD or heterozygous familial hypercholesterolemia (HeFH).

A literature review will discuss key information regarding pharmacologic therapy of hyperlipidemia, including the place of PCSK9 inhibitor's LDL-C lowering properties in the prevention of cardiovascular morbidity and mortality, as shown in the 2017 FOURNIER study. The PCSK9 inhibitor's efficacy, safety, and proper utilization will be

defined. Finally, the implications of the high annual cost of evolocumab in the United States will be discussed in terms of its current place in clinical therapy.

Lipoprotein Structure and Function

To fully understand the role lipid dysfunction plays in the development of atherosclerotic pathology, it is important to review lipoprotein structure and function and the effect it has on the cardiovascular system. The following is a brief discussion of the biochemistry behind plasma lipoproteins and cholesterol, followed by an explanation of two diseases, ASCVD and FH, both associated with dysfunction of the lipoprotein pathway.

Lipoproteins transport lipids through the blood to tissues in concentrations above their solubility in body fluids due to their specialized, spherical structure, detailed in **Figure 1** (Harisa et al., 2014). The lipoprotein inner core consists of nonpolar hydrophobic lipids such as cholesterol ester (CE) and triacylglycerol (TAG), surrounded by an amphipathic shell of phospholipids, free cholesterol, and proteins (Harisa et al., 2014). Special proteins, called apoproteins (Apo), serve as ligands for cell receptors and cofactors for enzymes in metabolism (Harisa et al., 2014).

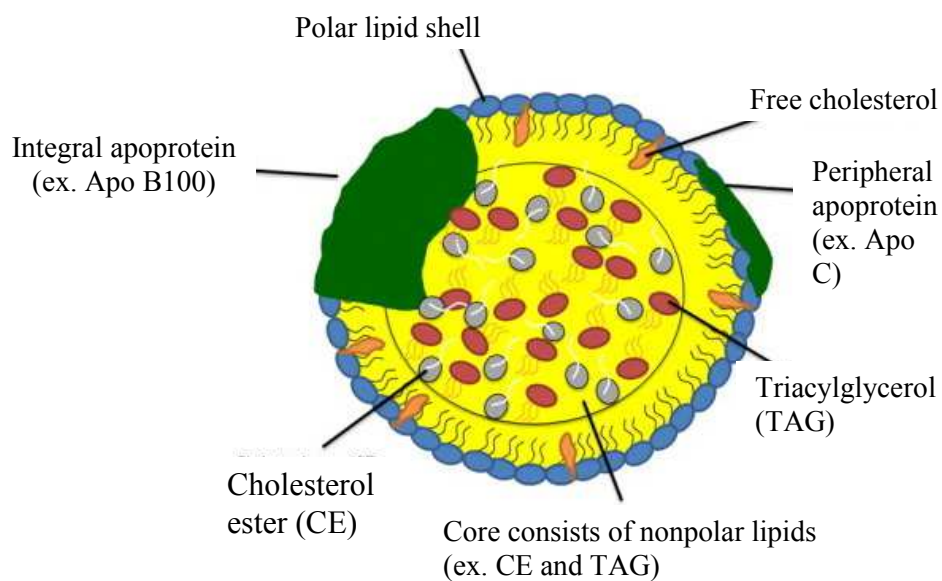


Figure 1. Diagram of plasma lipoprotein general structure. The amphipathic molecule consists of a polar shell and a nonpolar inner core. Apoproteins serve as enzyme cofactors and receptor ligands (Image taken from Harisa et al., 2014).

The function of plasma lipoproteins include supplying TAG to peripheral tissues for storage and fuel, distributing TAG and cholesterol for creating signal molecules and the cell membrane, as well as assisting with cholesterol homeostasis (Venugopal et al., 2018). Plasma lipoproteins are classified into five categories based on density and diameter as a result of differing protein and lipid concentrations, as shown in **Table 1** (Venugopal et al., 2018).

Table 1. Characteristics of Human Lipoproteins.

	Chylomicrons	VLDL	IDL	LDL	HDL
Density (g/mL)	<0.95	0.95-1.006	1.006-1.019	1.019-1.063	1.063-1.210
Diameter (nm)	75-1,200	30-80	25-35	18-25	5-12
Composition (%)					
Protein	2	10	18	25	33
Triglycerides	83	50	31	9	8
Cholesterol	8	22	29	45	30
Apolipoproteins	B 48, A1, C1, CII, CIII	B 100, E, C1, CII, CIII	B 100, E, CI, CII, CIII	B 100	AI, AII, CI, CII, CIII, E

*Lipoproteins are classified according to their lipid and protein content, which also gives them a distinct density and size as well as determines their biological function. Lipoproteins include chylomicrons, very-low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low-density lipoprotein (LDL) and the antiatherogenic high-density lipoprotein (HDL). (Table taken from Venugopal et al., 2018).

The liver, and partially the small intestine, are responsible for regulating TAG and cholesterol homeostasis (Cohen, 2009). Cholesterol in the circulation originates from either the exogenous or endogenous lipoprotein pathway (Cohen, 2009). The rate of cholesterol absorption in the exogenous pathway varies widely in the population; some adults absorb 25% of consumed cholesterol while others absorb up to 80% (Cohen, 2009). To maintain cholesterol balance, the exogenous pathway synthesizes roughly the same amount of cholesterol lost in the feces minus the dietary cholesterol (Cohen et al., 2009). Together, the endogenous and exogenous pathways work to maintain cholesterol homeostasis (Cohen, 2009).

In the exogenous pathway, chylomicrons are assembled from dietary TAG in enterocytes and then travel to the systemic circulation where they distribute TAG to

peripheral tissues for energy and storage (Feingold et al., 2018). Apo CII on the chylomicron surface activates the enzyme lipoprotein lipase (LPL), expressed mainly in muscle and adipose capillaries, to catalyze the reaction that hydrolyzes TAG to free fatty acids (Feingold et al., 2018). As the chylomicron courses through the periphery, the metabolism and removal of TAG from the core results in the gradual loss of Apo CII and formation of chylomicron remnants (Venugopal et al., 2018). Chylomicron remnants are enriched with CE and gain Apo E while giving up Apo AI and CII to HDL (Feingold et al., 2018). The liver remnant receptor recognizes Apo E and takes up chylomicron remnants via receptor-mediated endocytosis (Venugopal et al., 2018). In the hepatocyte, dietary cholesterol has four routes for metabolism (Dose et al., 2016). It is secreted directly into bile, converted into bile acids and then secreted into bile, esterified and stored as CE, or enters the endogenous pathway and is packaged into VLDL and secreted into the plasma (Dose et al., 2016).

In the endogenous pathway, VLDL is created in the liver from excess CE, TAG, Apo CII, Apo E, and the core structural protein Apo B-100 (Feingold et al., 2018). VLDL travels through the systemic circulation where Apo CII activates LPL on the surface of endothelial cells to hydrolyze TAG (Venugopal et al., 2018). Similar to chylomicron metabolism, as TAG is removed from VLDL, remnants, or IDL, are created (Venugopal et al., 2018). IDL is cleared by the liver or with continued removal of TAG from IDL, metabolized to LDL (Venugopal et al., 2018). The liver clears approximately 50% of IDL (Venugopal et al., 2018).

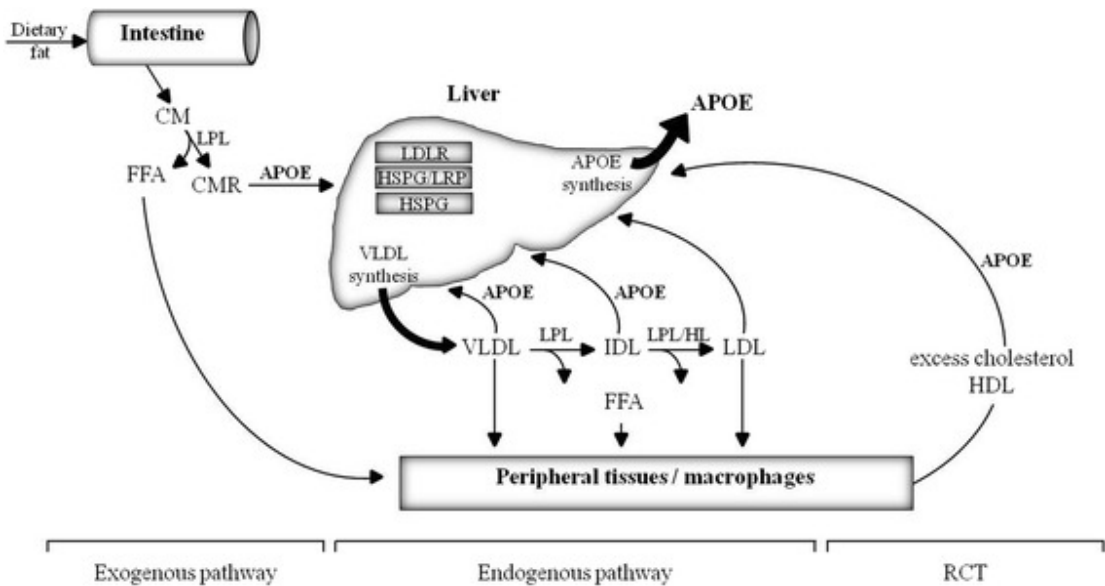


Figure 2. Diagram of exogenous pathway, endogenous pathway, and reverse cholesterol transport in humans. In the exogenous pathway, chylomicrons are created in enterocytes from dietary cholesterol and TAG to deliver to peripheral tissues and the liver. In the endogenous pathway, VLDL is created from excess cholesterol and triglycerides. VLDL is metabolized to LDL, which deposits cholesterol to peripheral tissues or is returned to the liver via receptor-mediated endocytosis. In the reverse cholesterol transport pathway (RCT), HDL removes excess cholesterol from peripheral tissues and returns it to the liver. (Image taken from Dose et al., 2016)

LDL is the end product of VLDL metabolism (Feingold et al., 2018). LDL consists of primarily CE and one structural protein, Apo B-100, which controls LDL cholesterol's interaction with the LDL receptor on hepatocytes as well as peripheral tissues such as the adrenal gland, muscle, gonads, and adipose tissue (Feingold et al., 2018). After internalization, lysosomes degrade the LDL particle, releasing cholesterol into the cell, as depicted in **Figure 3** (Feingold et al., 2018).

HDL, characterized by the presence of Apo A1, are synthesized and secreted by the liver to remove excess cholesterol from peripheral tissues and return it to the liver for further breakdown or excretion (Feingold et al., 2018). This process of clearing

cholesterol from peripheral tissues, importantly vascular tissue, is known as reverse cholesterol transport (Feingold et al., 2018).

The amount of circulating LDL is dependent on two factors: the amount of LDL created from VLDL and the rate of LDL clearance from the plasma (Feingold et al., 2018). Both of these factors are dependent on the number of LDL receptors on hepatocytes (Feingold et al., 2018). When there are numerous LDL receptors, more IDL is cleared, reducing the amount of LDL created from IDL (Feingold et al., 2018). Likewise, where there are few LDL receptors present, less IDL is removed from the circulation, so more IDL is metabolized to LDL (Feingold et al., 2018). In terms of the clearance of LDL from the plasma, the liver normally removes 70% of LDL (Feingold et al., 2018). LDL binds to the LDL receptor on hepatocytes and is taken up through endocytosis in clathrin-coated vesicles, which was famously deduced by Goldstein and Brown in 1973 (Goldstein and Brown, 1973). The clearance of LDL is also dependent on the number of LDL receptors on hepatocytes (Feingold et al., 2018). An increase in LDL receptors increases the clearance of LDL from the plasma; conversely, a decrease in LDL receptors decreases the clearance of LDL from the plasma (Feingold et al., 2018). **Figure 3** depicts the LDL receptor pathway and outlines the regulatory actions of increased cholesterol in hepatocytes.

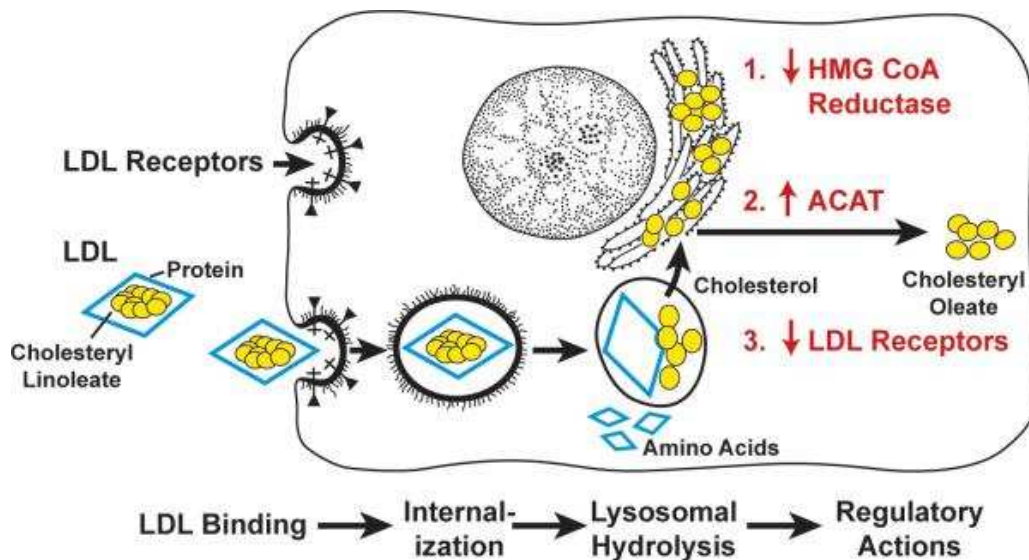


Figure 3: LDL receptor pathway and regulatory actions in hepatic cells. Apo B100 on the surface of LDL binds to LDL receptors on the hepatocyte and activates receptor-mediated endocytosis forming an endosome. LDL receptors are recycled to the plasma membrane at an internal pH of 5.0, and LDL particles are degraded in a lysosome to amino acids, fatty acids, and CE, which are degraded by lysosomal lipase to cholesterol and fatty acids. Genetic defects in the LDL pathway lead to increased plasma levels of LDL, such as in familial hypercholesterolemia. The cholesterol released from the hydrolyzed LDL then acts in a negative feedback manner by reducing the amount of LDL receptors on the hepatocyte membrane, increasing the activity of cholesterol acyltransferase (ACAT), and decreasing the activity of HMGCA Reductase, a regulatory enzyme in the biosynthesis of cholesterol, through the sterol regulatory element-binding protein (SREBP) pathway. (Image taken from Goldstein, 2010).

The number of LDL receptors available on hepatocytes is primarily regulated by the amount of free intracellular cholesterol in an attempt to prevent too much cholesterol from entering the cell (Feingold et al., 2018). Sterol regulatory element binding proteins (SREBPS) are transcription factors that work to increase the expression of LDL receptors and other genes promoting cholesterol and fatty acid metabolism (Feingold et al., 2018). If cholesterol levels in the cell are too high, inactivated SREBPS stay in the endoplasmic

reticulum and are unable to travel to the Golgi apparatus to be cleaved into the active transcription factors which travel to the nucleus to promote LDL receptor gene expression (Feingold et al., 2018).

Atherosclerosis and Familial Hypercholesterolemia

LDL- C is commonly referred to as “bad cholesterol” as it carries approximately 60-70% of the body’s plasma cholesterol to deposit in peripheral tissues (Kumar et al., 2015). Many studies have shown a positive link between high circulating LDL-C causing CHD and ASCVD compared to moderate circulating levels, as shown in **Figure 4** (Ferenec et al., 2017; Grundy et al., 2004). Over the past two decades, statin trials have shown the clinical benefit of lowering LDL-C levels to 70 mg/dL to directly reduce cardiovascular events (Cannon et al., 2015). In 2015, the IMPROVE-IT trial demonstrated that ezetimibe added to moderate-intensity statins led to an even further reduction in LDL-C levels (LDL-C below 55 mg/dL), and reduced cardiovascular events even further compared to statin therapy alone (Cannon et al., 2015).

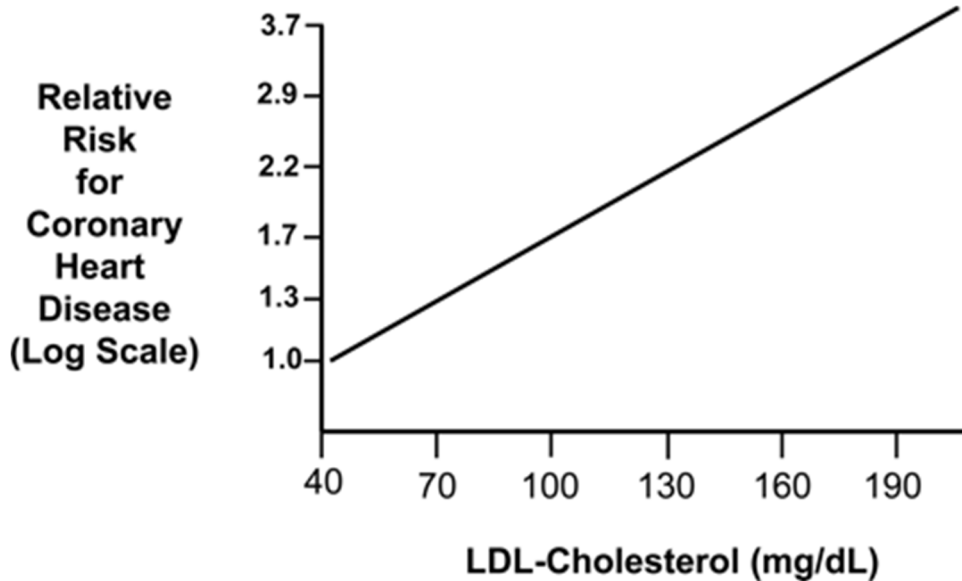


Figure 4. Log-linear relationship of serum LDL cholesterol concentrations to coronary heart disease risk. Serum LDL-C levels are correlated with coronary heart disease risk over a wide range of values. For every 30 mg/dL increase in LDL-C, the relative risk for coronary heart disease increases by 30% (Taken from Grundy et al., 2004).

Cardiovascular disease accounts for 31% of all deaths worldwide, and in the United States, cardiovascular disease kills more than the next two conditions, cancer and chronic lower respiratory disease, combined (Doonan et al., 2018). The AHA estimates that 1 in 3 people in the United States will be affected by cardiovascular disease in their lifetime (Doonan et al., 2018). The most prevalent form of cardiovascular disease is coronary artery disease, (CAD) representing approximately 45% of all cases, followed by stroke, representing 16.5% of all cases (Doonan et al., 2018). Both CAD and stroke are conditions directly caused by atherosclerosis, a chronic disorder that underlies coronary, cerebral, and peripheral vascular disease (Kumar et al., 2015).

In ASCVD, CE accumulate in the endothelium, thickening the artery wall and reducing or blocking blood flow, leading to complications such as myocardial infarction, ischemic heart disease, or stroke (Kumar et al., 2015). Risk factors for developing atherosclerosis are both modifiable (such as cigarette smoking, diabetes, inflammation, hypertension, and hyperlipidemia) as well as non-modifiable (genetic abnormalities, male gender, increasing age) (Kumar et al., 2015). The INTERHEART study, an international case-controlled study looking at 30,000 patients, found that out of nine easily measured and modifiable risk factors for a myocardial infarction, LDL accounted for 50% of the population attributable risk, followed next by smoking at 36% (Yusuf et al., 2014).

Atherosclerosis is initiated by endothelial injury, due to inflammation within lipid filled plaques at sites prone to hemodynamic disturbance (Kumar et al., 2015). Lipoproteins, mostly LDL, enter the damaged endothelium and are oxidized, which activates the endothelial cells to undergo an inflammatory response, causing monocytes to enter and aggregate in the intima (Lu et al., 2015). Factor release from the leukocytes then causes smooth muscle cell proliferation, which converts the fatty streak into a mature atheroma (Kumar et al., 2015). The monocytes then convert into macrophages and internalize oxidized LDL via scavenger receptors, themselves becoming foam cells (Lu et al., 2015). Smooth muscle then migrates into the plaque, helping to form a fibrous cap to cover the plaque (Lu et al., 2015). Atherosclerotic plaques consist of a necrotic center of cholesterol, foam cells, and calcium, as well as a fibrous cap consisting of smooth muscle cells, macrophages, foam cells, collagen and lymphocytes (Kumar et al., 2015).

Atherosclerotic plaques accumulate in blood vessels, especially medium and large arteries, thickening the wall and reducing or blocking blood flow (Lu et al., 2015). When the cap ruptures, the acute reaction between the ruptured cap and the blood can cause a thrombotic event (Kumar et al., 2015). If limited, the vessel may be able to heal itself and the clotting doesn't obstruct the vessel, which would be a minimal event (Kumar et al., 2015). However, a ruptured cap completely blocking a vessel in the heart or brain leads to a myocardial infarction or stroke, respectively (Kumar et al., 2015). In addition, atherosclerosis may cause vessel wall remodeling after injury and possible aneurysm formation (Kumar et al., 2015). Increased LDL-C has been demonstrated to increase atherosclerosis-related cardiovascular events while increases in HDL-C levels have been demonstrated to reduce atherosclerosis (Lu et al., 2015).

Familial hypercholesterolemia is an autosomal dominant genetic disorder caused by mutations that lead to an increase in total plasma cholesterol, LDL-C, and greatly accelerated atherosclerosis and heart disease (Kumar et al., 2015). Mutations in the genes *LDLR* (85-90% of cases), *ApoB* (5-10% of cases), *LDLRAP1* (<5% of cases), as well as *PCSK9* (<5% of cases) have been deduced to result in FH (Kumar et al., 2015). Approximately 70% of plasma LDL is cleared by the LDL receptor, so as a result of the receptor defect, patients with heterozygous FH have a two- fold to three-fold elevation in their plasma cholesterol levels due to the inability of the liver to clear LDL, while homozygous FH patients have a five-fold to six-fold increase in plasma cholesterol levels (Kumar et al., 2015). Therefore, FH patients have chronically severely elevated LDL concentration in the plasma, commonly above 200 mg/dL (Kumar et al., 2015). Due to

the severe dyslipidemia, FH patients are at high risk for developing atherosclerosis as well as skin xanthomas, which are firm, painless, red-yellow nodules on the skin in extensor surfaces of joints and pressure areas of the body of accumulated lipid and cholesterol (Poonia et al., 2013). **Table 2** includes diagnostic categories for determining if a patient has either heterozygous or homozygous FH.

Table 2: Adult Familial Hypercholesterolemia Diagnostic Categories*

HeFH	LDL-C \geq 190 mg/dL and with 1 first- degree relative affected or with premature CAD or with genetic testing positive for a LDL-C raising gene defect
HoFH	LDL-C \geq 400 mg/dL and 1 or both parents with FH, genetic testing positive for a LDL-C raising gene defect OR Autosomal-recessive FH if LDL-C > 560 mg/dL or LDL-C > 400 mg/dL with aortic valve disease or xanthomata at <20 years old
Family history of FH	LDL-C level not a clinical criteria, but is determined by having a first-degree relative with FH

*For Heterozygous Familial Hypercholesterolemia (HeFH), Homozygous Familial Hypercholesterolemia (HoFH), and a family history of FH, diagnostic criteria are given. (Table recreated from Kumar et al., 2015).

Cholesterol Level Recommendations

According to the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, approximately 48.6% of American adults over the age of 40 are eligible for statin therapy (Benjamin et al., 2018). However, the foundation for reducing the risk of ASCVD and other cardiovascular events lies in lifestyle

modifications such as following a heart-healthy diet, regular exercise, maintaining a healthy weight, and avoiding tobacco products (Benjamin et al., 2018). Patients should make these lifestyle changes both before or in conjunction with a cholesterol-lowering therapy for maximal benefit (Benjamin et al., 2018).

In 2013, the ACC and AHA deviated from the previous guidelines, the Adult Treatment Panel III Guidelines, in regards to the treatment of cholesterol to reduce atherosclerotic cardiovascular risk (Stone et al., 2014). The new guidelines identify an additional 13 million Americans that are now eligible for statin therapy (Stone et al., 2014). The expert panel decided to move away from determining a specific goal for LDL-C levels, opting rather to identify four groups in which ASCVD risk reduction from statin therapy clearly outweighed the risk of adverse events. (Stone et al., 2014). This change was implemented due to the thought that a “treating to goal” mentality may result in treatment with suboptimal statin intensity or result in adding non-statin therapy in the absence of evidence that it improves outcomes (Stone et al., 2014). The four identified treatment groups and treatment recommendations are detailed in **Table 3**. The primary prevention population is defined as those who have not had a cardiovascular event, while the secondary prevention population is defined as those who have had cardiovascular events such as an acute coronary syndrome, a history of myocardial infarction, angina, coronary revascularization, stroke, transient ischemic attack, or peripheral arterial disease of atherosclerotic origin (Stone et al., 2014).

Table 3: The four major statin benefit groups with ACC/AHA treatment recommendations*

Benefit Group	Major Recommendations
Secondary prevention in patients with clinical ASCVD	<ol style="list-style-type: none"> 1. If patient ≤ 75 years old, consider a high intensity statin 2. If patient > 75 years old, consider a moderate-intensity statin
Primary prevention in individuals with LDL-C ≥ 190 mg/L	<ol style="list-style-type: none"> 1. Consider high intensity statin therapy to lower LDL-cholesterol by 50% 2. Consider combining statin with additional therapy to lower LDL- cholesterol 3. Screen immediate family members to determine if others would benefit from lipid lowering therapy
Primary prevention in patients with diabetes 40-75 years old with LDL-C 70-189 mg/dL	<ol style="list-style-type: none"> 1. Consider a moderate- intensity statin 2. If at high risk for ASCVD (10 year risk $\geq 7.5\%$, consider high intensity statin)
Primary prevention in patients without diabetes and 10 year ASCVD risk greater than or equal to 7.5%, 40-75 years old who have LDL-C of 70-189 mg/dL	<ol style="list-style-type: none"> 1. Estimate 10-year ASCVD risk: If $\geq 7.5\%$, moderate- or high-intensity statin If ≥ 5 to $< 7.5\%$, moderate-intensity statin. 2. In individuals with 10-year ASCVD risk $< 5\%$, or age < 40 or > 75 years, individualize statin therapy 3. Before beginning statin therapy, discuss with the patient the potential for ASCVD risk-reduction benefits and adverse effects and drug–drug interactions. Also consider patient preferences before starting statin therapy.

*In 2013, the ACC and AHA modified the cholesterol treatment guidelines, creating four groups that would benefit the most from statin therapy. (Table modified from Stone et al., 2013).

The ACC and AHA expert panel was intentionally broad when discussing guidelines for clinicians to follow when treating high-risk patients who could not tolerate statin therapy due to severe adverse events such as hepatotoxicity and muscle problems

(Lloyd-Jones et al., 2017). Statin intolerance can be either complete (intolerant of all statins at any dose) or partial (intolerant to only some statins at some doses (Fitchett et al., 2015). Up to 15% of patients taking statins develop statin intolerance due to adverse events such as muscle aches, pains, myalgias, or elevated markers of liver or muscle function (Fitchett et al., 2015). These symptoms disappear when the patient stops statin therapy (Fitchett et al., 2015). Some patients can tolerate statin therapy, but do not exhibit the desired effects of lowered LDL-C levels, possibly due to genetic variations in genes related to statin metabolism such as intestinal P-glycoprotein, organic anion transporter 2, coenzyme Q10, or cytochrome P450 3A4 (Doonan et al., 2018). Only 21% of patients achieve guideline recommended LDL-C levels while on statin therapy alone (Boekholdt et al., 2014). Additionally, only 44% of patients achieved their target LDL-C level when prescribed combination therapy (ezetimibe and a statin) (Bandyopadhyay et al., 21018). To determine if a patient is responsive to statin therapy, an initial fasting lipid panel (TC, triglycerides, HDL-C, and LDL-C) should be compared to a second fasting lipid panel 4 to 12 weeks after starting statin therapy (Lloyd- Jones et al., 2017).

For patients who are stain intolerant, it is recommended that clinicians continue to emphasize lifestyle modifications, as well as consider prescribing a non-statin cholesterol lowering therapy that has been shown to provide risk-reducing benefits that outweigh potential adverse effects and drug-drug interactions (Lloyd-Jones et al., 2017). Examples of different therapies to lower LDL-C levels are outlined in **Figure 5**. Notably, patients are often prescribed ezetimibe, which lowers intestinal absorption of cholesterol by blocking the Niemann-Pick C1-Like 1 protein, and is commonly used as a placebo in

clinical trials investigating LDL-C lowering therapies (Savarese et al., 2015). While ezetimibe has been shown to lower LDL-C by an additional 20-25%, there is a lack of efficacy data as well as safety concerns about the therapeutic (Savarese et al., 2015).

Statin Therapy and PCSK9 Inhibitors

The mechanism of action of statins is to competitively inhibit the rate-limiting enzyme for endogenous cholesterol biosynthesis, HMGCR, preventing the formation of mevalonate, a cholesterol precursor (Doonan et al., 2018). By inhibiting HMGCR, statins result in reduced cholesterol biosynthesis in hepatocytes for export in VLDL as well as an increase in LDL receptor levels due to stimulated SREBP, which promotes LDLR transcription (Doonan et al., 2018). Statins have other effects in the body; for instance, statins can increase circulating PCSK9 levels (Lin et al., 2018). Notably, a study by Caresky et al. found that atorvastatin increased PCSK9 levels by 34% in patients (Lin et al., 2018). This is significant as it could be an explanation for why increasing doses of some statins, such as atorvastatin, fail to proportionally lower plasma LDL-C levels (Lin et al., 2018).

Statins function by a dose-dependent effect: doubling a statin dose reduces LDL-C level by 6% (Illingworth et al., 2017). Although statins are a well-established first line therapy to reduce the amount of cholesterol synthesized in the body, statins are not without drawbacks (Doonan et al., 2018). As detailed above, statins are not universally effective; some patients do not respond to statins and others are statin intolerant due to significant adverse effects such as elevated hepatic transaminases, myalgias, myositis,

and rhabdomyolysis (Kashani et al., 2006). Additionally, a meta-analysis found a 9% increase in diabetes developed by patients on statins (Doonan et al., 2018).

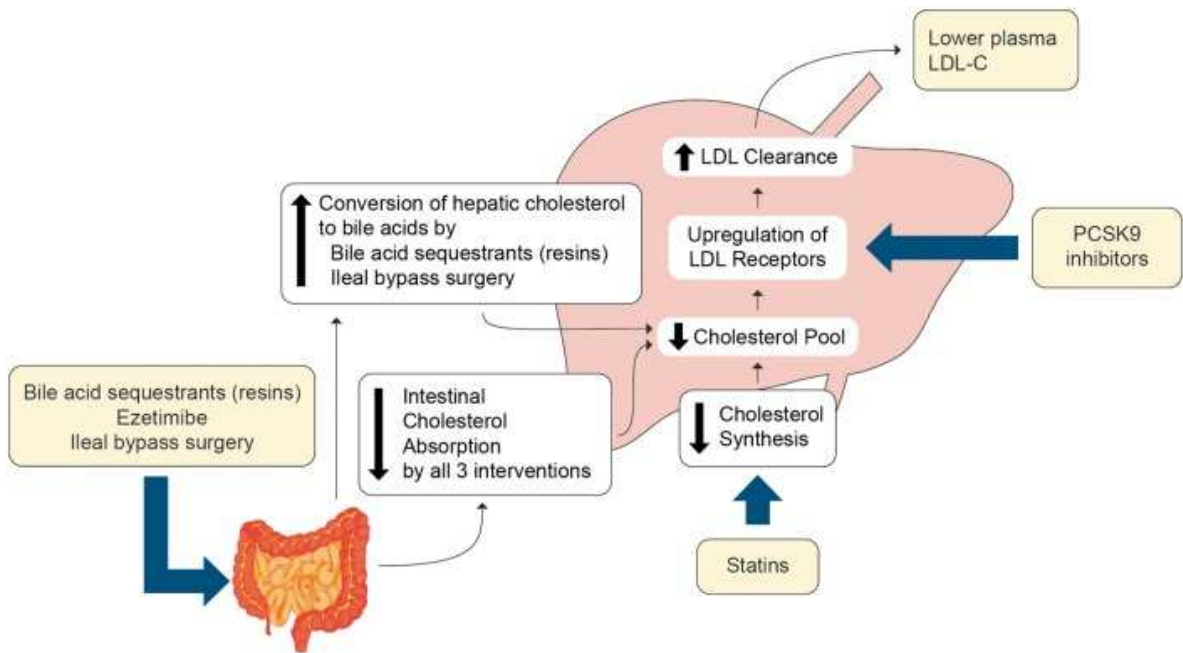


Figure 5: Additional therapies to lower plasma LDL levels. Statins competitively inhibit HMG-CoA Reductase to block endogenous cholesterol synthesis in the liver. Bile acid sequestrates (resins) act to bind bile acids in the intestine and block their reabsorption. This effectively decreases the bile acid pool, increasing the conversion of cholesterol to bile acids in hepatocytes, increasing the need for cholesterol in hepatocytes. This need then increases the activity of HMG Co-A Reductase as well as up regulates LDL receptors on the hepatocyte, clearing more LDL from the plasma. Another non-statin therapy includes Ezetimibe, which inhibits dietary cholesterol absorption in the small intestines. In addition, ileal bypass surgery lowers LDL-C by shortening the length of the small intestine. Finally, PCSK9 Inhibitors increase the amount LDL receptors on hepatocytes, increasing LDL-C clearance (Image taken from Ference et al., 2017).

PCSK9 is a vital protein in the role of lysosomal degradation of the LDL receptor (Hovingh et al., 2014). Abifadel and coworkers discovered PCSK9 in 2003 when by identifying a gain of function mutation in PCSK9 in patients with FH (Hovingh et al.,

2014). Located on chromosome 1, the PCSK9 gene codes for the serine protease expressed mainly in the liver, intestine, and kidney (Farnier et al., 2014). The protein is synthesized as a 692 amino acid glycoprotein, and then the zymogen undergoes processing in the endoplasmic reticulum to yield a 14kDa prodomain and a functional 63kDa PCSK9 (Hovingh et al., 2014).

Normally, LDL binds to the LDL receptors on the hepatocyte membrane and then the entire complex undergoes endocytosis (Dixon et al., 2017). PCSK9 binds to the LDL receptor with LDL, and the complex is internalized into the hepatocyte and degraded by lysosomes (Dixon et al., 2017). Since the LDL receptor is metabolized, it is then unable to be recycled back to the hepatocyte membrane to clear more LDL from the circulation (Dixon et al., 2017). A gain of function mutation of PCSK9 will lead to an elevated LDL level and cardiovascular disease, as seen in patients with FH (Dixon et al., 2017). A loss of function mutation of PCSK9 will lead to a more LDL receptors on the hepatocyte level to clear more LDL from the plasma resulting in a reduced risk for cardiovascular disease (Dixon et al., 2017). A Danish study found that the loss of function mutation in PCSK9 accounted for a 12% reduction in LDL-C and a 28% reduction in cardiovascular disease risk (Farnier et al., 2014).

PUBLISHED STUDIES

The following literature review will first analyze evolocumab's development by AMGEN and safety ratings in humans with dyslipidemia. Next, the efficacy and clinical

utility of the PCSK9 inhibitor will be analyzed, along with its ability to reduce cardiovascular events as shown by the recent breakthrough FOURNIER clinical trial. Additionally, a review of cost-effective assessments of evolocumab will provide insight into evolocumab's present place in lipid lowering therapy. The role of evolocumab in today's society as well as future implications will also be explored.

Evolocumab: safety, tolerability, and efficacy in humans

Repatha, or generic name Evolocumab, was developed and manufactured by AMGEN Incorporated and was approved by the Food and Drug Administration (FDA) on August 27, 2015 (FDA, 2015). Evolovumab is a human monoclonal immunoglobulin G2 against human PCSK9 indicated to lower LDL-C in adult patients who have, despite dietary and lifestyle changes and maximally tolerated statin dose, continued suboptimal lipid levels with either ASCVD or HeFH (FDA, 2015). Evolocumab was not the first PCSK9 inhibitor on the market; the FDA approved Alicoumab, known by its brand name Praluent, on July 24, 2015 (FDA, 2015).

Two Evolocumab Phase I studies evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 145, (the development name for evolocumab), on healthy adult humans (Phase 1a) and adults with hypercholesterolemia on statin therapy (Phase 1b) (Dias et al., 2012). In the Phase 1a trials, AMG 145 reduced LDL-C levels up to 64% compared to the placebo after one dose, and AMG 145 reduced LDL-C levels by 81% with continued therapy (Dias et al., 2012). Pharmacodynamic analysis revealed that single administration of AMG 145 decreased mean LDL-C with a

return to baseline levels within 71 days (Dias et al., 2016). Due to the structure of AMG 145, a human monoclonal antibody, the best route of administration for highest bioavailability is through subcutaneous injection to the thigh, abdomen, or upper arm (FDA, 2015). In the safety analysis, no significant adverse events were reported throughout the duration of the study, and adverse event incidences were similar in treatment versus placebo groups (Dias et al., 2016). AMG 145 then continued to Phase II trials to further evaluate the drug’s safety and efficacy.

The PROFICIO trial pooled data from 4 randomized, twelve week, placebo-controlled phase II trials (MENDEL, LAPLACE-TIMI 57, RUTHERFORD, and GAUSS) to better assess the safety, tolerability, and efficacy of AMG 145 in over 1300 patients (Stein et al., 2014). The four phase II studies analyzed in the PROFICIO trial are detailed in **Table 4** below.

Table 4. Phase II AMG 145 studies analyzed in the PROFICIO clinical study.

Study Name	Number of Patients	Background Lipid Therapy	Length (weeks)	Dosing	Study Aim
LAPLACE-TIMI	631	Statin (+/- ezetimibe)	12	70, 105, 140 mg Q2W Evolocumab or placebo	Combination therapy with

				OR 280, 350, 420 mg Q4W Evolocumab or placebo	statins
RUTHERFORD	167	Statin (+/- ezetimibe)	12	350, 420 mg Q4W Evolocumab or placebo	HeFH
GAUSS	157	Non ezetimibe lipid lowering therapy	12	280, 350, 420 Q4W Evolocumab OR Ezetimibe 10 mg+ SC placebo Q4W OR Ezetimibe 10 mg + Evolocumab 420mg Q4W	Statin intolerant patients
MENDEL	406	No background anti-lipid therapy	12	70, 105, 140 mg Q2W Evolocumab or placebo OR 280, 350, 420 mg Q4W Evolocumab or placebo	Stand-alone monotherapy

Study name, patient number, background lipid therapy, study length, dosing, and aim of the four AMG 145 clinical trials detailed in the PROCIFIO study. Q2W, every 2 weeks; Q4W, every 4 weeks; GAUSS (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects); LAPLACE-TIMI 57 (LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy); MENDEL (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy for Easing Lipid Levels); RUTHERFORD (Reduction of LDL-C With PCSK9 Inhibition in HeFH Disorder) (Table taken from Stein et al., 2014).

PROFICIO trial safety assessments show that adverse events were reported in 56.8% of evolocumab treated groups and 49.2% of placebo groups (Stein et al., 2014). In order of highest prevalence, nasopharyngitis, upper respiratory infection, headache, diarrhea, myalgia, and back pain were the adverse events most commonly reported in the evolocumab treatment group (Stein et al., 2014). Serious adverse events were reported in 2% of evolocumab treated groups and 1.2% of placebo treated groups, and investigators considered none of the events to be treatment related (Stein et al., 2014).

The tolerability of subcutaneous administration was also assessed with injection site reactions reported in 4.1% of evolocumab patients and in 3.3% of placebo patients (Stein et al., 2014). This reaction rate is significantly lower than mipomersen (an Apo B antisense molecule), another FDA approved subcutaneous administered lipid lowering therapy, which caused injection site reactions in 92% of patients (Stein et al., 2014). The only contraindication on the FDA label for evolocumab is in patients with a history of a serious hypersensitivity reaction, such as a rash or urticaria, to evolocumab (FDA, 2015).

In terms of LDL-C reduction, the PROFICIO trial found mean percentage reduction levels ranging from 40.2% to 59.3% among all evolocumab groups compared to placebo, as shown in **Figure 6** (Stein et al., 2014). The greatest decrease in LDL-C levels was seen with the 140 mg dose Q2W (Stein et al., 2014). Additionally, significant reductions in Apo B, non HDL-C, triglycerides, and lipoprotein (a) were observed (Stein et al., 2014). The safe and effective results of these studies allowed evolocumab to continue to larger, longer studies in Phase III clinical trials.

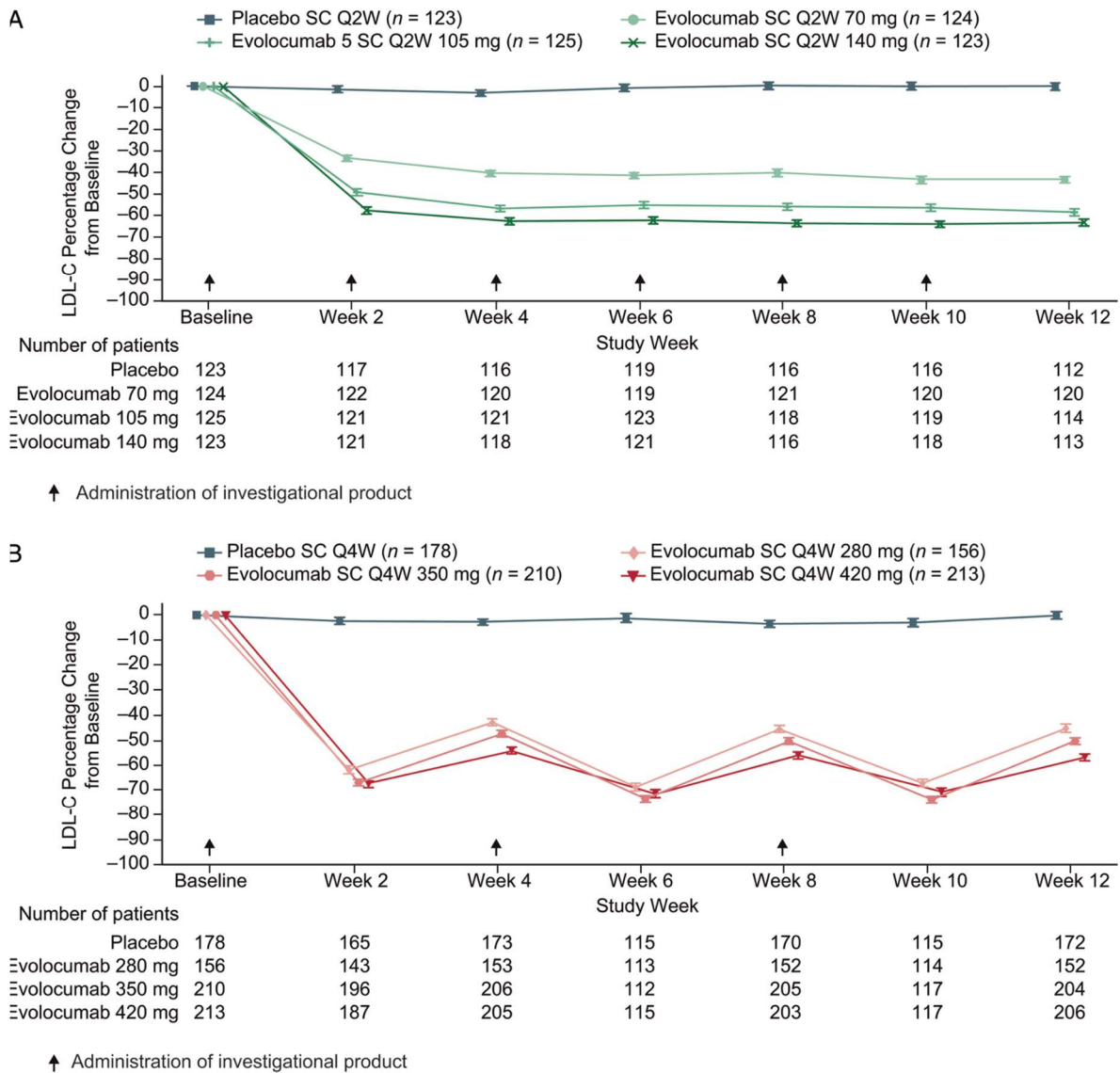


Figure 6. Evolocumab Q2W (Figure A) and Q4W (Figure B) lowers LDL-C significantly from baseline levels compared to placebo. Data compiled in the PROFICIO study taken from four phase II evolocumab 12-week clinical trials shows percentage changes from baseline in LDL-C levels. (Figure taken from Stein et al., 2014)

The landmark Evolocumab outcomes study, FOURIER, an international, double blind, randomized, placebo-controlled trial, was designed to evaluate cardiovascular risk reduction by dramatically lowering LDL-C (Sabatine et al., 2017). A total of 27,564

patients met the following study criteria: age greater than or equal to 40 and less than or equal to 85, patient history of a prior myocardial infarction, prior stroke, or symptomatic peripheral arterial disease, fifteen weeks on a stable background lipid-lowering therapy such as a statin with or without ezetimibe, and LDL-C > 70 mg/dL or non HDL-C > 100 mg/dL (Sabatine et al., 2017). Many patients who enrolled in the study are patients that are at high risk for another cardiovascular event; the mean baseline LDL-C was 92 mg/dL and 70% of patients were on high-intensity statins (Sabatine et al., 2017). Patients were randomized 1:1 to either evolocumab 140 mg Q2W or 40 mg Q4W and a statin, or placebo and a statin (Sabatine et al., 2017). The primary efficacy end point of the study was “the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization” (Sabatine et al., 2017).

After 48 weeks, the evolocumab treatment group had LDL-C levels reduced to ≤ 70 mg/dL in 87% of patients, ≤ 40 mg/dL in 67% of patients, and ≤ 25 mg/dL in 42% of patients, compared with the placebo group, which was 18%, 0.5%, and less than 0.1% respectively (Sabatine et al., 2017). These data are shown in **Figure 7**. Additionally, after 48 weeks, the evolocumab treatment group had non HDL-C levels reduced by 52% and Apo B levels reduced by 49% (Sabatine et al., 2017).

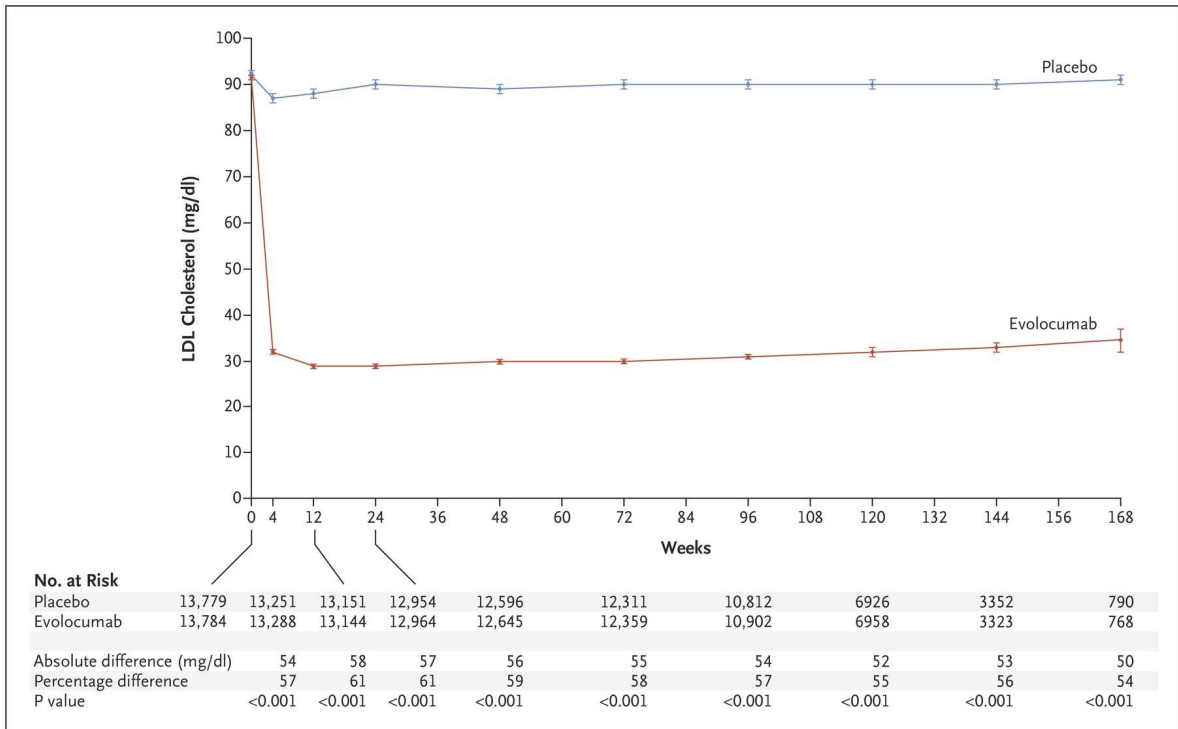


Figure 7. Evolocumab lowers LDL-C levels significantly compared to placebo. After 48 weeks, evolocumab lowered LDL-C by a mean of 56 mg/dL compared to placebo. (Image taken from Sabatine et al., 2017).

Importantly, the addition of evolocumab with a statin was shown to reduce the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization by 15% as shown in **Figure 8** (Sabatine et al., 2017). These results show that patients with ASCVD will have reduced morbidity and mortality by lowering LDL-C cholesterol levels with evolocumab (Sabatine et al., 2017).

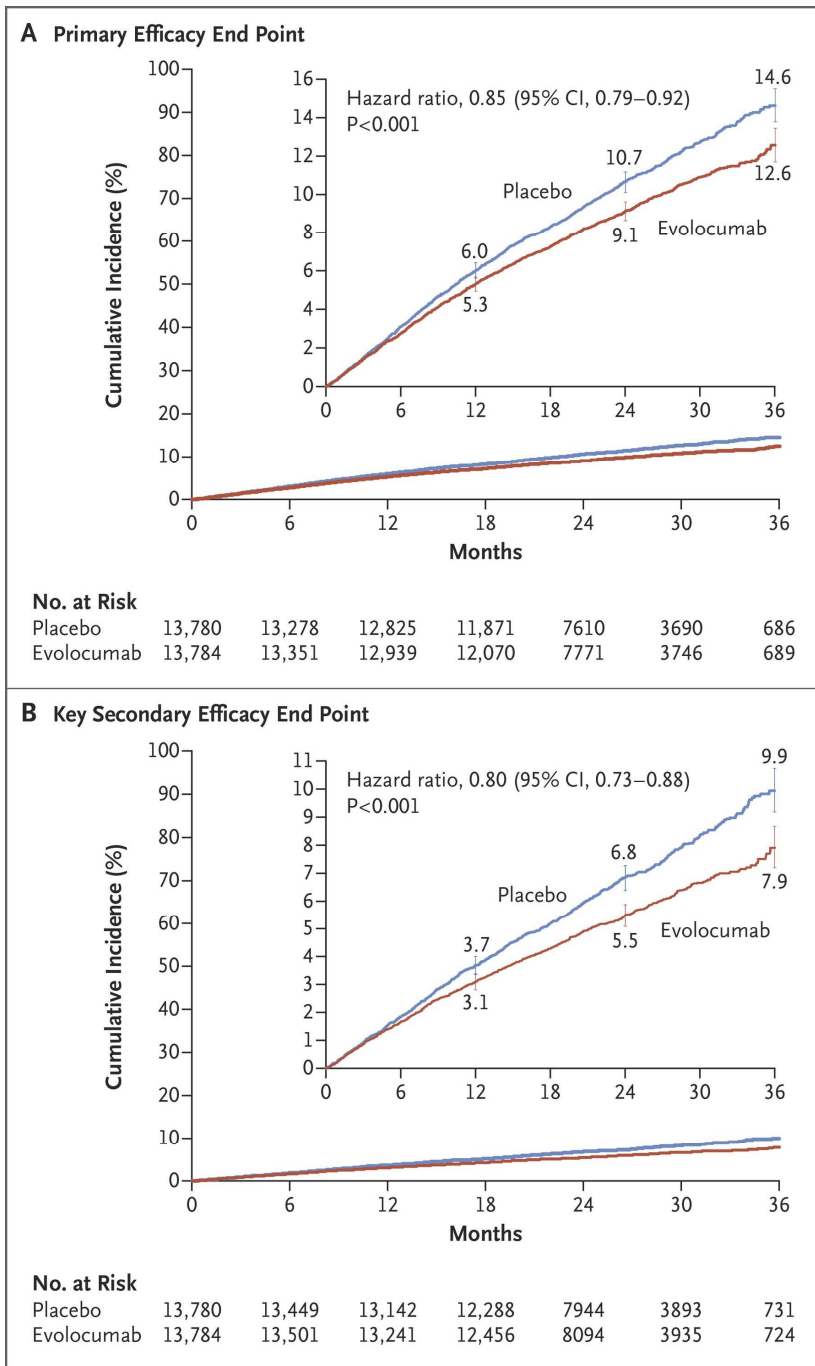


Figure 8. Incidence of cardiovascular events in the FOURNIER trial. (Table taken from Sabatine et al., 2017).

Cost-Effectiveness Assessments of Evolocumab

According to the AHA, cardiovascular disease costs more than any other ailment in the United States, estimating an annual cost of over \$650 billion for cardiovascular disease in 2011 (Mozaffarian et al., 2015). These costs are projected to double by the year 2030 despite widespread statin therapy (Mozaffarian et al., 2015). Therefore, the cost-effectiveness of new therapies aimed to lower the risk of cardiovascular disease has become increasingly important as healthcare costs rise.

The PCSK9 inhibitor evolocumab has been shown to lower plasma LDL-C levels and risk for cardiovascular events in conjunction with other lipid lowering therapies. Evolocumab is safe and effective, but its high cost may limit its routine use (Turgeon et al., 2018). The yearly cost of evolocumab in the United States was \$14,350 in 2015 (Kazi et al., 2016). In comparison, the cost of a generic statin, simvastatin, according to the *Red Book* was \$11 per year per patient in 2015 making evolocumab significantly more expensive (Luo and Kesselheim, 2015). However, studies to determine the cost effectiveness of evolocumab have found differing conclusions.

Cost-effective analyses examine a particular therapy by asking, “How much health benefit do we get for our money?” (Owens et al., 1999). There are two definitions from the World Health Organization (WHO) and the ACC/AHA that are commonly used as cost-effective thresholds, or the amount of money society is willing to spend to gain one year of life (Gandra et al., 2016). These definitions are detailed in **Table 5**, which portrays the thresholds in terms of cost per quality-adjusted life year (QALY) (Gandra et al., 2016). The National Institute of Health and Clinical Excellence (NICE) has defined

QALY as a “measure of the state of health of a person in which the benefits, in terms of length of life, are adjusted to reflect the quality of life” (Owens et al., 1999). QALYs are calculated by estimating the possible years of life left for a patients following a treatment and weighting each year with a quality-of-life score (Owens et al., 1999). This quality of life score is from 0 to 1; absence of life is worth zero QALYs and a one-year of perfect health is worth 1 QALY (Owens et al., 1999). Cost-effectiveness ratio is most effective when expressed as dollars per QALY, as this allows one to compare the efficiency of interventions for different conditions using the same units (Owens et al., 1999).

Table 5. Cost-effective threshold definitions from the WHO and AHA/ACC

WHO thresholds based on 2014 US gross domestic product per capita	
Highly cost-effective	< \$55,000/ QALY
Cost-effective	\$55,000- \$165,000/ QALY
Not cost effective	> \$165,000/ QALY
AHA/ACC thresholds based on level of value to society	
High	< \$50,000/ QALY
Intermediate	\$50,000 to < 150,000/ QALY
Low	>\$150,000/ QALY

*Thresholds defined in terms of United States dollar cost per QALY. (Table taken from Gandra et al., 2016).

To compare the cost of standard of care to standard of care plus the treatment, the incremental cost-effectiveness ratio (ICER) is used to summarize the cost-effectiveness of the intervention (ICER) (Gandra et al., 2016). ICER is defined as the difference in cost between two possible interventions, divided by the difference in their effect (Gandra et al., 2016). In this study, ICER is the difference in cost between evolocumab added to standard of care and just standard of care divided by the difference in their effect in terms of LDL-C lowering (Gandra et al., 2016). This study determined ICERs of \$75,863/ QALY gained in HeFH, \$141,699/ QALY gained in ASCVD, and \$100,309/ QALY gained in patients with ASCVD with statin intolerance (Gandra et al., 2016). These ICERS meet the WHO definition of cost effective and the ACC/AHA definition for high/intermediate thresholds (Gandra et al., 2016). Ultimately, the study found evolocumab to be more cost-effective in patients with HeFH than ASCVD or ASCVD with statin intolerance (Gandra et al., 2016).

Others have concluded that Repatha is not cost effective in patients with HeFH or ASCVD, and believe it will add to increasing health care costs in the United States (Kazi et al., 2016; Fonarow et al., 2017). The following studies argue that reducing the annual drug price is necessary to meet cost effective thresholds; otherwise, the drug will result in an increase US health care spending by about \$120 billion (Kazi et al., 2016).

In 2016, Dhruv Kazi and coworkers found that evolocumab therapy in patients with both HeFH and ASCVD does not meet acceptable cost-effective thresholds (Kazi et al., 2016). The study was designed using the Cardiovascular Disease Policy Model, and

evaluated statin therapy compared with addition of either ezetimibe or PCSK9 inhibitors (Kazi et al., 2016).

The results found that adding PCSK9 inhibitors to statins in HeFH prevented 316,300 major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, or stroke (Kazi et al., 2016). This would cost \$503,000 /QALY gained (Kazi et al., 2016). In patients in ASCVD, adding a PCSK9 inhibitor to statins would prevent 4.3 million MACE and cost \$414,000/ QALY gained, which is significantly over the willingness to pay threshold of \$100,000/ QALY gained (Kazi et al., 2016). To be cost effective at the willingness to pay threshold of \$100,000/ QALY, evolocumab's price would need to be lowered by 70% to \$4,536 annually in the United States (Kazi et al., 2016). **Figure 7** shows the proportion of optimal simulations as a function of drug price in the United Kingdom, Austria, Finland, and United States, with the United States having the highest price out of all the countries (Kazi et al., 2016). At 2015 prices, evolocumab was estimated to increase cardiovascular care costs by \$29 billion over five years if used in every eligible patient in the United States (Kazi et al., 2016).

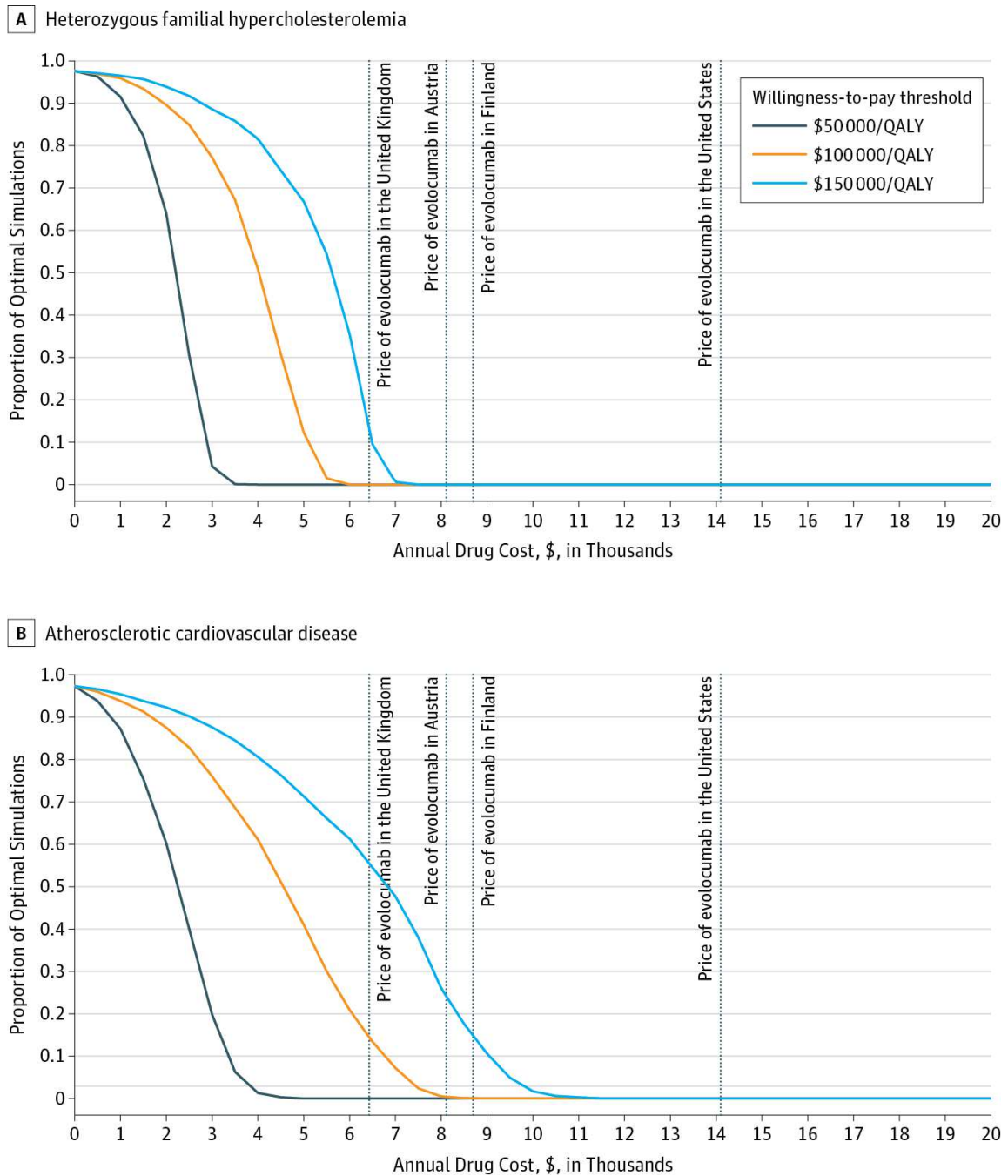


Figure 11. At 2015 prices for evolocumab and a threshold of \$100,000 per QALY gained, evolocumab is not cost effective in FH (a) or ASCVD (b). The price of evolocumab for one year in the United Kingdom, Austria, and Finland is \$6427, \$8110, and \$8700 respectively. This is in comparison to the US price of \$14100 annually. (Image taken from Kazi et al., 2016).

Evolocumab is currently approved for use in 50 countries including the United States, Japan, Canada, and the 26 members of the European Union (Lee et al., 2018). Countries outside of the United States have also agreed that although evolocumab treatment is effective in lowering cardiovascular events, the drug is not cost effective in other health care systems. In Spain, evolocumab's annual cost is 11 134.78€ compared to the standard treatment (statins plus ezetimibe) cost of 393.83€ (Olry de Labry Lima et al., 2018). The ICER ratio was > 600 000€ (Olry de Labry Lima et al., 2018). In Canada, evolocumab costs \$7500 annually and was still deemed to be not cost effective, and for the drug to have a 50% probability of being cost effective. It was found that the price would need to be lowered to \$1200 per year and \$2300 per year in a willingness to pay threshold of \$50,000/ QALY gained and a willingness to pay threshold of \$100,000/ QALY gained, respectively (Lee et al., 2018).

DISCUSSION

Cardiovascular disease is the number one killer in the United States, and accounts for 31% of all deaths worldwide. Over 45% of those deaths are due to coronary artery disease, a direct result of atherosclerosis. Atherosclerosis is a process where plaques of fatty material build up in an artery's wall. Atherosclerosis is directly correlated with elevated LDL levels as LDL is deposited in the artery's wall and causes an inflammatory immune response which triggers the creation of foam cells and fatty plaques which can rupture, directly causing cardiovascular events such as myocardial infarction or stroke.

Recently, treatment guidelines for treating hyperlipidemia have changed. The new AHA/ACC treatment guidelines identify an additional 13 million Americans that are now eligible for statin therapy based on four categories of patients who would receive the most benefit from a lipid lowering therapy. Statins, functioning as a HMGCR inhibitor, are the first drug of choice to treat elevated LDL-C and act by inhibiting cholesterol biosynthesis in hepatocytes. However, some patients are statin resistant or statin intolerant and either do not respond to the therapy or do not benefit from the therapy because of significant adverse side effects including hepatic dysfunction and severe myalgias. Additionally, patients with FH, an autosomal dominant genetic disorder caused by mutations that lead to an increase in total plasma cholesterol require additional lipid lowering therapies as they are prone to greatly accelerated atherosclerosis and heart disease.

A new therapy approved in 2015 to dramatically reduce LDL-C levels is a human monoclonal antibody, Evolocumab, developed by AMGEN. Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDL receptor, preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the LDL receptor from binding to PCSK9, evolocumab increases the amount of LDL receptors available to clear LDL from the blood, effectively lowering LDL-C levels. Evolocumab is FDA indicated for adults, in addition to diet and maximally tolerated statin therapy for patients with HeFH or ASCVD who are not meeting acceptable LDL-C level. Additionally, evolocumab is FDA approved for adults with HoFH, in addition to diet and other lipid lowering therapies such as statins and ezetimibe, to help further lower their LDL-C level.

Clinical studies have shown evolocumab is safe and effective in patients. Evolocumab was determined to be safe and well tolerated, as the only significant contraindication is an allergic reaction to the drug. However, some patients reported an injection site reaction as evolocumab is administered as an injection to the leg, stomach or arm due to its structure as a monoclonal antibody. The Phase II clinical trial “Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations (PROFICIO), pooled data from 4 randomized, twelve week, placebo-controlled phase II trials (MENDEL, LAPLACE-TIMI 57, RUTHERFORD, and GAUSS) to assess the safety, tolerability, and efficacy of Evolocumab in over 1,300 patients. In the PROFICIO study, it was found that Evolocumab reduced LDL-C levels

by 47-56% compared to placebo on top of maximally tolerated statins and a proper diet regiment.

In the breakthrough clinical trial, further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER), after 48 weeks, the evolocumab treatment group's LDL-C levels reduced to ≤ 70 mg/dL in 87% of patients, compared with the placebo group, in which only 18% achieved that traditionally appropriate LDL-C level. In addition to lowering LDL-C levels, evolocumab reduces morbidity and mortality caused by cardiovascular events from dyslipidemia, as shown in the FOURNIER trial. The trial reported a 15% reduction in the risk of death, MI, stroke, hospitalization for angina or revascularization compared to placebo. This study has huge implications for the future of evolocumab as it was shown to save lives and prevent a reduction in quality of life due to cardiovascular disease in patients with FH and ASCVD. However, clinicians were hoping the outcomes trial would show evolocumab to be a "blockbuster drug" worthy of its expensive price tag of over \$14,000 annually.

Evolocumab's place in therapy for the treatment of hypercholesterolemia is controversial due to the high annual cost of \$14,542 in the United States. In addition, one has to consider the impact the cost of the drug has on the healthcare system as a whole. Some studies found evolocumab would increase United States health care spending by over \$120 billion. Furthermore, studies in Spain and Canada also found the drug to be not cost effective for their health care systems. Additional analysis shows that the drug is more cost effective in patients with HeFH compared to patients with ASCVD or patients

ASCVD who are unresponsive to statin therapy. It was determined that to be cost effective at the willingness to pay threshold of \$100,000/ QALY for widespread use in the United States, significant cost reductions, as much as 70% of the current annual price (\$4,536 annually), are needed. The use of Evolocumab in every eligible patient is discouraged due to the high costs associated with the therapy.

Amgen faces competition as manufactures of other PCSK9 inhibitors, including Sanofi and Regeneron, have published their own cardiovascular outcomes studies with results similar to evolocumab. These companies have also implied a willingness to reduce the cost of their PCSK9 inhibitors in certain high-risk patient populations, such as patients with a history of a myocardial infarction or stroke as well as high LDL levels despite statin therapy. Ultimately, evolocumab is an effective, safe new therapy to significantly lower LDL levels in adult patients with FH and ASCVD unresponsive to statin therapy; however, in order for evolocumab to become a therapy for primary prevention of cardiovascular disease, the price needs to be significantly lowered to be cost-effective in the United States.

REFERENCES

- A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia | *New England Journal of Medicine*. (n.d.). Retrieved June 19, 2018, from http://www.nejm.org/doi/10.1056/NEJMoa1316222?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov
- Bandyopadhyay, D., Ashish, K., Hajra, A., Qureshi, A., & Ghosh, R. K. (2018). Cardiovascular Outcomes of PCSK9 Inhibitors: With Special Emphasis on Its Effect beyond LDL-Cholesterol Lowering [Research article]. <https://doi.org/10.1155/2018/3179201>
- Boekholdt, S. M., Hovingh, G. K., Mora, S., Arsenault, B. J., Amarenco, P., Pedersen, T. R., ... Kastelein, J. J. P. (2014). Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events: A Meta-Analysis of Statin Trials. *Journal of the American College of Cardiology*, *64*(5), 485–494. <https://doi.org/10.1016/j.jacc.2014.02.615>
- Cohen, D. E. (2008). Balancing Cholesterol Synthesis and Absorption in the Gastrointestinal Tract. *Journal of Clinical Lipidology*, *2*(2), S1–S3. <https://doi.org/10.1016/j.jacl.2008.01.004>
- Dias, C. S., Shaywitz, A. J., Wasserman, S. M., Smith, B. P., Gao, B., Stolman, D. S., ... Stein, E. A. (2012). Effects of AMG 145 on Low-Density Lipoprotein Cholesterol Levels. *Journal of the American College of Cardiology*, *60*(19), 1888–1898. <https://doi.org/10.1016/j.jacc.2012.08.986>
- Doonan, L. M., Fisher, E. A., & Brodsky, J. L. (2018). Can modulators of apolipoproteinB biogenesis serve as an alternate target for cholesterol-lowering drugs? *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, *1863*(7), 762–771. <https://doi.org/10.1016/j.bbalip.2018.03.010>
- Dose, J., Huebbe, P., Nebel, A., & Rimbach, G. (2016). APOE genotype and stress response - a mini review. *Lipids in Health and Disease*, *15*. <https://doi.org/10.1186/s12944-016-0288-2>
- Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes | *New England Journal of Medicine*. (n.d.). Retrieved June 23, 2018, from http://www.nejm.org/doi/10.1056/NEJMoa1410489?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov

- Feingold, K. R., & Grunfeld, C. (2000). Introduction to Lipids and Lipoproteins. In L. J. De Groot, G. Chrousos, K. Dungan, K. R. Feingold, A. Grossman, J. M. Hershman, ... A. Vinik (Eds.), *Endotext*. South Dartmouth (MA): MDText.com, Inc. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK305896/>
- Ference, B. A., Ginsberg, H. N., Graham, I., Ray, K. K., Packard, C. J., Bruckert, E., ... Catapano, A. L. (2017). Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *European Heart Journal*, *38*(32), 2459–2472. <https://doi.org/10.1093/eurheartj/ehx144>
- Fitchett, D. H., Hegele, R. A., & Verma, S. (2015). Statin Intolerance. *Circulation*, *131*(13), e389–e391. <https://doi.org/10.1161/CIRCULATIONAHA.114.013189>
- Goldstein, J. L., & Brown, M. S. (1973). Familial Hypercholesterolemia: Identification of a Defect in the Regulation of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Activity Associated with Overproduction of Cholesterol. *Proceedings of the National Academy of Sciences of the United States of America*, *70*(10), 2804–2808.
- Goldstein, J. L., & Brown, M. S. (2009). History of Discovery: The LDL Receptor. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *29*(4), 431–438. <https://doi.org/10.1161/ATVBAHA.108.179564>
- Grundy, S. M., Cleeman, J. I., Merz, C. N. B., Brewer, H. B., Clark, L. T., Hunninghake, D. B., ... Stone, N. J. (2004). Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*, *110*(2), 227–239. <https://doi.org/10.1161/01.CIR.0000133317.49796.0E>
- Harisa, G. I., & Alanazi, F. K. (2014). Low density lipoprotein bionanoparticles: From cholesterol transport to delivery of anti-cancer drugs. *Saudi Pharmaceutical Journal : SPJ*, *22*(6), 504–515. <https://doi.org/10.1016/j.jsps.2013.12.015>
- Interpretation of Cost-Effectiveness Analyses. (1998). *Journal of General Internal Medicine*, *13*(10), 716–717. <https://doi.org/10.1046/j.1525-1497.1998.00211.x>
- Kashani, A., Phillips, C. O., Foody, J. M., Wang, Y., Mangalmurti, S., Ko, D. T., & Krumholz, H. M. (2006). Risks Associated With Statin Therapy: A Systematic Overview of Randomized Clinical Trials. *Circulation*, *114*(25), 2788–2797. <https://doi.org/10.1161/CIRCULATIONAHA.106.624890>

- Lee, S., & Cannon, C. P. (2018). Combination Lipid-Lowering Therapies for the Prevention of Recurrent Cardiovascular Events. *Current Cardiology Reports*, 20(7), 55. <https://doi.org/10.1007/s11886-018-0997-4>
- Lee, T. C., Kaouache, M., & Grover, S. A. (2018a). Evaluation of the cost-effectiveness of evolocumab in the FOURIER study: a Canadian analysis. *Canadian Medical Association Journal Open*, 6(2), E162–E167. <https://doi.org/10.9778/cmajo.20180011>
- Lu, H., & Daugherty, A. (2015). Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 35(3), 485–491. <https://doi.org/10.1161/ATVBAHA.115.305380>
- Luo, J., & Kesselheim, A. S. (2015). Cost-effectiveness of Statin Therapy for ASCVD. *The Journal of the American Medical Association*, 314(20), 2191–2191. <https://doi.org/10.1001/jama.2015.12919>
- Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., ... Turner, M. B. (2015). Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association. *Circulation*, 131(4), e29–e322. <https://doi.org/10.1161/CIR.0000000000000152>
- Olry de Labry Lima, A., Gimeno Ballester, V., Sierra Sánchez, J. F., Matas Hoces, A., González-Outón, J., & Alegre Del Rey, E. J. (2018). Cost-effectiveness and Budget Impact of Treatment with Evolocumab Versus Statins and Ezetimibe for Hypercholesterolemia in Spain. *Revista Espanola De Cardiologia (English Ed.)*. <https://doi.org/10.1016/j.rec.2018.05.003>
- Poonia, A., & Giridhara, P. (2017). Xanthomas in Familial Hypercholesterolemia. *New England Journal of Medicine*, 377(5), e7. <https://doi.org/10.1056/NEJMicm1616147>
- Raal, F., Scott, R., Somaratne, R., Bridges, I., Li, G., Wasserman, S. M., & Stein, E. A. (2012). Low-Density Lipoprotein Cholesterol–Lowering Effects of AMG 145, a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease in Patients With Heterozygous Familial Hypercholesterolemia Clinical Perspective: The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) Randomized Trial. *Circulation*, 126(20), 2408–2417. <https://doi.org/10.1161/CIRCULATIONAHA.112.144055>
- Savarese, G., De Ferrari, G. M., Rosano, G. M. C., & Perrone-Filardi, P. (2015). Safety and efficacy of ezetimibe: A meta-analysis. *International Journal of Cardiology*, 201, 247–252. <https://doi.org/10.1016/j.ijcard.2015.08.103>

- Stein, E. A., Giugliano, R. P., Koren, M. J., Raal, F. J., Roth, E. M., Weiss, R., ... PROFICIO Investigators. (2014). Efficacy and safety of evolocumab (AMG 145), a fully human monoclonal antibody to PCSK9, in hyperlipidaemic patients on various background lipid therapies: pooled analysis of 1359 patients in four phase 2 trials. *European Heart Journal*, *35*(33), 2249–2259. <https://doi.org/10.1093/eurheartj/ehu085>
- Stone, N. J., Robinson, J. G., Lichtenstein, A. H., Bairey Merz, C. N., Blum, C. B., Eckel, R. H., ... Wilson, P. W. F. (2014). 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, *63*(25, Part B), 2889–2934. <https://doi.org/10.1016/j.jacc.2013.11.002>
- Stroes, E., Colquhoun, D., Sullivan, D., Civeira, F., Rosenson, R. S., Watts, G. F., ... Rocco, M. (2014). Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients With Statin Intolerance: The GAUSS-2 Randomized, Placebo-Controlled Phase 3 Clinical Trial of Evolocumab. *Journal of the American College of Cardiology*, *63*(23), 2541–2548. <https://doi.org/10.1016/j.jacc.2014.03.019>
- Sullivan, D., Olsson, A. G., Scott, R., Kim, J. B., Xue, A., GebSKI, V., ... Stein, E. A. (2012). Effect of a Monoclonal Antibody to PCSK9 on Low-Density Lipoprotein Cholesterol Levels in Statin-Intolerant Patients: The GAUSS Randomized Trial. *The Journal of the American Medical Association*, *308*(23), 2497–2506. <https://doi.org/10.1001/jama.2012.25790>
- Venugopal, S. K., & Jialal, I. (2018). Biochemistry, Low Density Lipoprotein. In *StatPearls*. Treasure Island (FL): StatPearls Publishing. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK500010/>
- Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., ... Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet*, *364*(9438), 937–952. [https://doi.org/10.1016/S0140-6736\(04\)17018-9](https://doi.org/10.1016/S0140-6736(04)17018-9)

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