Chapter 19
Pharmacometrics of Hyperlipidemia

Maurice G. Emery, Peter C. Haughney and John P. Gibbs

19.1 Introduction

Arteriosclerosis of the coronary and peripheral vasculature is the undisputed leading cause of death worldwide resulting from cardiovascular disease, peripheral vascular disease, and stroke. Identified risk factors for cardiovascular disease and the successful mitigation of these risk factors in reducing the risk for cardiovascular disease has been the topic of recent state-of-the-art reviews (WHO et al. 2011; Smith et al. 2012; Lloyd-Jones 2010). Effective treatment of lipid disorders as a risk factor through combinations of diet and drug therapy has led to the dramatic reduction in the risk of cardiovascular disease. Despite the improvements in therapies, there is still residual cardiovascular risk which remains untreated and drives the search and development for additional treatments of these grievous illnesses.

Deposition of cholesterol into the vessel wall is a key factor in the process of arteriosclerosis. Almost all lipoproteins are an integral part of cholesterol transport processes forming the core of circulating lipids and are central in the pathogenesis of cardiovascular disease. Therefore, it is no surprise that lipoproteins represent a surrogate for cardiovascular risk, and the rich use of mathematical models describing lipoprotein kinetics have been investigated for nearly the past 50 years. These efforts represent some of the earliest applications of mathematical modeling to understand the basic physiology of lipoprotein metabolism, the influence of disease, and mechanism of action of drug treatments modifying these pathways.

J. P. Gibbs (✉)
Department of Pharmacokinetics and Drug Metabolism, Amgen Inc, Thousand Oaks, CA, USA
e-mail: gibbsj@amgen.com

M. G. Emery
Department of Pharmacokinetics and Drug Metabolism, Amgen, Inc, Seattle, WA, USA
e-mail: keokiemery@gmail.com

P. C. Haughney
Department of Pharmacokinetics and Drug Metabolism, Amgen Inc., Seattle, WA, USA
e-mail: haughney@amgen.com

S. Schmidt, H. Derendorf (eds.), *Applied Pharmacometrics,* AAPS Advances in the Pharmaceutical Sciences Series 14, DOI 10.1007/978-1-4939-1304-6_19

The application of pharmacometrics in hyperlipidemia is an emerging area. Both semi-mechanistic and empirical pharmacokinetic and pharmacodynamic (PK/PD) models have been developed to describe dose response and time course of effects for lipids. The application of pharmacometrics has been shown to effectively guide drug development decision making by accurately simulating trials, optimizing dosing regimens, and informing early termination of programs with unacceptable risk to benefit ratios. These approaches can support the development of the next wave of new treatments to meet therapeutic goals and further reduce cardiovascular risk. This chapter provides an overview of quantitative lipid metabolism, current treatments, and reviews the current state-of-the-art PK/PD modeling as applied to hyperlipidemia treatments.

19.2 Overview of Biology of Lipid Disorders

19.2.1 Lipoprotein Metabolism Overview

Lipoproteins are spherical molecules consisting of apolipoproteins, cholesterol, triglycerides, and phospholipids and serve to carry lipids with limited aqueous solubility in plasma water. They are characterized by their density, lipid composition, and the associated lipoproteins, which provide specificity with respect to functional interactions (Table 19.1).

Lipoprotein metabolism can be conveniently divided into two general pathways and are discussed in greater detail below. In healthy individuals, the first pathway functions to distribute cholesterol whereas the second pathway is often referred to as “reverse cholesterol transport” which returns cholesterol from the periphery for reuse and/or elimination. In individuals with lipid disorders, these two pathways are hypothesized to contribute to the degree of vascular pathology by either leading to deposition of excess cholesterol into or participating in removal of cholesterol from the vessel walls. Therefore, from a quantitative pharmacology perspective, the understanding of lipid and lipoprotein kinetics describes the process of lipid movement providing mechanistic insight into normal and pathological processes. In this manner, lipoprotein kinetics can help to characterize the mechanism of action and magnitude of treatment effects.

Mathematical models are applied to quantify lipoprotein metabolism. Kinetic parameters of production and elimination of circulating lipids, their precursors, and lipoproteins are obtained through direct measurement of either production or elimination of these species using tracers. These tracers can be either stable-labeled or radiolabeled molecules. The tracers can be either incorporated into lipids and lipoproteins inside the body, or labeled outside the body and then reintroduced. There are pros and cons for each approach depending on the objective of the study. The fundamental principles and major assumptions behind these quantitative tracer studies are: (1) steady-state conditions (i.e., zero-order synthesis and first-order elimination), (2) the tracer amount does not perturb the system, and (3) the tracer is

Table 19.1 Summary of major circulating lipoproteins

Lipoprotein	Density (g/dL)	Approximate molecular mass (kD)	Lipid composition (%)			Associated apolipoprotein
			TG	Chol	Phospholipid	
Chylomicron	0.95	400,000	80–95	2–7	3–9	B48, C, E, A
VLDL	0.95–1.006	10,000–80,000	55–80	5–15	10–20	B100, C, E
IDL	1.006–1.019	5000–10,000	20–50	20–40	15–25	B100, C, E
LDL	1.019–1.063	2300	5–15	40–50	20–25	B100
HDL	1.063–1.210	1700–3600	5–10	15–25	20–30	A, C, E

Chol cholesterol, *HDL* high-density lipoprotein, *IDL* intermediate-density lipoprotein, *LDL* low-density lipoprotein, *TG* triglycerides, *VLDL* very-low-density lipoprotein

representative of the disposition of the tracee. The data are fit using compartmental analyses in order to derive either the production and/or elimination rates directly or from a steady-state assumption. In older studies, exogenously radiolabeled lipoproteins were used. With the advent of sensitive mass spectrometry, incorporation of stable isotopes into proteins has been utilized with greater frequency over the past 20 years. Excellent reviews of the methodologies, models, and assumptions have been published (Barrett et al. 1996; Ji et al. 2006).

19.2.2 Production and Transport of Exogenous and Endogenous Lipids

A schematic describing the transport of exogenous or dietary lipids as well as the de novo synthesis of new lipids and their incorporation into lipoproteins is depicted in Fig. 19.1. Dietary lipids are absorbed and incorporated into nascent chylomicrons containing apo B48, apo AI, apo AII, and apo AIV. The mature chylomicron is a sphere consisting of primarily triglyceride with smaller amounts of phospholipids and free cholesterol. These particles are transported into the circulation via the thoracic duct. Once in circulation, apo C proteins are transferred from high-density lipoprotein (HDL). Apo CII appears to be responsible for the subsequent hydrolysis of triglycerides through their activation of lipoprotein lipase (LPL) residing in the capillaries of muscle and adipose tissues where the resulting fatty acids can be utilized. Once hydrolysis has occurred, apo CI and apo CII are transferred back to the surface of HDL. Apo E is then picked up by these chylomicron remnants that can be recognized by low-density lipoprotein receptors (LDLR). In this manner, the free cholesterol and phospholipids from chylomicron remnants are supplied to the liver.

Through the uptake and/or synthesis of triglycerides and cholesterol, the liver produces the majority of endogenous lipids supplying cholesterol to peripheral tissues. These lipids are combined with phospholipids and apo B100 and then secreted into the circulation as nascent very low-density lipoprotein (VLDL) particles. Other apolipoproteins (apo CI, apo CII, apo E) are inserted into VLDL particles. As with chylomicrons, VLDL is subject to action by LPL to intermediate-density lipoprotein

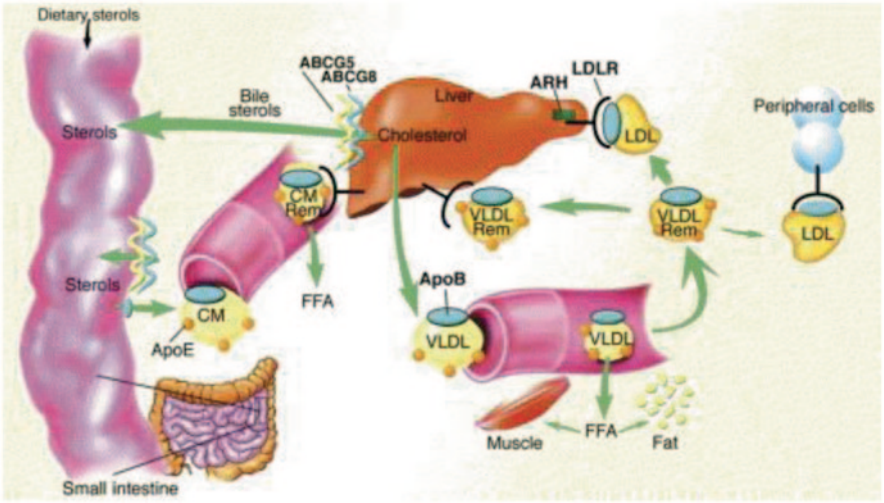

Fig. 19.1 Absorption and production of cholesterol. chylomicrons (*CM*), chylomicron remnants (*CM Rem*), VLDL remnants (*VLDL Rem*), LDL-receptor (*LDLR*), autosomal recessive hypercholesterolemia (*ARH*), ATP-binding cassette family G type 5 or 8 (*ABCG5/8*). (Reprinted from Rader DJ et al (2003) Monogenic hypercholesterolemia: new insights into pathogenesis and treatment. J Clin Invest 111/12:1796, permission conveyed through Copyright Clearance Center, Inc.)

(IDL; VLDL remnants). These particles are then converted to smaller LDL particles through the action of hepatic triglyceride lipase and apo E. The liver takes up most LDL and removal of LDL (and other apo B100 particles) occurs through the LDLR on the hepatocyte. The primary signal in the regulation of hepatic cholesterol production for secretion and hepatic cholesterol uptake by LDL and interaction with LDLR is the intracellular concentration of cholesterol. This regulation is mediated through transcription factors primarily sterol regulatory element-binding proteins (SREBP). This level of regulation has been reviewed in depth and may serve as the basis of a model-based systems biology approach to understanding the effects of dyslipidemia and treatment on circulating cholesterol. (Brown and Goldstein 2006; Dietschy 1997; van der Wulp et. al. 2012)

19.2.3 Reverse Cholesterol Transport

The concept of reverse cholesterol transport (RCT) was proposed half a century ago in describing the process of the lecithin-cholesterol acyltransferase enzyme (LCAT) activity (Glomset and Wright 1964). The role of HDL in the removal and return of excess cholesterol to the liver for reuse and efflux from the body is continuing to evolve and a current understanding is shown in Fig. 19.2.

The RCT pathway consists of lipoproteins with apo AI as their core and is believed to be protective against atherosclerosis. Pre-beta (electorphoretic mobility)

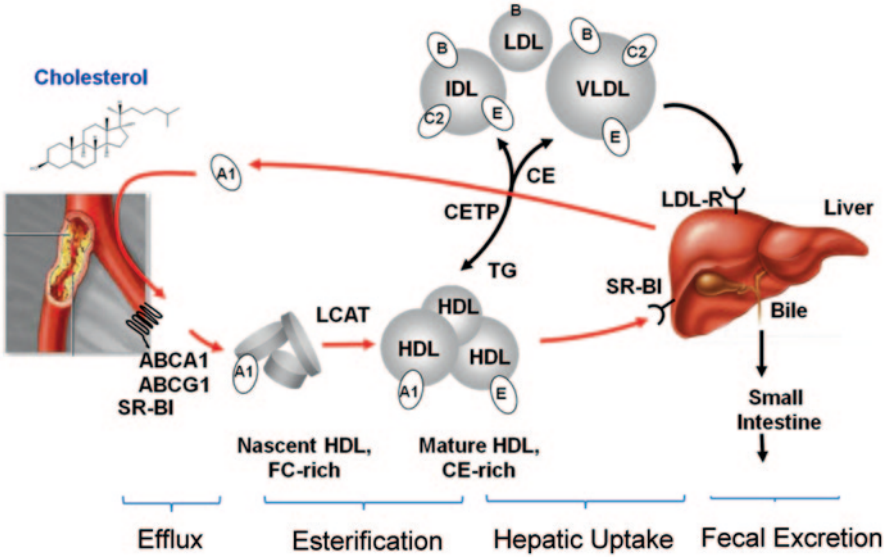

Fig. 19.2 Reverse cholesterol transport. Efflux esterification hepatic uptake fecal excretion. cholesteryl ester (*CE*), cholesteryl ester transfer protein (*CETP*), high-density lipoprotein (*HDL*), low-density lipoprotein (*LDL*), very-low-density lipoprotein (*VLDL*), LDL-receptor (*LDLR*), triglyceride (*TG*), lecithin-cholesterol acyltransferase (*LCAT*), apolipoprotein (*A1*), apolipoprotein (*B*), apolipoprotein (*C2*), apolipoprotein (*E*), scavenger receptor (*SR-BI*), free cholesterol (*FC*), ATP-binding cassette family A or G type 1 (*ABC A/G1*)

particles arise from secretion by the intestine and liver or are generated from chylomicrons which have undergone lipolysis or removal of cholesteryl ester from HDL_2 particles. The role of these discoid shaped particles is to accept unesterified cholesterol from the peripheral tissues. Cholesterol appears to be transported by members of the ATP-binding cassette transporter family from peripheral tissues including macrophages. These identified transporters include ABCA1 and ABCG1. The molecular mechanisms of HDL function and the associated cellular events by which peripheral lipid homeostasis is achieved is the subject of a recent review (Orso et al. 2011). Once the cholesterol is transferred to HDL particles, they undergo esterification through the action of lecithin-cholesterol acyltransferase (LCAT) leading to the development of spherical shaped particles. These maturing HDL particles pack cholesteryl esters into the core, and continue to grow in size while reducing their density. These particles continue to mature into HDL_2 and HDL_3 particles which constitute the largest amount of circulating HDLs. The further expansion of cholesteryl ester (CE) into the core of these HDL particles occurs as a result of apo E incorporation.

The steps in elimination of the acquired HDL cholesterol from the plasma in humans involve a number of pathways. These include the transfer of CE from HDL to VLDL/LDL particles by the action of cholesteryl ester transfer protein (CETP) and subsequent recycling to the periphery or delivery to the liver through the LDLR, di-

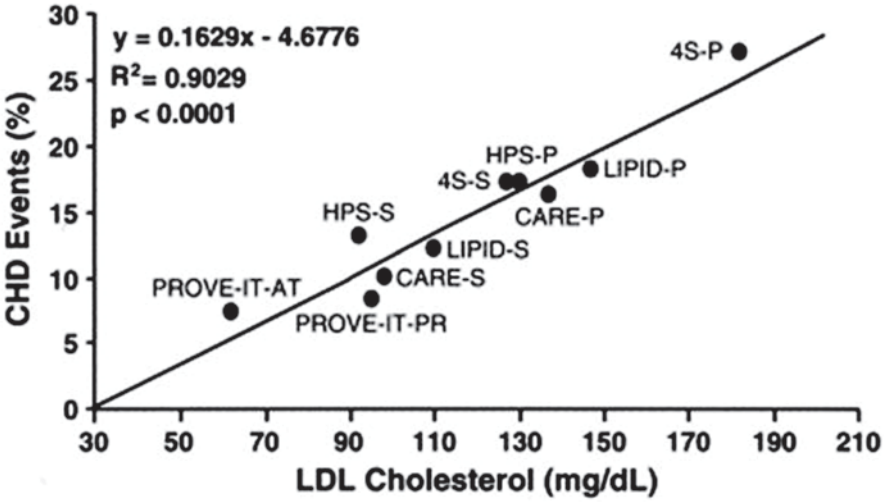

Fig. 19.3 Linkage between LDL-C and CHD events in secondary prevention trials. (Reprinted from O'Keefe et al. 2004, © 2004 by the American College of Cardiology Foundation)

rect removal of apo AI-containing particles through the hepatic scavenger receptor class B type I (SR-BI) and direct interaction of the apo E-containing HDL particles with the LDLR. Cholesterol in the liver is then subject to excretion into the bile and the feces. It is estimated that approximately 90 % of excreted cholesterol is through the formation of bile acids whose metabolic path is tightly and coordinately regulated by orphan nuclear receptors (Russell 2009; Repa and Mangelsdorf 2000). The remaining 10 % is through direct secretion into the bile by canilicular transporters and incorporation in the synthesis of biologically active steroids.

19.3 Linkage Between LDL-C and Cardiovascular Risk

A wide range of research methods including experimental animal models, laboratory investigations, epidemiology, clinical, and genetic studies indicate that elevated LDL-C is a major cause of coronary heart disease (CHD; National Heart, Lung, and Blood Institute (NHLBI) 2004). The linkage between other lipoproteins and CHD is less clear. Given the strong linkage, LDL-C is a standard primary endpoint for clinical trials evaluating the efficacy of new hypercholesterolemia drugs (European Medicines Agency 2010).

Using meta-analysis of trial level data involving ten controlled clinical studies, there was a direct relationship between on-treatment LDL-C and absolute risk of CHD in the primary and secondary prevention settings (O'Keefe et al. 2004). Figure 19.3 shows the relationship between LDL-C and CHD event rates in secondary prevention trials.

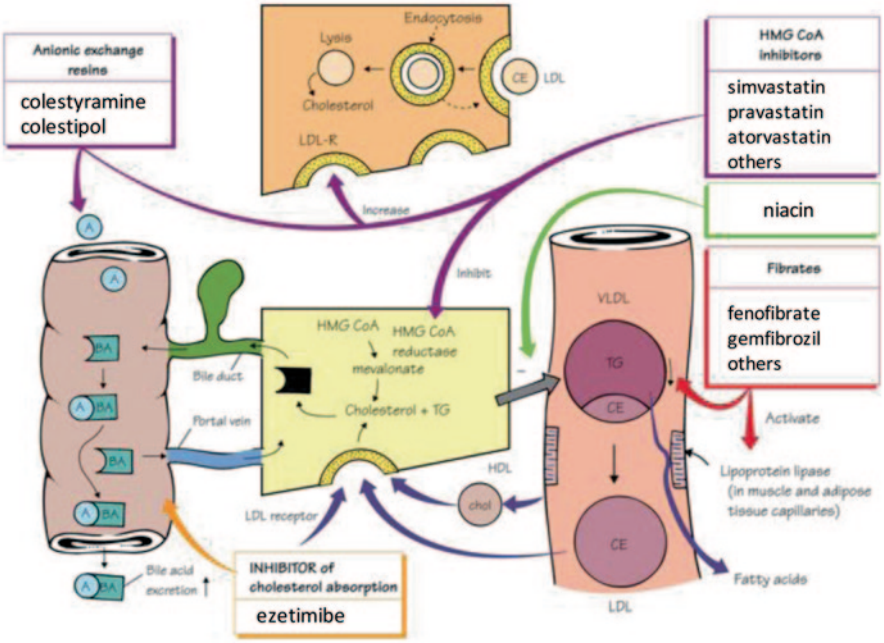

Fig. 19.4 Mechanism of action for hyperlipidemia drugs: anion exchange resins (*A*), bile acids (*BA*), cholesteryl ester (*CE*), high-density lipoprotein (*HDL*), 3-hydroxy-3-methylglutaryl coenzyme A (*HMG CoA*), low-density lipoprotein (*LDL*), LDL-receptor (*LDL-R*), very-low-density lipoprotein (*VLDL*), triglyceride (*TG*). (Reprinted from Neal MJ (2012) Medical pharmacology at a glance, 7th edn, with permission from John Wiley and Sons)

Another large-scale meta-analysis provides additional support for the linkage between LDL-C and CHD risk reduction (CTT Collaboration 2010). In a meta-analysis of individual data involving 170,000 patients participating in controlled clinical studies, relative risk reduction was calculated from studies investigating either high- versus low-dose statin or statin versus placebo. The key findings from the analysis indicated that a reduction in LDL-C of 38.6 mg/dL (or 1 mmol/L) reduced CHD risk by ~20 % for both high versus low statin and statin versus placebo trials. The authors conclude that the primary goal for patients at risk of CHD should be to achieve the largest LDL-C reduction possible.

19.4 Mechanisms of Action of Hyperlipidemia Therapies

A number of therapeutic options exist for the treatment of hyperlipidemia. All of the therapies lower cholesterol but have differential effects on lipoprotein pathways. Therapies with different mechanisms of action are often combined to achieve clinical goals. Individual classes of hyperlipidemia treatments are discussed below. Figure 19.4 highlights the mechanism of action of hyperlipidemia treatments.

Statins (including generic names of lovastatin, rosuvastatin, atorvastatin, simvastatin, pravastatin, pitavastatin, fluvastatin) inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Their role in lowering LDL-C involves inhibition of HMG-CoA reductase, preventing the conversion of HMG-CoA to mevalonic acid (MVA), and further subsequent reactions involved in LDL-C synthesis in hepatocytes of the liver (Istvan and Deisenhofer 2001). Statin treatment also induces decreases in intracellular cholesterol and increased cell-surface expression of LDLR (Goldstein and Brown 2009).

Ezetimibe (Zetia) limits the absorption of dietary cholesterol across the intestine into circulation (Merck, Zetia highlights of Prescribing Information 2013; Sweeney and Johnson 2007; Van Heek et al. 2000). Limiting dietary cholesterol results in a reduced production of VLDL and LDL-C. Ezetimibe is also available in a combination product known as Vytorin (simvastatin/ezetimibe).

Fibrates are a class of drugs (such as fenofibrate, gemfibrozil, fenofibric acid, and others) that work via oxidation of fatty acids resulting in multiple pharmacological effects reducing triglycerides and LDL-C in circulation. In the nuclei of liver hepatocytes, fibrates interact with the peroxisome proliferator-activated receptor alpha (PPAR-α), a nuclear transcription factor, and induce lipoprotein lipolysis, removal of LDL-C by altering affinity for LDL-C receptor, and increasing HDL-C production (Staels et al. 1998; Caslake et al. 1993).

Niacin also works to increase HDL-C, however, the mechanism by which niacin alters lipid profiles has not been well defined (AbbVie, Niaspan Highlights of Prescribing Information 2013). The mechanism may involve several actions including partial inhibition of release of free fatty acids from adipose tissue, and increased LPL activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases the rate of hepatic synthesis of VLDL and LDL, and does not appear to affect fecal excretion of fats, sterols, or bile acids. The benefit of niacin therapy on cardiovascular risk is unclear in the current era of statins and ezetimibe as approved therapies. Investigation of niacin, prior to the availability of statins, did demonstrate a benefit (Canner et al. 1986). However, a 2011 study conducted by the NHLBI investigating adding high-dose, extended-release niacin to statin treatment was ended early. Results showed the combination treatment did not reduce the risk of cardiovascular events, including heart attacks and stroke (NHLBI 2011). Most recently, niacin failed to show an additional benefit when added to simvastatin (Merck press release 2012).

Omega-3-acid ethyl esters are also prescribed as treatment for lowering LDL-C and triglycerides. The mechanism of action of omega-3-acid ethyl esters is not well understood (Glaxo Smith Kline, Lovaza Highlights of Prescribing Information 2013). Potential mechanisms may include inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, or increased plasma LPL activity. Omega-3-acid ethyl esters also may reduce the synthesis of triglycerides in the liver.

Mipomersen (Kynamro™) is an antisense oligonucleotide inhibitor of apolipoprotein B-100 (apo B100) ribonucleic acid synthesis inhibiting apo B100 protein synthesis (Isis, Kynamro™ Highlights of Prescribing Information 2013). Reduced

protein synthesis of apo B100 results in reduced production of VLDL, LDL, and cholesterol.

Lomitapide (Juxtapid™) directly binds and inhibits microsomal triglyceride transfer protein (MTP), which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apo B100-containing lipoproteins in enterocytes and hepatocytes. This action inhibits the synthesis of chylomicrons and VLDL leading to reduced levels of LDL-C in circulation (Aegerion, Juxtapid Highlights of Prescribing Information 2013).

Inhibitors of CETP are being investigated for the treatment of dyslipidemia. As CETP is involved in the exchange of cholesteryl esters from HDL-C to VLDL, inhibition of CETP increases HDL-C, and may variably reduce LDL-C (Barter and Rye 2012). Preclinical efficacy studies have demonstrated that a CETP inhibitor can inhibit the progression of atherosclerosis in rabbits (Okamoto et al. 2000). This is a challenging area of investigation as two development programs have been halted due to safety outcomes or lack of efficacy (Barter and Rye 2012). Programs for at least two molecules (evacetrapib and anacetrapib) are still ongoing at this time (Nicholls et al. 2011; Bloomfield et al. 2009).

Mutations in the gene for proprotein convertase subtilisin/kexin type 9 (PCSK9) were identified as the third locus of autosomal dominant hypercholesterolemia (Abifadel et al. 2003), and inhibitors of PCSK9 are being investigated for the treatment of hyperlipidemia. PCSK9 is involved in the regulation of LDLR (Derek et al. 2007; Lambert et al. 2009). Preclinical efficacy studies have demonstrated that a PCSK9 inhibitor lowers LDL-C up to 70–80 % (Chan et al. 2009; Liang et al. 2011). Clinical studies have confirmed the effect of PCSK9 inhibition on the lowering of circulating LDL-C (Dias et al. 2012; Giugliano et al. 2012; Stein et al. 2012; Koren et al. 2012).

19.5 Drug Effect Models

19.5.1 Overview

Several types of pharmacometric analysis have been undertaken to describe the effects of hyperlipidemia drugs. In general, LDL-C has been the primary focus of these analyses, though recent examples have included MVA and HDL. A summary of drug effect models describing LDL-C is shown in Table 19.2. Models have been developed for HMG-CoA reductase inhibitors, CETP inhibitors, ezetimibe, gemcabene, and methylprednisolone. An I_{max} model was developed to characterize the steady-state drug effects. In addition, a semi-mechanistic PK/PD model was developed to capture dose response and time course of LDL-C. Models have employed dose or concentration to predict LDL-C response to treatment.

One challenge in the application of pharmacometrics in this area was the lack of a clear exposure–response relationship for statins. For example, it was reported that dose was a better predictor of LDL-C reduction than exposure (as measured

Table 19.2 Summary of drug effect models to describe LDL-C

Mechanism of action	Drug	Model	Predictor variable	Reference
HMG-CoA reductase inhibitors (Statins)	Atorvastatin, simvastatin, fluvastatin	Indirect response	Dose	Faltaos et al. 2006
	Rosuvastatin[a]	Indirect response	Concentration	Aoyama et al. 2010
	Simvastatin	Indirect response	Concentration (simvastatin acid)	Kim et al. 2011
	Rosuvastatin	I_{max}	Dose	Yang et al. 2011
	Atorvastatin	Indirect response	Dose	Oh et al. 2012
CETP inhibition	Anacetrapib[b]	I_{max}	Concentration	Krishna et al. 2011
Multiple mechanisms	Ezetimibe (cholesterol absorption inhib), gemcabene (novel mechanism), Atorvastatin (HMG-CoA)	I_{max}	Dose	Mandema et al. 2005
Glucocorticoid receptor agonist	Methylprednisolone	Indirect response	LDL receptor mRNA	Hazra et al. 2008

[a] PK/PD model was developed to predict mevalonic acid
[b] PK/PD model was developed to predict LDL-C and HDL

by C_{max} and AUC) after 2 weeks of atorvastatin treatment (Cilla et al. 1996). Challenges exist to measure active drug species which can be confounded by active metabolites and active uptake/efflux transport. However, LDL-C can be accurately measured after collection of blood samples and serves as a surrogate of efficacy. Thus, dose–response relationships can adequately characterize the drug effect after statin treatment. In addition, doses of statins can be titrated after approximately 2 weeks of treatment to optimize LDL-C reduction and minimize side effects.

19.5.2 I_{max} Models

The time course of pharmacodynamic effects can be viewed as either direct or indirect. For direct PK/PD relationships, concentrations are correlated with effects in a reversible manner with the peak pharmacodynamic effect observed at the same time as peak drug concentrations. The sigmoid I_{max} model (Hill Equation) is based on the receptor occupancy theory and used to describe the nonlinear concentration–effect relationship as shown below in Eq. 19.1:

$$E = \frac{I_{max} \cdot C^n}{IC_{50}{}^n + C^n}, \tag{19.1}$$

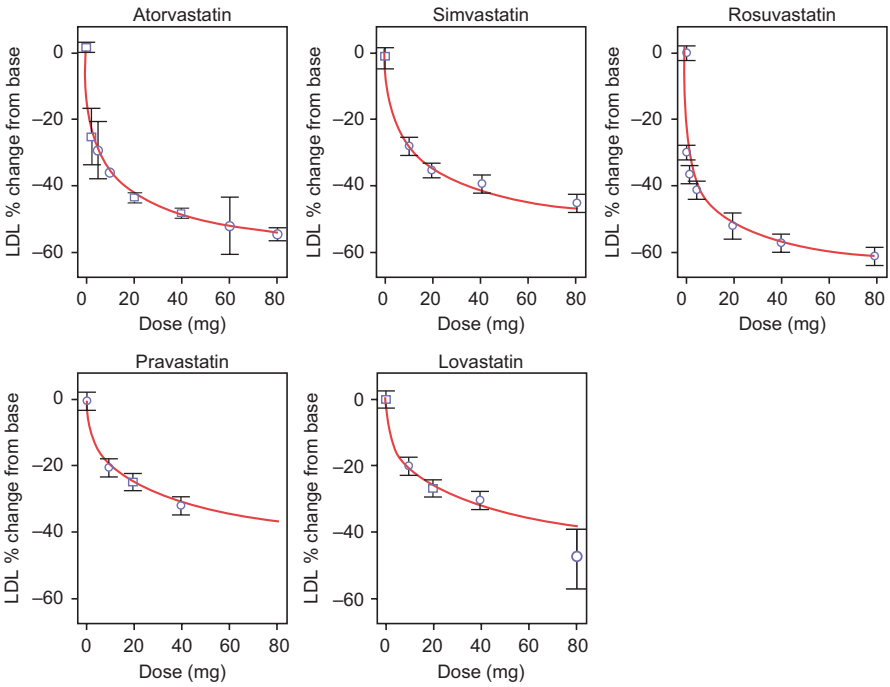

Fig. 19.5 Dose–response relationship for statins as monotherapy treatment. The *solid red line* represents the model-predicted LDL-C reduction expressed as % change from baseline in LDL-C. *Symbols* and *bars* represent the observed mean and 95% confidence interval. (With kind permission from Springer Science + Business Media: Mandema et al (2005) AAPS J 7(3):E513–522; Fig. 19.1)

where the effect of the drug (E) can be described by some maximal inhibitory effect (I_{max}) and the concentration associated with half of the maximal inhibitory effect (IC_{50}). In addition, dose–response analysis can be performed and the dose associated with the half-maximal inhibitory effect (ID_{50}) can be estimated. The Hill slope coefficient (n) increases or decreases the steepness of the concentration–effect relationship depending on whether the value of n is greater or less than 1, respectively. Alternatively, for drugs that increase the response, an alternate model can be selected with an E_{max}, EC_{50}, and n parameters in the form of Eq. 19.1.

The sigmoid I_{max} model was applied to describe the dose–response relationship of statins to facilitate drug development of gemcabene, a new chemical entity for the treatment of hypercholesterolemia (Mandema et al. 2005). The objective of the analysis was to use model-based meta-analysis to guide decision making for gemcabene, using a model of statin, ezetimibe, and gemcabene alone or in combination. Trial level data was obtained from 21 randomized clinical trials involving atorvastatin, rosuvastatin, simvastatin, lovastatin, pravastatin, and ezetimibe following multiple-dose treatment for at least 4 weeks as monotherapy. The statins shared a common I_{max} and n, and unique ED_{50} values were estimated for each drug. LDL-C

Table 19.3 Summary of PK/PD parameters (±95% confidence intervals) from I_{max} models of LDL-C response

Drug	E_0 (%)	I_{max} (%)	ID_{50} (mg)	*n*	Reference
Atorvastatin	0.802 (0.0598, 1.54)	−78.7 (−90.7, −66.7)	13.1 (6.57, 26.2)	0.451 (0.366, 0.557)	Mandema et al. 2005
Rosuvastatin			4.35 (2.19, 8.62)		
Simvastatin			30.5 (15–62.1)		
Lovastatin			82.8 (37.1–185)		
Pravastatin			97.3 (42.4, 223)		
Ezetimibe		−19.6 (−20.6, −18.6)	0.302 (0.151, 0.604)	1	Mandema et al. 2005
Rosuvastatin	0.802 (fixed)[a]	−57.0 (−61.3, −52.7)	1.74 (1.00, 2.48)	1 (fixed)	Yang et al. 2011
Anacetrapib[b]	107 (3)[c] 140(1)[d]	−80 (4)	237(25)[e]	1 (fixed)	Krishna et al. 2011

[a] Fixed value from Mandema et al. (2005)
[b] Parameter estimate (±SE)
[c] Baseline in mg/dL for healthy volunteers
[d] Baseline in mg/dL for patients
[e] IC_{50} in ng/mL

values were expressed as percentage change from baseline. Figure 19.5 shows the dose–response relationship for statins, and Table 19.3 gives a summary of the parameter estimates.

The sigmoid I_{max} model effectively described the shape of the dose–response curve for each statin. The mean response after placebo was 0.802% change from baseline indicating a small placebo response relative to the effect of statins. An estimated mean I_{max} of −78.7% change from baseline and *n* of 0.451 was observed, which is consistent with the common pharmacological mechanism of action for statins. The statin ID_{50} values varied from 4.35 to 97.3 mg reflecting in vivo potency for each statin. In addition, the I_{max}, ID_{50}, and *n* for ezetimibe and gemcabene as monotherapy were characterized.

Because gemcabene was under development for use in combination with statins, the pharmacodynamic interaction was investigated for comparison to ezetimibe, an approved therapy for use in combination with statins. The pharmacodynamic interaction model included the effect of placebo, dose response for statin or non-statin, and an interaction term to characterize the nature of the pharmacodynamic interaction. The interaction term between statin and ezetimibe was estimated to be 1, which indicated pharmacological independence. In contrast, the interaction term between statin and gemcabene was 1.69 which indicated a less than independent interaction. Moreover, limited additional LDL-C reduction was predicted when adding gemcabene to the highest doses of statins. The model-based meta-analysis supported the decision to discontinue the development of gemcabene preventing costly additional clinical studies.

Differences in the response to rosuvastatin in Western and Asian hypercholesterolemia patients were examined using a sigmoid I_{max} model (Yang et al. 2011). Trial-level data from 14 dose-ranging, and 22 one-dose trials with rosuvastatin were combined for model-based meta-analysis. The placebo response was fixed at 0.802 % change from baseline based on Mandema et al. The mean I_{max} and ID_{50} were estimated at −57 % change from baseline and 1.74 mg/day, respectively. Asian patients had a mean ID_{50} value that was approximately half (0.564) of the Western patient population estimate. The analysis supports the current dosing recommendation of 5–20 mg in Asian and 10–40 mg in Western populations which was based on bridging pharmacokinetic exposure across populations. It was reported that Asian patients have a lower oral clearance of rosuvastatin compared to Western patients (Lee et al. 2005). The resulting higher exposures may explain the lower ID_{50} in Asian populations. Results from the I_{max} model indicate that race differences in rosuvastatin pharmacodynamics were consistent with the pharmacokinetic differences, suggesting that the underlying PK/PD relationship is consistent for Asian and Western populations. A trend towards higher approved maximal doses for cardiovascular drugs has been observed for Westerners relative to Japanese and Asians in general (Liao 2007; Arnold et al. 2010).

Recently, the I_{max} model was applied to describe the effects of anacetrapib, a CETP inhibitor (Krishna et al. 2011). Because anacetrapib may be used in combination with statins, the pharmacodynamic interaction between anacetrapib and atorvastatin was characterized. Individual subject level data was obtained from phase 1 and phase 2b studies. Trough anacetrapib concentrations were found to be most predictive of HDL and LDL-C response. The effect of anacetrapib was modeled as proportional to the baseline of LDL-C. Mean baseline LDL-C values of 107 and 140 mg/dL were estimated for healthy subjects and patients, respectively, with 24 % intersubject variability in the baseline. The I_{max} and IC_{50} were −78 % and 240 ng/mL, respectively, for anacetrapib as monotherapy. Treatment with atorvastatin (20 mg/day) lowered LDL-C values by −44.5 %. The pharmacodynamic interaction term for anacetrapib and atorvastatin was estimated to be 0.99 which indicated pharmacological independence. A similar approach was applied to define the trough exposure-response for HDL. Simulations were performed using the model to predict the effect of food, patient status, and dose on LDL-C decrease and HDL increase. The I_{max} model effectively characterized the trough exposure–response relationship and provided quantitative support for phase 3 dose selection.

19.5.3 Indirect Response Models

The indirect response model has been used extensively to characterize drug effects for drugs which act on turnover processes such as production or elimination (Dayneka et al. 1993; Sharma and Jusko 1996; Mager et al. 2003). The indirect response model will describe a time delay between peak plasma concentrations and the maximal response which can be useful to help define the onset and offset of pharmacological effects. Figure 19.6 shows the compartmental model structure for the indirect response model.

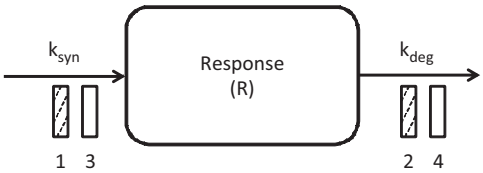

Fig. 19.6 Compartmental model structure for the indirect response model. Inhibitory effects are represented by the *shaded bar* such that models 1 and 2 represent inhibition of production rate constant (k_{syn}) or elimination rate constant (k_{deg}), respectively. Stimulatory effects are represented by the *open bar* such that models 3 and 4 represent stimulation of k_{syn} or k_{deg}, respectively

The general equation for the indirect response model is shown in Eq. 19.2:

$$\frac{dR}{dt} = k_{syn} - k_{deg} \cdot R, \tag{19.2}$$

where R is the response, k_{syn} is the zero-order synthesis rate, and k_{deg} is the first-order degradation rate. A family of four indirect effect models has been applied. Drug effects can include (1) inhibition of input, (2) inhibition of output, (3) stimulation of input, and (4) stimulation of output, where model selection is based on an understanding of the mechanism of drug action. Models 1 and 4 have been most commonly used to describe the time course of effect on LDL-C by statins.

The indirect response model was applied to characterize the hyperlipidemic effects of corticosteroids after single-dose administration in normal male Wistar rats (Hazra et al. 2008). Corticosteroids induce effects through binding to glucocorticoid receptors. Through a cascade of events, the glucocorticoid receptors modulate the expression of LDL receptors in the liver. As noted in Sect. 19.2.2, hepatocyte LDL receptors are the predominant elimination mechanism for LDL-C in humans and preclinical species, accounting for 50–80 % of the elimination of LDL-C in preclinical species (Bilheimer 1984). The authors proposed a mechanistic model where reduction in messenger RNA (mRNA) levels of the LDL receptor reduces the k_{deg} of LDL-C under the assumption that LDL receptor mRNA levels are correlated with the activity of LDL receptor. The model described the time course of LDL-C elevations after a single dose of 50 mg/kg methylprednisolone by intramuscular injection. The initial value of LDL-C was 35.8 mg/dL, and k_{deg} was 0.51 h^{-1}. The mechanistic model successfully described the time delay between methylprednisolone concentrations (t_{max} of ~1 h) and peak LDL-C response (t_{max} of ~18 h) after administration of methylprednisolone in rats giving biological insights into corticosteroid-induced hyperlipidemia.

The indirect response modeling approach was applied to simvastatin to characterize the dose–response relationship of LDL-C reduction in Koreans (Kim et al. 2011). Healthy volunteers recruited to participate in a drug–drug interaction study received simvastatin 40 mg daily for 14 days. Intensive PK measurements were obtained for simvastatin and simvastatin acid on days 1, 7, and 14, with trough measurements on days 5, 6, 12, and 13. A two-compartment model with first-order

Table 19.4 Summary of PK/PD parameters (±95% confidence intervals) from basic and precursor-pool indirect response models of LDL-C

Drug	INH	ID_{50} (mg)	k_{in} (g/L/day)	k_{out} (1/day)	BSV k_{in}	BSV ID_{50}	Reference
Atorvastatin	0.21 (0.19–0.28)	26 (19–66)	0.14 (0.10–0.24)	NR	72	160	Faltaos et al. 2006
Simvastatin		1.3 (1.0–3.7)					
Fluvastatin		15 (9–34)					
Simvastatin	NE	0.0868[a] (0.000150–0.396)	0.274 (0.208–0.346)	0.297	50.2	93.2	Kim et al. 2011
Atorvastatin	0.09	11.9 (3.8–31.8), patients 2.0 (0.2–5.9) healthy	0.15 (0.12–0.20)	0.105 (0.08–0.144)	1.6	98	Oh et al. 2012

NR not reported, *BSV* between subject variability (%)
[a] IC_{50} in ng/mL

absorption described the pharmacokinetics of simvastatin with 70% of the dose eliminated as simvastatin (central compartment), and 30% of the dose eliminated as simvastatin acid (represented as a peripheral compartment). Simvastatin acid was the active pharmacological species that inhibited k_{syn} of LDL-C in the PK/PD model. Table 19.4 gives a summary of the PK/PD parameter estimates. The system parameters baseline LDL-C and k_{syn} were 92 mg/dL and 0.274 g/L x day, respectively. Simvastatin acid had an I_{max} and IC_{50} of 0.489 and 0.0868 ng/mL, respectively. Intersubject variability was greatest for the IC_{50} with 93.2% CV, and less for I_{max}, k_{syn}, and baseline LDL-C at 15.7, 50.2, and 20.5% CV, respectively. The authors noted that the IC_{50} and intersubject variability in IC_{50} may have been poorly estimated because simvastatin acid concentrations were much higher than the IC_{50} for the 40 mg dose. A visual predictive check of concentration and LDL-C indicated that the model fit the data well and explained the observed variability, as shown in Fig. 19.7.

Simulations were performed using the PK/PD model to compare the predicted dose–response relationship with observed dose–response data. To determine if the concentration–response model could predict the effect of simvastatin on LDL-C in patients, the authors overlayed the model-predicted dose–response relationship with available data from a meta-analysis and the Zocor label. This analysis demonstrated the successful prediction of steady-state LDL-C response in patients from healthy subjects using population PK/PD modeling. Overall, the indirect response model successfully described the dose–response relationship for simvastatin in Korean patients.

The indirect response model proposed by Kim et al. was used as the basis investigating LDL-C reductions after morning or evening administration of simvastatin

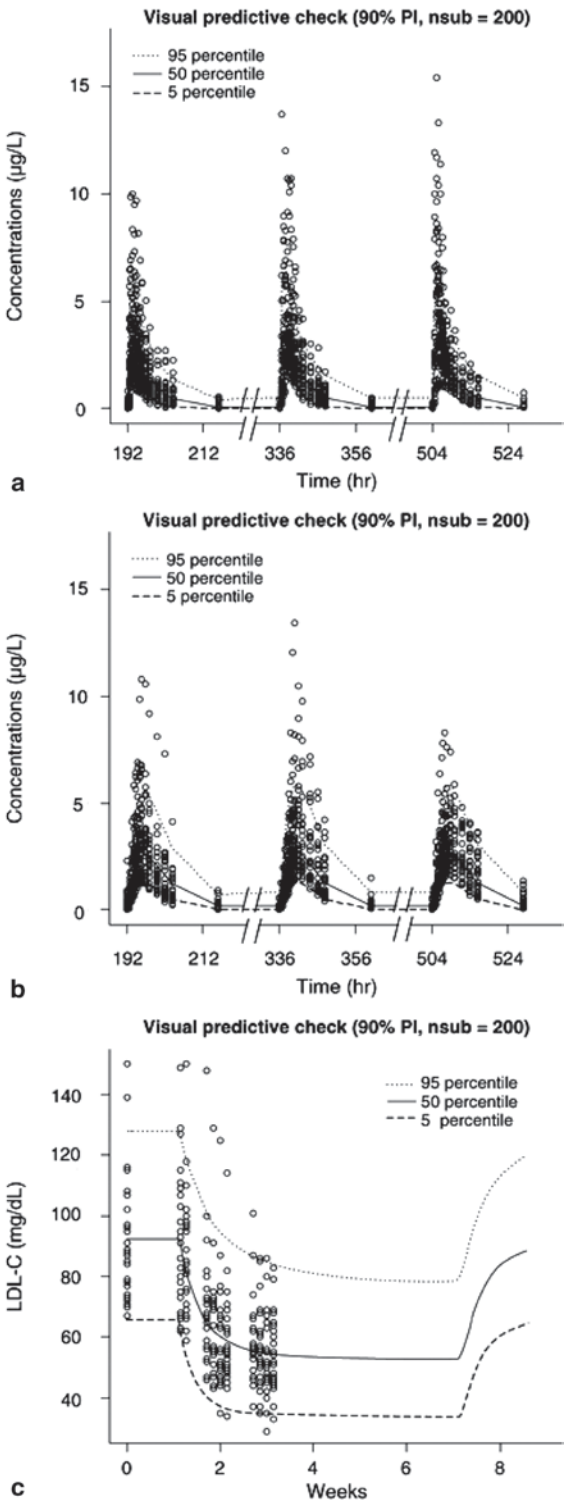

Fig. 19.7 Application of the indirect response model to LDL-C turnover after administration of simvastatin 40 mg/day for 14 days in healthy, Korean subjects. (Reprinted from Kim et al. 2011, with permission from John Wiley and Sons and © 2011 The Authors Basic & Clinical Pharmacology & Toxicology © 2011 Nordic Pharmacological Society)

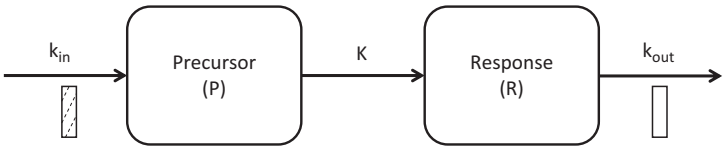

Fig. 19.8 Precursor pool indirect response model. Inhibitory effects are represented by the *shaded bar*. Stimulatory effects are represented by the *open bar*. k_{in} production rate constant, K transfer rate constant, k_{out} elimination rate constant

in a simulation study (Wright et al. 2011). It has been reported that the effects of statins are more prominent after administration in the evening, but are also associated with a 5–25% reduction in compliance relative to morning administration (Vrijens et al. 2008). The authors modified the indirect response model to include a circadian production of LDL-C, and performed simulations to compare the impact of morning versus evening administration for 10, 20, 40, and 80 mg/day simvastatin. In addition, the effect of 10% noncompliance was considered for subjects receiving the evening dose. The difference in LDL-C reduction for morning, evening, and evening with 10% noncompliance was 30.6, 33.0, and 31.6%, respectively, after 10 mg/day simvastatin. The model predictions suggested a relatively small advantage for evening administration that could be almost completely eliminated by noncompliance.

The indirect response model has been used to characterize the inhibitory effects of rosuvastatin on MVA (Aoyama et al. 2010). HMG-CoA reductase converts HMG-CoA to MVA as the rate-limiting step in de novo cholesterol biosynthesis. The data source for the modeling was based on a previously published report of the administration of 10 mg/day rosuvastatin to 24 subjects in a two-way crossover study comparing the effects of morning versus evening administration (Martin et al. 2002). The indirect response model was modified to account for the circadian production of MVA throughout the course of a day. A 7.7% reduction in the area under the effect curve over 24 h was reported for MVA for morning administration relative to evening administration. The extended indirect response model successfully described the circadian fluctuations in MVA and effects of rosuvastin after morning or evening administration. The implications of the findings with MVA on steady-state LDL-C are not entirely clear as the link between MVA and LDL-C has not been defined.

19.5.4 Precursor Pool Indirect Response Model

A modified version of the indirect response model which we refer to as the precursor pool indirect response model was proposed to describe the LDL-C reduction after multiple dose administration of atorvastatin, simvastatin, and fluvastatin in hypercholesterolemia patients (Faltaos et al. 2006). The model included a precursor compartment which represented the production of LDL-C in hepatocytes, and a response compartment which represented circulating LDL-C pool as shown in Fig. 19.8.

Distinct from the precursor-dependent indirect response model which describes tolerance and rebound phenomena (Sharma et al. 1998), the precursor pool indirect response model in this case was developed based on the known pharmacological mechanism of statins (described in Sect. 19.6.3). The general equation for the precursor pool indirect response model is shown below in Eqs. 19.3 and 19.4:

$$\frac{dP}{dt} = k_{in} \cdot (1 - INH) - K \cdot P \tag{19.3}$$

$$\frac{dR}{dt} = K \cdot P - (1 + STIM) \cdot k_{out} \cdot R, \tag{19.4}$$

where P is the precursor compartment, R is the response compartment, k_{in} is the zero-order synthesis rate, K is the transfer rate from precursor to response compartment, and k_{out} is the first-order elimination rate. INH and STIM represent the drug effects of statins, namely inhibition of synthesis and stimulation of elimination, respectively. Pharmacokinetic data were not available from the study, so the effect of each statin on k_{out} was proposed to be dose-dependent in the form of an E_{max} model while the INH function was independent of dose and/or statin. One of the limitations of the precursor pool indirect response model was reported (Kim et al. 2011), where the authors found that the model was overparameterized when applied to simvastatin data from healthy Korean subjects.

The precursor pool indirect response model was applied to describe the effect of atorvastatin, simvastatin, and fluvastatin on LDL-C in hypercholesterolemic patients (Faltaos et al. 2006). LDL-C observations ($n = 309$) were collected from 100 patients after daily administration of atorvastatin (10–40 mg/day), simvastatin (10–80 mg/day), and fluvastatin (10–80 mg/day) at different times (ranging from 14 to 150 days). Table 19.4 gives a summary of the PK/PD parameter estimates. The model described the data adequately, and suggested a k_{in} value of 0.14 g/L/day that was inhibited by 21 % by statin treatment. The potency of simvastatin, fluvastatin, and atorvastatin as measured by the ED_{50} for stimulating k_{out} was 1.3, 15, and 26 mg/day, respectively. Extensive intersubject variability in k_{in} and ED_{50} were reported (72 and 160 %, respectively). The model was one of the first examples to describe the time course of LDL-C reduction, and could be a useful platform for the design of clinical studies. Unfortunately, the authors did not provide an estimate for K or k_{out} in the publication, limiting the general application of the model by other scientists.

The precursor pool indirect response model was subsequently utilized to describe the PK/PD relationship of atorvastatin to gain insights into the dose–response relationship in Korean dyslipidemic patients and nonpatient volunteers (Oh et al. 2012). The study included 15 dyslipidemic patients that participated in a two-step dose escalation trial where the dose of atorvastatin was initiated at either 10 or 20 mg/day and escalated to 40 or 80 mg/day after 21 days of dosing. In addition, 11

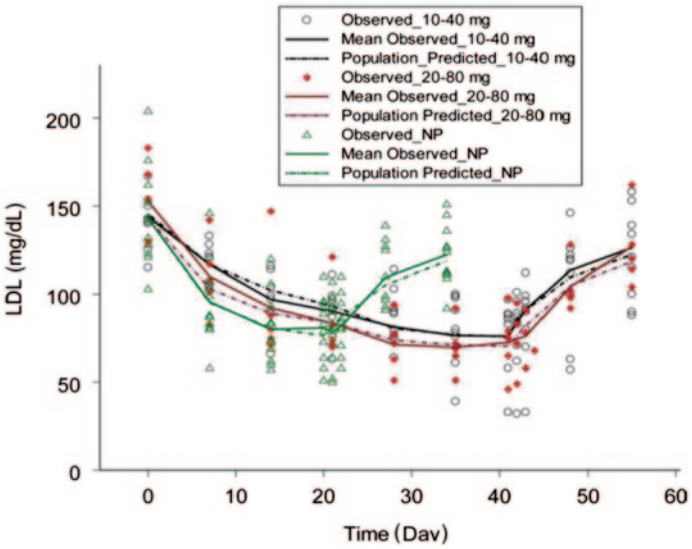

Fig. 19.9 Application of the precursor pool indirect response model to LDL-C turnover after administration of atorvastatin in Korean dyslipidemic patients and nonpatient (*NP*) volunteers. (Reprinted from Oh et al. 2012, with permission from Dustri-Verlag and © 2012 Dustri-Verlag and Dr. K Feistle)

healthy subjects were included in the study and received 10 mg/day atorvastatin for 21 days. Blood samples were collected to measure lipids for 56 days. Figure 19.9 shows the predicted and observed LDL-C reduction after administration of atorvastatin to Korean patients and healthy subjects.

Based on the analysis, the k_{in} for LDL-C was 0.15 g/L/day in the Korean subjects with a low intersubject variability of 13%. The elimination rate constant for LDL-C was 0.105 day^{-1} which suggested a half-life of 6.6 days. Atorvastatin inhibited k_{in} by 9% which was slightly less than the 21% reported by Faltaos et al. The ID_{50} in patients and healthy subjects were 11.9 and 2.0, respectively, which suggested that healthy subjects might be more sensitive to the effects of atorvastatin. However, due to the imprecision of the ID_{50} estimates, there was an overlap in the 95% confidence intervals of the ID_{50} estimates. Extensive intersubject variability in the ID_{50} of atorvastin (99% CV) was reported. The implications of a sixfold difference between patients and healthy subjects were not discussed by the authors. Because dose was the predictor of pharmacodynamic response, pharmacokinetic differences between healthy subjects and patients were not investigated. The atorvastatin ID_{50} value from Oh et al. was in close agreement to the value reported by Mandema et al. (11.9 vs. 13 mg/day atorvastatin, respectively). Application of the precursor pool indirect response model enabled the characterization of atorvastatin dose–response relationship in Korean patients and healthy subjects. The model could be used to help optimize drug therapy in dyslipidemic patients.

19.5.5 Other Applications

Examples of other applications of pharmacometrics that are not solely focused on drug effects are presented. A systems biology approach was applied to characterize the impacts of aging on LDL-C (McAuley et al. 2012). The model captured the known physiology of cholesterol metabolism, and included six compartments to describe intake, intestinal absorption, excretion, plasma, hepatic, and peripheral tissues. The influence of changes in cholesterol absorption and elimination by LDL receptors was simulated to give insights into their respective importance in cholesterol balance. Based on the simulations, a 50% reduction in hepatic clearance of LDL-C can result in a 116 mg/dL increase in plasma LDL-C. Also, increasing the bioavailability of cholesterol from 50 to 80% can increase plasma LDL-C by 34 mg/dL. The findings from a systems biology model give insights into the fundamental biology of lipoproteins, and suggest that plasma LDL-C levels were most sensitive to changes in the rate of hepatic elimination.

There may be an opportunity for pharmacometrics to guide dosing decisions in order to optimize the risk to benefit ratio of hyperlipidemia treatments. Use of high-dose simvastatin (80 mg) has been associated with an increased risk of myopathies and in rare cases rhabdomyolysis compared to lower doses (Egan and Colman 2011). In addition, the risk of myopathies can be increased with drug interactions such as coadministration of CYP3A inhibitor and/or OATP1B1 inhibitor (Neuvonen et al. 2006). Additional concentration-safety analysis may support ongoing efforts to identify intermittent dosing strategies that maintain benefit and reduce risk of myopathy with statin treatment (Keating et al. 2013).

In the area of cardiovascular disease progression, the focus of research has been on defining short-term risk estimates of cardiovascular events to define treatment algorithms (NHLBI 2004). More recently, the question of duration of LDL-C exposure as it pertains to cardiovascular risk has been raised, where it was noted that longer treatment with statins was associated with reduced risk of CHD (Brown and Goldstein 2006). In addition, it was proposed that the cumulative exposure to LDL-C may serve as surrogate of lifetime cardiovascular risk based on outcomes from human genetic observational studies (Horton et al. 2009). In the future, a pharmacometric disease progression model may serve to unify the effect of LDL-C reduction on cardiovascular risk reduction.

19.6 Summary and Conclusions

Cardiovascular disease produces significant worldwide morbidity and mortality. Lipoproteins represent a major risk factor for cardiovascular disease. Therefore, treatment of lipoproteins is important to the goal of reducing cardiovascular risk given its relationship to arteriosclerosis. PK/PD models have been used to characterize the effect on LDL-C for a wide variety of drugs including statins, CETP inhibitors, and ezetimibe. Both empirical and semi-mechanistic models have been

used to characterize dose response and the time course of effects of hyperlipidemia therapies. The application of pharmacometrics has been shown to effectively guide drug development decision making by accurately simulating trials, optimizing dosing regimens, and informing early termination of programs with unacceptable risk to benefit ratios. In conclusion, pharmacometrics will continue to be an important tool to facilitate the development of new drug therapies to alleviate the burden of cardiovascular disease.

Summary of Key Messages

- PK/PD models have been used to characterize the effect on LDL-C for hyperlipidemia drugs including statins, CETP inhibitors, and ezetimibe.
- Both empirical and semi-mechanistic models have been used to characterize dose response and the time course of effects of hyperlipidemia therapies.
- The application of pharmacometrics in the cardiovascular area has been shown to effectively guide drug development decision making by accurately simulating trials, optimizing dosing regimens, and informing early termination of programs with unacceptable risk/benefit ratios.

References

AbbVie Niaspan highlights of prescribing information (2013) http://www.rxabbvie.com/pdf/niaspan.pdf. Accessed 24 April 2013

Abifadel M, Varret M, Rabès J-P et al (2003) Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 34:154–156. doi:10.1038/ng1161

Aegerion Juxtapid highlights of prescribing information (2013) http://www.juxtapid.com/_pdf/Prescribing_Information.pdf. Accessed 24 April 2013

Aoyama T, Omori T, Watabe S, Shioya A, Ueno T, Fukuda N, Matsumoto Y (2010) Pharmacokinetic/pharmacodynamic modeling and simulation of rosuvastatin using an extension of the indirect response model by incorporating a circadian rhythm. Biol Pharm Bull 33:1082–1087. doi:10.1248/bpb.33.1082

Arnold FL, Kusama M, Ono S (2010) Exploring differences in drug doses between Japan and Western countries. Clin Pharmacol Ther 87:714–720. doi:10.1038/clpt.2010.31

Barrett R, Hugh P, Foster DM (1996) Design and analysis of lipid tracer kinetic studies. Curr Opin Lipidol 7:143–148

Barter PJ, Rye KA (2012) Cholesteryl ester transfer protein inhibition as a strategy to reduce cardiovascular risk. J Lipid Res 53:1755–1766. doi:10.1194/jlr.R024075

Bilheimer DW (1984) Regulation of LDL receptors *in vivo*. Agents Actions Suppl 16:191–203

Bloomfield D, Carlson GL, Sapre A, Tribble D, McKenney JM, Littlejohn TW, Sisk CM, Mitchel Y, Pasternak RC (2009) Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients. Am Heart J 157:352–360. doi:10.1016/j.ahj.2008.09.022

Brown MS, Goldstein JL (2006) Lowering LDL-Not only how low, but how long? Science 311:1721–1723. doi:10.1126/science.1125884

Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W, Coronary Drug Project Research Group (1986) Fifteen year mortality in coronary drug project patients: long-term benefit with niacin. J Am Coll Cardiol 8:1245–1255. doi:10.1016/S0735-1097(86)80293-5

Caslake MJ, Packard CJ, Gaw A, Murray E, Griffin BA, Vallance BD, Shepherd J (1993) Fenofibrate and LDL metabolic heterogeneity in hypercholesterolemia. Arterioscler Thromb 13:702–711. doi:10.1161/01.ATV.13.5.702

Chan JCY, Piper DE, Cao Q, Liu D, King C, Wang W, Tang J, Liu Q, Higbee J, Xia Z, Di Y, Shetterly S, Arimura Z, Salomonis H, Romanow WG, Thibault ST, Zhang R, Cao P, Yang XP, Uy T, Lu M, Retter MW, Kwon G, Henne K, Pan O, Tsai MM, Fuchslocher B, Yang E, Zhou L, Lee KJ, Daris M, Sheng J, Wang Y, Shen WD, Yeh WC, Emery M, Walker NPC, Shan B, Schwarz M, Jackson SM (2009) A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. PNAS 106:9820-9825. doi: 10.1073/pnas.0903849106

Cholesterol Treatment Trialists'(CTT) Collaboration (2010) Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 376:1670–1681. doi:10.1016/S0140-6736(10)61350-5

Cilla DC, Whitfield LR, Gibson DM, Sedman AJ, Posvar EL (1996) Multiple-dose pharmacokinetics, pharmacodynamics, and safety of atorvastatin, an inhibitor of HMG-CoA reductase, in healthy subjects. Clin Pharmacol Ther 60:687–695. doi:10.1016/S0009-9236(96)90218-0

Dayneka NL, Garg V, Jusko WJ (1993) Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Pharmacodyn 21:457–478. doi:10.1007/BF01061691

Derek E, Piper DE, Jackson S, Liu Q, Romanow WG, Shetterly S, Thibault ST, Shan B, Walker NPC (2007) The crystal structure of PCSK9:a regulator of plasma LDL-cholesterol. Structure 15:545–552. doi:10.1016/j.str.2007.04.004

Dias CS, Shaywitz AJ, Wasserman SM, Smith BP, Gao B, Stolman DS, Crispino CP, Smirnakis KV, Emery MG, Colbert A, Gibbs JP, Retter MW, Cooke BP, Uy ST, Matson M, Stein EA (2012) Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. J Am Coll Cardiol 60:1888–1898. doi:10.1016/j.jacc.2012.08.986

Dietschy JM (1997) Theoretical considerations of what regulates low-density-lipoprotein and high-density-lipoprotein cholesterol. Am J Clin Nutr 65(5 Suppl):1581S–1589S

Egan A, Colman E (2011) Weighing the benefits of high-dose simvastatin against risk of myopathy. N Engl J Med 365:285–287. doi:10.1056/NEJMp1106689

European Medicines Agency (2010) Guideline on lipid lowering agents. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/12/WC500100189.pdf. Accessed 24 April 2013

Faltaos DW, Urlen S, Carreau V, Chauvenet M, Hulot JS, Giral P, Bruckert E, Lechat P (2006) Use of an indirect effect model to describe the LDL cholesterol-lowering effect by statins in hypercholestrerolaemic patients. Fundam Clin Pharmacol 20:321–330. doi:10.1111/j.1472-8206.2006.00404.x

Giugliano RP, Desai NR, Kohli P et al for the LAPLACE-TIMI 57 investigators (2012) Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet 380:2007–2017. doi:10.1016/S0140-6736(12)61770-X

Glaxo Smith Kline, Lovaza highlights of prescribing information (2013) http://us.gsk.com/products/assets/us_lovaza.pdf. Accessed 18 Feb 2013

Glomset JA, Wright JL (1964) Some properties of a cholesterol esterifying enzyme in human plasma. Biochim Biophys Acta 89:266–276. doi:10.1016/0926-6569(64)90215-9

Goldstein JL, Brown MS (2009) The LDL receptor. Arterioscler Thromb Vasc Biol 29:431–438. doi:10.1161/ATVBAHA.108.179564

Hazra A, Pyszczynski NA, DuBois DC, Almon RR, Jusko WJ (2008) Modeling of corticosteroid effects on hepatic low-density lipoprotein receptors and plasma lipid dynamics in rats. Pharm Res 25:769–780. doi:10.1007/s11095-007-9371-8

Horton JD, Cohen JC, Hobbs HH (2009) PCSK9: a convertase that coordinates LDL catabolism. J Lipid Res 50:S172–S177. doi:10.1194/jlr.R800091-JLR200

Isis Kynamro™ highlights of prescribing information (2013) http://www.kynamro.com/~/media/Kynamro/Files/KYNAMRO-PI.pdf. Accessed 24 April 2013

Istvan E, Deisenhofer J (2001) Structural mechanism for statin inhibition of HMG-CoA reductase. Science 292:1160–1164. doi:10.1126/science.1059344

Ji J, Watts GF, Johnson AG et al (2006) High-density lipoprotein (HDL) transport in the metabolic syndrome: application of a new model for HDL particle kinetics. J Clin Endocrinol Metab 91:973–979. doi:10.1210/jc.2005-1895

Keating AJ, Bova Campbell K, Guyton JR (2013) Intermittent nondaily dosing strategies in patients with previous statin-induced myopathy. Ann Pharmacother 47:398–404. doi:10.1345/aph.1R509

Kim J, Ahn B-J, Chae H-S, Han S, Doh K, Choi J, Jun YK, Lee YW, Yim D-S (2011) A population pharmacokinetic-pharmacodynamic model for simvastatin that predicts low-density lipoprotein-cholesterol resduction in patients with primary hyperlipidemia. Basic Clin Pharmacol Toxicol 109:156–163. doi:10.1111/j.1742-7843.2011.00700.x

Koren MJ, Scott R, Kim JB, Knusel B, Liu T, Lei L, Bolognese M, Wasserman SM (2012) Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. Lancet 380:1995–2006. doi:10.1016/S0140-6736(12)61771-1

Krishna R, Bergman AJ, Green M, Dockendorf MF, Wagner JA, Dykstra K (2011) Model-based development of anacetrapib, a novel cholesteryl ester transfer protein inhibitor. AAPS J 13:179–190. doi:10.1208/s12248-011-9254-0

Lambert G, Charlton F, Rye K-A, Piper DE (2009) Molecular basis of pcsk9 function. Atherosclerosis 203:1–7. doi:10.1016/j.atherosclerosis.2008.06.010

Lee E, Ryan S, Birmingham B, Zalikowski J, March R, Ambrose H et al (2005) Rosuvastatin pharmacokinetics and pharmacogenetics in white and asian subjects residing in the same environment. Clin Pharmacol Ther 78:330–341. doi:10.1016/j.clpt.2005.06.013

Liang H, Chaparro-Riggers J, Strop P et al (2011) Proprotein convertase substilisin/kexin type 9 antagonism reduces low-density lipoprotein cholesterol in statin-treated hypercholesterolemic nonhuman primates. J Pharmacol Exp Ther 340:228–236. doi:10.1124/jpet.111.187419

Liao JK (2007) Safety and efficacy of statins in Asians. Am J Cardiol 99:410–414. doi:10.1016/j.amjcard.2006.08.051

Lloyd-Jones DM (2010) Cardiovascular risk prediction: basic concepts, current status, and future directions. Circulation 121:1768–1777. doi:10.1161/Circulationha.109.849166

Mager DE, Wyska E, Jusko WJ (2003) Diversity of mechanism-based pharmacodynamic models. Drug Metab Dispos 31:510–519. doi:10.1124/dmd.31.5.510

Mandema JW, Hermann D, Wang W, Sheiner T, Milad M, Bakker-Arkema R, Hartman D (2005) Model-based development ofgemcabene, a new lipid-altering agent. AAPS J 7:E513–E522. doi:10.1208/aapsj070352

Martin PD, Mitchell PD, Schneck DW (2002) Pharmacodynamic effects and pharmacokinetics of a new HMG-CoA reductase inhibitor, rosuvastatin, after morning or evening administration in healthy volunteers. Br J Clin Pharmacol 54:472–477. doi:10.1046/j.1365-2125.2002.01688.x

McAuley M, Wilkinson DJ, Jones JJL, Kirkwood TBL (2012) A whole-body mathematical model of cholesterol metabolism and its age-related dysfunction. BMC Syst Biol 6:130. doi:10.1186/1752-0509-6-130

Merck press release (December 20, 2012) http://www.mercknewsroom.com/press-release/prescription-medicine-news/merck-announces-hps2-thrive-study-tredaptive-extended-relea. Accessed 24 April 2013

Merck, Zetia highlights of prescribing information. http://www.merck.com/product/usa/pi_circulars/z/zetia/zetia_pi.pdf. Accessed 24 April 2013

National Heart, Lung, and Blood Institute (2004) Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III). http://www.nhlbi.nih.gov/guidelines/cholesterol/. Accessed 24 April 2013

National Heart, Lung, and Blood Institute (2011) NIH stops clinical trial on combination cholesterol treatment. http://www.nih.gov/news/health/may2011/nhlbi-26.htm. Accessed 11 March 2013

Neuvonen PJ, Niemi M, Backman JT (2006) Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther 80(6):565–581. doi:10.1016/j.clpt.2006.09.003

Nicholls SJ, Brewer HB, Kastelein JJP, Krueger KA, Wang MD, Shao M, Hu Bo, McErlean BE, Nissen SE (2011) Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. JAMA 306:2099–2109. doi:10.1001/jama.2011.1649

Oh ES, Lee S-H, Park MS, Park K, Chung J-Y (2012) Modeling of the LDL cholesterol-lowering effect of atorvastatin in Korean dyslipidemic patients and non-patient volunteers. Int J Clin Pharmacol Ther 50:647–656. doi:10.5414.CP201699

Okamoto H, Yonemori F, Wakitani K, Minowa T, Maeda K, Shinkai H (2000) A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. Nature 406:203–207. doi:10.1038/35018119

O'Keefe JH, Cordain L, Harris WH, Moe RM, Vogel R (2004) Optimal low-density lipoprotein is 50 to 70 mg/dL Lower is better and physiologically normal. J Am Coll Cardiol 43:2142–2146. doi:10.1016/j.jace.2004.03.046

Orso E, Grandl M, Schmitz G (2011) Oxidized LDL-induced endolysosomal phospholipidosis and enzymatically modified LDL-induced foam cell formation determine specific lipid species modulation in human macrophages. Chem Phys Lipids 164:479–487. doi:10.1016/j.chemphyslip.2011.06.001

Repa JJ, Mangelsdorf DJ (2000) The role of orphan nuclear receptors in the regulation of cholesterol homeostasis. Annu Rev Cell Dev Biol 16:459–481. doi:10.1146/annurev.cellbio.16.1.459

Russell DW (2009) Fifty years of advances in bile acid synthesis and metabolism. J Lipid Res 50:S120–S125. doi:10.1194/jlr.R800026-JLR200

Sharma A, Jusko WJ (1996) Characterization of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm 24:611–635. doi:10.1007/BF02353483

Sharma A, Ebling WF, Jusko WJ (1998) Precursor-dependent indirect pharmacodynamic response model for tolerance and rebound phenomena. J Pharm Sci 87:1577–1584. doi:10.1021/js98017q

Smith SC, Collins A, Ferrari R et al (2012) Our time: a call to save preventable death from cardiovascular disease (heart disease and stroke). J Am Coll Cardiol 60:2343–2348. doi:10.1016/j.jacc2012.08.962

Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart J-C (1998) Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 98:2088–2093. doi:10.1161/01.CIR.98.19.2088

Stein EA, Mellis S, Yancopoulos GD et al (2012) Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med 366:1108–1118. doi:10.1056/NEJMoa1105803

Sweeney ME, Johnson RJ (2007) Ezetimibe: an update on the mechanism of action, pharmacokinetics and recent clinical trials. Expert Opin Drug Metab Toxicol 3:441–450. doi:10.1517/17425255.3.3.441

van der Wulp MY, Verkade HJ, Groen AK (2012) Regulation of cholesterol homeostasis. Mol Cell Endocrinol 368:1–16. doi:10.1016/j.mce.2012.06.007

Van Heek M, Farley C, Compton DS, Hoos L, Alton KB, Sybertz EJ, Davis HR Jr (2000) Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663. Br J Pharmacol 129:1748–1754. doi:10.1038/sj.bjp.0703235

Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M (2008) Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. Br Med J 336:1114–1117. doi:10.1136/bmj.39553.670231.25

WHO (World Health Organization), World Heart Federation, and World Stroke Organization (2011) Global atlas on cardiovascular disease prevention and control. http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf. Accessed 11 March 2013

Wright DFB, Kumar VVP, Al-Sallami HS, Duffull SB (2011) The influence of dosing time, variable compliance and circadian low-density lipoprotein production on the effect of simvastatin: simulations from a pharmacokinetic–pharmacodynamic model. Basic Clin Pharmacol Toxicol 109:494–498. doi:10.1111/j.1742-7843.2011.00757.x

Yang J, Li LJ, He YC, Sheng YC, Xu L, Huang XH, Guo F, Zheng QS (2011) Race differences: modeling the pharmacodynamics of rosuvastatin in Western and Asian hypercholesterolemia patients. Acta Pharmacol Sin 32:116–125. doi:10.1038/aps.2010.169