REPUBLIC OF TURKEY
YEDITEPE UNIVERSITY
GRADUATE SCHOOL OF HEALTH SCIENCES

ADVERSE EFFECTS OF STATINS AND COST CALCULATION FOR RHABDOMYOLYSIS

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ISTANBUL – 2012

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A THESIS SUBMITTED TO

THE GRADUATE SCHOOL OF HEALTH SCIENCE

OF

THE YEDITEPE UNIVERSITY

BY

EMINE DERYA IKIZLERLI

IN THE PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN PHARMACOECONOMICS AND PHARMACOEPIDEMIOLOGY MASTER PROGRAMME

ADVISOR

Assist. Prof. Dr. NAZLI SENCAN

ISTANBUL - 2012

Yüksek Lisans (Master) öğrencisi Emine Derya İkizlerli'nin çalışması jürimiz tarafından Farmakoekonomi ve Farmakoepidemioloji Anabilim Dalı Master tezi olarak uygun görülmüştür.

İMZA

Başkan : Prof. Dr. Hülya AKGÜN
Üniversite : Yeditepe Üniversitesi

Üye : Yrd. Doç. Dr Latif ÖZBAY
Üniversite : Yeditepe Üniversitesi

Üye : Yrd. Doç. Dr Nazlı ŞENCAN
Üniversite : Yeditepe Üniversitesi

ONAY

Yukarıdaki jüri kararı Enstitü Yönetim Kurulu'nun 21/05/2012 tarih ve 5-3 sayılı kararı ile onaylanmıştır.

Prof. Dr. Selçuk YILMAZ

To my precious family...

ÖZET

İkizlerli ED. Statinlerin Yan Etkileri ve Rabdomiyolizin Maliyet Hesaplaması. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü Farmakoekonomi ve Epidemiyoloji Mastır Tezi. İstanbul, 2012.

Amaç: Bu tezin amacı statin grubu ilaçların yan etkilerini vurgulamak ve bu grup ilaçların nadir ancak hastaneye yatışa sebebiyet veren en ciddi yan etkilerinden biri olan rabdomiyolizin örnek bir hasta için farklı senaryolar üzerinden Türkiye'deki maliyetini hesaplamaktır. Aynı zamanda bu advers etkinin önlenebilmesi için oluşacak maliyet de hesaplanarak bu iki sonucu karşılaştırmalı olarak değerlendirilmesi de hedeflenmektedir.

Materyal & Metot: Anahtar kelimeler kullanılarak ulusal ve uluslararası literatür taraması yapılmıştır. Bu amaçla Ulakbim, Pubmed ve Sciencedirect internet siteleri kullanılmıştır. Bunun yanında Türkiye ve diğer ülkelere ait sağlık kurumlarının resmi internet siteleri taranarak konuyla ilgili uyarılar değerlendirilmiştir. IMS (Intercontinental Marketing Services) Satış verileri değerlendirilmiştir. Yan etki maliyetinin hesaplanması için laboratuar testlerinin belirlenmesinde Türkiye Cumhuriyeti Sağlık Bakanlığı'na ait güncel Sağlık Uygulama Tebliği (SUT)'nde belirtilen fiyatlar esas alınmıştır. Yan etki tedavisinde kullanılan ilaçlar için ise RxMediaPharma web tabanlı programdan yararlanılmıştır. Tespit edilen fiyatlar fiyat bandındaki Sosyal Güvenlik Kurumu (SGK) tarafından ödenen minimum fiyatlar kullanılmıştır. Bu verilerin geçerliliğini teyit etmek amacıyla Kırklareli Devlet Hastanesi ve Şişli Etfal Eğitim ve Araştırma Hastanesi muhasebe bölümlerinden fiyat alınmıştır.

Bulgular ve sonuç: Statinlerin kasa bağlı advers etkilerin önlenebilmesi için gereken maliyet, bu advers etkinin farkedilmemesi veya önlenememesi durumunda ortaya çıkan maliyete göre oldukça düşüktür. Üstelik advers etkinin önlenememesi sonucunda ortaya çıkan akut tubular nekroz tedavisi ömür boyu diyaliz gerektirdiğinden ortaya çıkacak maliyet hesaplananın çok üstünde olacaktır. Bu noktada statinlerin kasa bağlı yan etkileri açısından hastanın bilinçlendirilmesi ve ayrıca doktorların bu konudaki farkındalığının arttırılması büyük önem taşımaktadır. Bu sayede oluşabilecek maliyetler azaltılabilir.

Anahtar kelimeler: Statinler, HMG-CoA reductaz inhibitörleri, advers etkiler, rabdomiyoliz, meta-analiz, kas toksisitesi.

ABSTRACT

Ikizlerli ED. Adverse Effects of Statins and Cost Calculation for Rhabdomyolysis. Yeditepe University Institute of Health Sciences Pharmacoeconomics and Epidemiology Master Program. Istanbul, 2012.

Purpose: The main aim of the study is to highlight the adverse effects of statins and to calculate the cost of rhabdomyolysis treatment for one patient in Turkey which is a rare but the most serious adverse effect of statins that cause to stay in hospital. In addition, cost of prevention of this adverse effect has also been calculated. These two results have been compared.

Materials & Methods: A review of national and international literature has been searched by using Ulakbim, Pubmed and Sciencedirect web sites. IMS data for statins have been used and safety of statins have been searched by using internet web sites among different countries' health authorities. In order to calculate the direct cost of muscle related adverse effect, Turkish Ministry of Health Health Application Announcement prices have been taken into consideration for laboratory tests. For the calculation of the cost of drugs used in the treatment of adverse effect, prices have been gathered from RxMediaPharma web based programme. Prices that have been used for calculation are the minimum prices which constitute the lowest prices of the price band reimbursed by Social Security Institution (SSI). In order to validate all of these data, prices of laboratory tests and drugs have been obtained from Kırklareli Public Hospital Accounting House and Şişli Etfal Public Education and Research Hospital Accounting House.

Findings and conclusion:
Cost of prevention of statin-induced muscle adverse effects is lower than the cost of the adverse effect in case of nonprevention or ignorance. In addition because of the treatment of acute tubular necrosis requires dialysis lifelong, cost of the adverse effect will be higher than the expected. At that point, it is very important to increase the patients' awareness and the doctors' attention for muscle related adverse effects of statins. Thus, all the costs related to statin-induced muscle adverse effects can be minimised.

Key words: Statins, HMG-CoA reductase inhibitors, adverse effects, rhabdomyolysis, meta-analysis, muscle toxicity

ACKNOWLEDGEMENT

I am grateful to all people who helped me to complete this study with their support, guidance and faith.

Firstly, I would like to thank to TUBITAK providing me support for my thesis.

Secondly, I would like to express my gratitude to Prof. Dr. Hülya Akgün for her support throughout my student years and graduate study in the School of Pharmacy at Yeditepe University.

Then, I am deeply indebted to my advisor Assist. Prof. Dr. Nazlı Şencan for her invaluable support, encouragement, good fellowship, and guidance during my thesis. I also extend my gratitude to Prof. Dr. Mehtap Tatar and Prof.Dr. Mustafa Arıcı for their advice and guidance. I am also thankful to all the teaching staff of Yeditepe University Faculty of Pharmacy who have a big role for being me a pharmacist and having adequate education level to write me this thesis.

Also, I would like to thank Belma Tekneci, Merve Işıklılar, Neşe Yıldız, Beril Çolak Günay and Funda Yenice who helped me to find data for my thesis.

In addition, I wish to express my heartfelt thanks to my manager Dr. Metin Topsakal and Pharm. Nezihe İçduygu for their patience, support and guidance during my thesis.

Lastly, I extend my eternal gratitude to my family and friends. I would like to thank my unique family especially my homemate and brother Naimcan İkizlerli for supporting me, always believing I had the ability to get achievements and always make me feel they are near me. I also would like to thank my friends Gözde Kaftan, Uğur Yalçınkaya, Tülin Önce and Can Rendeci for their patience and cheer on me.

CONTENT

ABBREVIATIONS

ADR:	Adverse Drug Reaction
AERS:	Adverse event reporting system
AGTR:	Angiotensin II Type 1 receptor
ALT:	Alanine aminotransferase
AMP:	Adenosine monophosphate
AST:	Aspartate aminotransferase
ATN:	Acute tubular necrosis
ATP:	Adenosine triphosphate
AUC:	Area under the curve
CETP:	Cholesteryl ester transfer protein
CHD:	Coronary heart disease
CIMT:	Carotid intimal media thickness
CK:	Creatine kinase
CPK:	Creatine phosphokinase
CPT:	Carnitine palmitoyl transferase
CRP:	c- Reactive protein
CT:	Computer tomography
CVD:	Cardiovascular disease
CYP:	Cytochrome P
DHA:	Docosahexaenoic acid
DI:	Drug interaction
DNA:	Deoxyribonucleic acid
ED:	Erectyle disfunction
EMEA:	European Medicines Evaluation Agency
EPA:	Eicosapentaenoic acid

EU:	European Union
FDA:	Food and Drug Administration
FPP:	Farnesyl pyrophosphate
GDP:	Guanosine diphosphate
GG-PP:	Geranylgeranyl pyrophosphate
GPP:	Geranyl pyrophosphate
GTP:	Guanosine triphosphate
HDL:	High denstiy lipoprotein
Hb-A_1C:	Hemoglobin A_1C
HC:	Health Canada
HF:	Heart failure
HIV:	Human immunodeficiency virus
HMG-CoA:	Hydroxymethylglutaryl coenzyme A
HTR:	Hydroxytryptamine receptor
IDL:	Intermediate density lipoprotein
IMS:	Intercontinental Marketing Services
IMT:	Intimal media thickness
IL:	Interleukin
IC:	Inhibitory concentration
IEGM:	İlaç ve Eczacılık Genel Müdürlüğü
IMP:	Inosine monophosphate
INR:	International normalized ratio
IVCT:	in vitro contracture test
IVUS:	Intravascular ultrasound
LDL:	Low density lipoprotein

LDH:	Lactate dehydrogenase
LFT:	Liver function tests
LLT:	Lipid lowering therapy
MADA:	Myoadenylate deaminase
MAH:	Marketing authorisation holder
MD:	Muscular dystrophies
MELAS:	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke syndrome
MHRA:	Medicines and Healthcare Products Regulatory Agency
MHS:	Malignant hyperthermia susceptibility
MI:	Myocardial infarction
MRI:	Magentic resonance imaging
MRP:	Multidrug resistance associated protein
NADPH:	Nicotinamide adenine dinucleotide phosphate
NDA:	New drug application
NCEP ATP:	National Cholesterol Education Program Adult Treatment Panel
NICE:	National Institute for Health and Clinical Exellence
NMR:	Nuclear magnetic resonance
NO:	Nitric oxide
NOS:	Nitric oxide synthase
OATP:	Organic anion transporting polypeptide
OECD:	Organization for Economic Cooperation and Development
PDR:	Physician’s desk reference
PIL:	Patient Information Leaflet
PPAR:	Peroxisome proliferator-activated receptors
PVD:	Peripheral vascular disease

RD:	Rhabdomyosarcoma cell line
RMD:	Rippling muscle disease
RNA:	Ribonucleic acid
RYR:	Ryanodine receptors
SGOT:	Serum Glutamic Oxaloacetic Transaminase
SGPT:	Serum glutamate pyruvate transaminase
SNP:	Single nucleotide polymorphisms
SPC:	Summary of product characteristics
SSI:	Social Security Institution
TC:	Total cholesterol
TG:	Triglyceride
TGA:	Therapeutics Goods Administration
TIA:	Transient ischemic attack
TUFAM:	Turkish Pharmacovigilance Center
UK:	United Kingdom
ULN:	Upper limit of normal
US:	United States
VLDL:	Very low density lipoprotein
VSMC:	Vascular smooth muscle cells
5- HT:	5-hydroxytryptamine

FIGURES

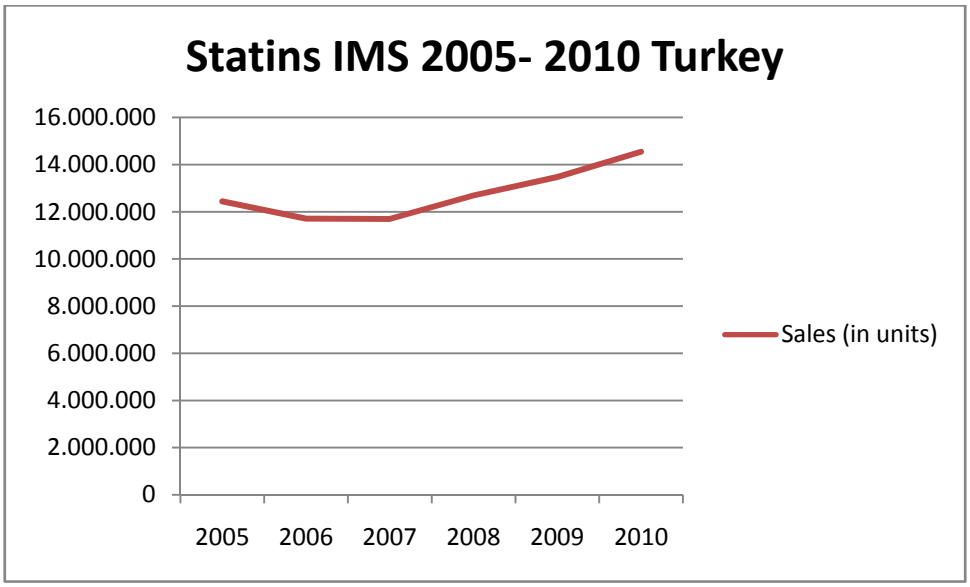
TABLES

1. INTRODUCTION

Today's dietary habits and sedentary lifestyle causes many diseases such as cardiac problems and most dangerously cancer. As coronary artery disease constitutes the most common cause of morbidity and mortality in developed countries **(1).** There are several ways of treating the disease but after the introduction of lovastatin to the market in 1987, the management of dyslipidemia was focused on the lipid lowering efficacy of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins and the significant impact these agents have on decreasing cardiovascular morbidity and mortality. Since then dyslipidemia products become among the most widely prescribed class of medications.

According to the Intercontinental Marketing Services (IMS) data; today there are 5 statins available in Turkey's pharmaceutical market namely; atorvastatin, rosuvastatin, fluvastatin, simvastatin and pravastatin. In the world, in addition to these 5 statins, there are also 2 more statins available on the market namely lovastatin and pitavastatin. When the IMS sales data of the statins is analyzed for Turkey for the last 5 years; it is seen that the total sales was 12.443.329 units per year 2005, 11.714.121 units per the year 2006, 11.697.815 units per the year 2007, 12.696.313 units per the year 2008, 13.475.557 units per the year 2009 and 14.544.928 units per the year 2010. When the growing ratio is calculated between 2005 sales and 2010 sales in units, approximately %16,9 growing of statin market was observed. Between the years 2007 and 2008, the increase in sales ratio was approximately %8.5. Between the years 2008- 2009 and 2009- 2010, this value was calculated as %6.1 and %7.9, respectively.

Table 1. IMS Sales data (2005-2010)



There is an increasing sales capacity (in unit). According to my opinion, this increase may be due to the increasing pattern of the incidence of the disease, increasing use of medicines and the incresing marketing activities of drug companies.

According to the sales data of statins in Turkey in the year 2010, atorvastatin had the highest sales with 7.466.673 units sales which is followed by rosuvastatin with 2.899.279 units sales. When the value based sales are analysed, it is seen that atorvastatin is also the leader statin in Turkey market with 284.682.590 TL sales volume. Rosuvastatin is the second in the value base with 98.995.935 TL sales volume in the Turkish market for the year 2010. It can easily be said that atorvastatin alone constitutes nearly more than half of the sales volume of statin market both in units and volume base. It is obvious that atorvastatin and rosuvastatin are the two statins that have the highest sales capacity in Turkey both in units and TL. For the year 2010, simvastatin had a 495.980 sales volume in units which is followed by fluvastatin and pravastatin with 377.522 and 198.260 sales volume in units, respectively. This sales volume in units makes the fluvastatin leader among these 3 statins with 6.130.706 TL sales volume in TL base. (2)

According to the RxMediaPharma, today there are 16 drugs in Turkey market with atorvastatin content one of which is original (brand name Lipitor®) and the remaining 15 are generics (brand names Alvastin®, Ateroz®, Ator®, Avitorel®, Cardyn®, Cholvast®, Colastin-L®, Divator®, Kolestor®, Lipidra®, Lipitaksin®, Lipsum®, Lipitor®,

Saphire®, Tarden® and Torvaxal®). For rosuvastatin, today there are 10 drugs in Turkey marketed with rosuvastatin content one of which is original (brand name Crestor®) and the remaining 9 are generics (brand names Colefix®, Colnar®, Kolros®, Reakt®, Rosucor®, Rosufix®, Rosuvas®, Stage® and Ultrox®). The number of generics of rosuvastatin was 5 in the year 2010. This incremental increase may be due to the growing market capacity of rosuvastatin for Turkey market (3).

Statin products available in Turkey's market is summarised in the table below (See Table 2):

Table 2. List of statin products in Turkey

Active ingredient name	**Original Product's Name**	**Generic Products' Name**
Atorvastatin	Lipitor® (First market launch date: 16.09.2005)	Alvastin®
		Ateroz®
		Ator®
		Avitorel®
		Cardyn®
		Cholvast®
		Colastin-L®
		Divator®
		Kolestor®
		Lipidra®
		Lipitaksin®
		Lipsum®
		Lipitor®
		Saphire®
		Tarden®
		Torvaxal®

Rosuvastatin	**Crestor®** (First market launch date: 27.09.2004)	Colefix®
		Colnar®
		Kolros®
		Reakt®
		Rosucor®
		Rosufix®
		Rosuvas®
		Stage®
		Ultrox®
Simvastatin	**Zocor®** (First market launch date: 26.08.1993)	Lipovas®
		Simvakol®
		Zovatin®
Pravastatin	**Pravachol®** (First market launch date: 15.10.2010)	Praxal®
Fluvastatin	**Lescol®** (First market launch date: 29.07.1997)	No generics available in Turkey

In addition to statins, according to IMS data 2010 results both in units and value perspective, fenofibrate (a drug used in hyperlipidemia) has high sales. This is probably due to high combination treatment rates of statin plus fenofibrate.

Statins are generally known as well-tolerated drugs and occurences of serious adverse effects (AEs) are generally rare (4). As it was also declared in the 2003 "Diagnosis and treatment guideline" for Turkey, major adverse effects of statins are increase in transaminases, rhabdomyolysis and myositis (5). It is told in a commentary that focus on the muscle related adverse effects was started with the withdrawal of cerivastatin (brand name Baycol® or Lipobay®) from the world market due to 52 deaths attributed to drug-related rhabdomyolysis that lead to kidney failure. (6) Rhabdomyolysis is a condition in which skeletal muscle is broken down, releasing muscle enzymes and electrolytes from inside the muscle cells.

After the withdrawal of cerivastatin from the world market, different countries published safety warnings about the muscle related adverse effects of statins on the market. Now, safety warnings of different countries's health authorities about muscle related adverse effects of statins will be mentioned below:

Statins and FDA Warnings (Food And Drug Administration of USA)

- In December 1999, Bayer Corporation changed the Baycol® prescribing information to include a contraindication with gemfibrozil. In this change it was mentioned that the combined use of cerivastatin and gemfibrozil was contraindicated due to a risk for rhabdomyolysis and concurrent use should not occur under any circumstances.
- In May 2001 Bayer published a dear doctor letter. In this letter Bayer Corporation had voluntarily made changes to the prescribing information for Baycol® in order to provide prescribers and patients with more specific guidance on initiating therapy with the product. These changes were:

- The "Dosage and Administration" section had been revised to highlight that 0.4 mg was the starting dose for Baycol®.
- The starting-dose of Baycol® was 0.4 mg once daily in the evening regardless of previous lipid therapy. Since the maximal effect of cerivastatin sodium was seen within 4 weeks lipid determinations should be performed at this time and the dose adjusted based upon patient response. Only patients requiring further lipid adjustment should be titrated to 0.8 mg. The dosage range was 0.2 mg to 0.8 mg. In patients with significant renal impairment (creatinine clearance <60 mL/min/1.73m^2) lower doses are recommended. Cerivastatin sodium might be taken with or without food.
- In the "Warnings – Skeletal Muscle" section a statement had been added reinforcing the starting dose of Baycol® was 0.4 mg. It was changed as "Beginning therapy above the 0.4 mg starting dose increases the risk of myopathy and rhabdomyolysis."
- The section "Patient Information about Baycol" under the heading "How should I take Baycol" had a statement added that explains to the patient that 0.4 mg was the starting dose of Baycol: "If you are taking Baycol for the first time, your daily dose should be 0.4mg or lower."

- In August 2001, Bayer announced the withdrawal of all dosages of its cholesterol-lowering drug with the brand names Baycol®/Lipobay® (active ingredient: cerivastatin), due to increasing reports of side effects involving muscular weakness (rhabdomyolysis). Fatal rhabdomyolysis associated with Baycol® had been reported most frequently when used at higher doses, when used in elderly patients, and particularly, when used in combination with gemfibrozil, another lipid lowering drug.
- In March 2010, the U.S. Food and Drug Administration (FDA) published a safety warning mentioning about an increased risk of muscle injury in patients taking the highest approved dose of the cholesterol-lowering medication, Zocor® (simvastatin) 80 mg, compared to patients taking lower doses of simvastatin and possibly other drugs in the "statin" class based on review of data from a large clinical trial and data from other sources.
- In June 2011, The U.S. Food and Drug Administration (FDA) recommended limiting the use of the highest approved dose of the cholesterol-lowering medication, simvastatin (80 mg) because of increased risk of muscle damage. Simvastatin 80 mg should be used only in patients who had been taking this dose for 12 months or more without evidence of muscle injury (myopathy). Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug. In addition to these new limitations, FDA was requiring changes to the simvastatin label to add new contraindications (should not be used with certain medications) and dose limitations for using simvastatin with certain medicines.

<u>Simvastatin Dose Limitations</u>

When used with simvastatin, the following medications could raise the levels of simvastatin in the body and increase the risk of myopathy. Taking no more than the recommended dose of simvastatin with these medications would help keep simvastatin levels in the body at a safer level.

According to new statin label:

- Simvastatin was found contraindicated with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine and danazol.
- 10 mg simvastatin does not be exceeded daily with amiodarone, verapamil, diltiazem

(Note: These drugs are contraindicated with Simcor as Simcor is only available with 20 mg or 40 mg of simvastatin.)

- 20 mg simvastatin does not be exceeded daily with amlodipine and ranolazine
- large quantities of grapefruit juice (>1 quart daily) should be avoided

- In December 2011, FDA notified healthcare professionals that it was recommending limiting the use of the highest approved dose of the cholesterol-lowering medication simvastatin (80 mg) because of increased risk of muscle damage. Patients taking simvastatin 80 mg daily had an increased risk of myopathy compared to patients taking lower doses of this drug or other drugs in the same class. This risk appeared to be higher during the first year of treatment, was often the result of interactions with certain medicines, and was frequently associated with a genetic predisposition toward simvastatin-related myopathy. The most serious form of myopathy, called rhabdomyolysis, could damage the kidneys and lead to kidney failure which could be fatal. FDA was requiring changes to the simvastatin label to add new contraindications (should not be used with certain medications) and dose limitations for using simvastatin with certain medicines.
- In 01 March 2012 FDA notified healthcare professionals of updates to the prescribing information concerning interactions between protease inhibitors and certain statin drugs. Protease inhibitors (antiviral drugs) and statins taken together may raise the blood levels of statins and increase the risk for muscle injury (myopathy). The most serious form of myopathy, called rhabdomyolysis, can damage the kidneys and lead to kidney failure, which can be fatal (7).

All these warnings focus on the risks of rhabdomyolysis that can be fatal. So FDA tried to warn both doctors and patients about muscle related adverse effects of statins.

Statins and EMEA Warnings (European Medicines Evaluation Agency for European Union)

- In 1999, warnings about the risk of myopathy, including rhabdomyolysis, as well as warnings about the interaction with gemfibrozil had been included in product

information since Lipobay® was first licensed in the EU. In the US a spesific contra-indication against co-prescription with gemfibrozil was added to product information.
The Europe-wide update of Lipobay product information (Type II variation), was under discussion when the Spanish authorities raised concerns about a number of reports in Spain of fatal cases of rhabdomyolysis in association with Lipobay®. There were concerns about a possibly increased risk of rhabdomyolysis associated with the use of cerivastatin-particularly in combination with gemfibrozil. Following discussions between UK, a reference member state for Lipobay®, Spain and the marketing authorisation holder (MAH), Bayer an "Urgent Safety Restriction" took place on 25/26 June 1999. The changes to the Summary of Product Characteristics (SPC) included the following: the introduction of a contraindication to the concomitant use of cerivastatin and gemfibrozil, restriction of the maximum dose to 0.4 mg and reinforcement of the importance of dose titration.

- On August 2001, Bayer announced that it was voluntarily suspending and distribution of cerivastatin from both the European and US markets pending further evaluation of the risk of rhabdomyolysis associated with its use (8).

EMEA carefully followed the withdrawal of cerivastatin from the European market. This follow up includes the changes to the SPC and floow up of individual case reports. According to my opinion, withdrawal of cerivastatin from EU and US markets due to safety issues shows the importance of pharmacovigilance.

Statins and HC Warnings (Health Canada for Canada)

- In March 2000, Bayer Inc. in Canada amended the cerivastatin product monograph to include a contraindication with gemfibrozil. In 08.08.2001 and 16.07.2001, dear doctor letters were published in Health Canada web site about cerivastatin to remind the contraindication. In this letters, Bayer Inc. had placed a contraindication in the Baycol® product monograph against coprescription with gemfibrozil and communicated to healthcare professionals warning against coprescription of these two drugs.

- In March 2001, in Health Canada internet web site a dear doctor letter was published to health care professionals to remind health care professionals that the combined use of cerivastatin and gemfibrozil was contraindicated due to the risk of rhabdomyolysis and concurrent use should not occur under any circumstances. Post-marketing spontaneous reports had highlighted the increased incidence of rhabdomyolysis in patients receiving cerivastatin and gemfibrozil concomitantly. Also the exact wording from the dosing and administration section of the Product Monograph was mentioned as follows:

- The recommended starting dose was expressed as 0.2 mg once daily in the evening. The recommended dosing range was 0.2 - 0.8 mg as a single dose in the evening. Baycol® might be taken with or without food since there are no apparent differences in the lipid lowering effects of Baycol® administered with the evening meal or at bedtime. Dosages should be individualized according to the recommended goal of therapy and the patient's response.

- In June 2004, Astra Zeneca after discussion with Health Canada informed health care profesionals about important safety information regarding the association between Crestor® (rosuvastatin) and rhabdomyolysis. In this letter; the following warnings were as mentioned below:

- Rosuvastatin had been associated with post-market reports of rhabdomyolysis in Canada. Internationally, all statins had been associated with rhabdomyolysis.

- The occurrence of muscle-related adverse events during statin therapy might be related to the statin dose. In Canada, of the eight reported cases of rhabdomyolysis with rosuvastatin, two cases occurred at the 10 mg daily starting dose, five cases at 40 mg, and in one case the dose was not specified. These individual case reports for Canada was remarkable for Canada Health Authority. Because incidence of an adverse effect may be variable according to race. So, it is really important for each country to follow their own population based individual case report incidence.

- All of the Canadian reported cases were associated with predisposing risk factors. Therefore, caution should be exercised when prescribing rosuvastatin in patients with pre-existing risk factors or concomitant medications which pose increased risk for statin induced myopathy or rhabdomyolysis.

Also it was mentioned in this letter that some patients are at higher risk for statin induced myopathy or rhabdomyolysis. Identifiable predisposing risk factors for statin therapy include the following:

• renal impairment
• hypothyroidism
• personal or family history of hereditary muscular disorders
• previous history of muscular toxicity with another statin or fibrate
• alcohol abuse
• situations where an increase in plasma levels may occur
• Japanese and Chinese patients
• concomitant use of fibrates

- In November 2004, Health Canada advised Canadians of safety concerned about Crestor®, a cholesterol lowering drug, when used at the highest recommended dosage of 40 mg daily, the risk of rhabdomyolysis (muscle breakdown) might be increased at higher doses. Health Canada recommended that all patients taking Crestor®, or any cholesterol lowering drug, should be used the lowest dose that would meet their treatment goal.
- In June 2004, Health Canada warned Canadians about a possible association between the cholesterol lowering drug Crestor®, and rhabdomyolysis. Because the risk of rhabdomyolysis is increased at higher doses, Health Canada (HC) repeated their warning about lowest effective dose and they also added that all patients taking Crestor®, or any cholesterol lowering drug, were advised to report any unexplained muscle pain, muscle weakness or cramps, or any brown or discoloured urine, to their physician immediately.
- In March 2005, Health Canada (HC) advised Canadians about important safety information for Crestor® (rosuvastatin). Health Canada (HC) also summarised that a US study has found that Asian patients might be at greater risk of developing muscle-related adverse events with this drug. The risk of rhabdomyolysis was increased at the highest recommended daily dose of Crestor® , which was 40 mg daily. For this reason, Health Canada had advised that the 40 mg dose must not be used in patients who had pre-existing medical conditions or other factors which put them at increased risk for rhabdomyolysis. These factors included:

•Personal or family history of muscle problems
•Past history of significant muscle pain or muscle weakness while using a "statin" drug
•Taking any other cholesterol-lowering medications
•Serious liver problems
•An underactive thyroid gland
•Alcohol abuse
•Asian ethnicity
•Asian patients (having either Filipino, Chinese, Japanese, Korean, Vietnamese or South Asian origin) might be at greater risk of developing muscle-related adverse events, including rhabdomyolysis, with Crestor® (rosuvastatin). In a U.S. study, levels of rosuvastatin were found to be approximately two times greater in Asian-Americans when compared to a Caucasian control group.

Health Canada (HC) recommends that all patients taking Crestor® should be using the lowest dose that would meet their treatment goal. A 5 mg starting dose was recommended for:
•Asian patients
•Patients with serious kidney problems
•Patients who might have other risk factors for muscle problems
In addition, Health Canada (HC) had asked all manufacturers of "statin" drugs to update the information in the Canadian Product Monographs to enhance the safe and effective use of this group of cholesterol-lowering medications. The medical conditions and other factors which might cause a patient to be at greater risk of muscle related adverse reactions were similar with the patient groups that HC warned above. In addition to these patient gorups, patients with diabetes, surgeries or injuries, excessive physical exercise, aged 70 or over, frial physical condition was also categorised as greater risk of patients.

- In March 2005, Health Canada (HC) pulished a dear doctor letter Health Canada has requested that all statin brand manufacturers complete a class Product Monograph revision due to a need for consistent safety information regarding rhabdomyolysis and myopathy. In line with actions being undertaken by all statin manufacturers, these class revisions had been incorporated into the revised Crestor® Product Monograph. Class changes included updates to the warnings, precautions, and dosage and administration

sections, which specify that some patients were at a higher risk of statin-induced myopathy and/or rhabdomyolysis. Specifically, statins should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors included:

• Personal or family history of hereditary muscular disorders
• Previous history of muscle toxicity with another HMG Co-A reductase inhibitor
• Concomitant use of a fibrate or niacin
• Hypothyroidism
• Alcohol abuse
• Excessive physical exercise
• Age >70 years
• Renal impairment
• Hepatic impairment
• Diabetes with hepatic fatty change
• Surgery and trauma
• Frailty
• Situations where an increase in plasma levels of "statin" may occur

The dosage of statin should be individualized according to baseline LDL-C, total-C/HDL-C ratio and /or TG levels to achieve the recommended target lipid values at the lowest possible dose.

The Information to the patient leaflet had also been revised as a result of this class update. The revised leaflet include:

• To help patients recognize if they have pre-disposing factors for myopathy/rhabdomyolysis.
• To advise those patients who did have pre-disposing factors to discuss these factors with a health care professional before starting a statin.
• To help patients recognize symptoms of potentially serious adverse events (myalgia, myopathy and rhabdomyolysis) for which timely consultation with a health care professional was advised.

- In July 2005, Health Canada advised Canadians for important safety information for all cholesterol-lowering drugs known as statins. These medications included Lipitor® (atorvastatin), Zocor® (simvastatin), Mevacor® (lovastatin), Lescol® and

Lescol® XL (fluvastatin), Pravachol® (pravastatin) and Crestor® (rosuvastatin). Health Canada had requested that all manufacturers of these drugs included a warning and description of this risk in the safety information sheets for each drug. Before taking a statin, patients should tell their doctor or pharmacist if they:

• are pregnant, intend to become pregnant, are breast-feeding or intend to breast-feed

• have thyroid problems

• regularly drink three or more alcoholic drinks daily

•are taking other cholesterol lowering medication such as fibrates (gemfibrozil, fenofibrate) or niacin

• are taking other medications, including prescription, non-prescription and natural health products, as drug interactions are possible

• have a family history of muscular disorders;

• have any past problems with the muscles (pain, tenderness), after using a statin;

have kidney or liver problems

• have diabetes

• have undergone surgery or other tissue injury

• do excessive physical exercise

Patients were advised to contact their physician promptly if they experienced any of the following while on statin therapy:

• muscle pain they cannot explain

• muscle tenderness or muscle weakness

• generalized weakness, especially if they do not feel well (i.e. fever or fatigue)

• brownish or discoloured urine (9).

Statins and Lareb Reports (Netherlands Pharmacovigilance Center for Netherlands)

- In August 2003, Lareb published a report mentioning about the concurrent use of verapamil or diltiazem and HMG-CoA reductase inhibitors increases the risk of muscle related ADRs. It was mentioned that The Lareb database contains 41 reports with muscle related ADRs during use of a statin combined with verapamil or diltiazem (10).

- Also Mantel-Teeuwisse A. et al estimated the number of expected cases of myopathy based on the prevalence of lipid-lowering drug use, and to compare this number with the observed number of cases of myopathy due to lipid-lowering drug use in the Netherlands. Based on the estimated prevalence of lipid-lowering drug use in the Netherlands in 1998, 60 cases of idiopathic myopathy due to hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) or fibric acid derivatives (fibrates) was observed. This low number was confirmed by data from Pharmaco-Morbidity-Record-Linkage-System (PHARMO) database and Lareb (11).

Statins and MHRA Warnings (Medicines and Healthcare Products Regulatory Agency for United Kingdom)

- In 2004, MHRA published a report about the safety of statins. In this report, it was told that some statins (particularly simvastatin and atorvastatin) were metabolised by cytochrome P450 (CYP3A4) and co-administration of potent inhibitors of this enzyme (such as 'azole' anti-fungal agents or HIV protease inhibitors) might particularly increase plasma levels of these drugs and so increase the risk of dose-related side effects, including rhabdomyolysis. The risk of serious myopathy was also increased when high doses of simvastatin were combined with less potent inhibitors of CYP3A4, including amiodarone, verapamil and diltiazem.
- In May 2010, MHRA also published an article pointing out that there was an increased risk of myopathy associated with high dose (80 mg) simvastatin. The 80 mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who had not achieved their treatment goals on lower doses, when the benefits were expected to outweigh the potential risks (12).

Statins and TGA Warnings (Therapeutic Goods Administration for Australia)

- In August 2001, it was published by Australian Health Authority that the use of the combination of cerivastatin and another cholesterol lowering drug, gemfibrozil, had caused severe damage to muscle in some patients. The damage could be in the form of rhabdomyolysis where there was breakdown of muscle cells and release of myoglobin

which in turn could lead to kidney damage. Severe muscle damage had also been reported following use of cerivastatin alone. Generally this had been related to use of doses higher than those recommended in Australia but there had been some cases reported with the recommended Australian doses. Similar severe effects on muscle were recognised as a rare adverse effect of other statins but evidence had been accumulating that they were more common with cerivastatin. There had been 141 Australian reports of suspected adverse reactions about cerivastatin since it was registered in Australian Health Authority, of which just over half (73 reports) included descriptions of unwanted effects on muscle. Twenty five reports described rhabdomyolysis - sixteen of these patients were also taking gemfibrozil. None of the Australian reports described a fatal outcome of the reaction. Fourteen of the reports explicitly stated that the patient had recovered. Other reports were either on the patient had not yet recovered at the time of reporting or the outcome was not stated. The sponsor companies in Australia commenced a recall of stocks of cerivastatin from pharmacies and would write to doctors at that time. The following advice was given to patients taking cerivastatin:

• There were no short term unwanted effects of stopping cerivastatin.

• Patients taking cerivastatin who had muscle aches and pains should stop taking cerivastatin immediately and arrange to see their doctor.

• All other patients taking cerivastatin should stop taking cerivastatin immediately and arrange to have a discussion with their doctor within the next week about changing to alternative therapy.

- In October 2010, TGA published a safety update report and in this report it was mentioned that the combination of a macrolide antibiotic and a statin together could increase the risk of myopathy and rhabdomyolysis. If a patient taking a statin was to be prescribed a macrolide antibiotic, consider temporarily stopping the statin or choosing a different antibiotic.
- In December 2011, TGA advised health professionals to limit the prescribing of high dose (80 mg/day) simvastatin and to be aware of new contraindications and precautions for the use of simvastatin with other medicines. TGA warned the patients and health care professional about the issues mentioned below:

Information for health professionals

Dosage

The TGA recommended that 80 mg/day simvastatin should only be used in patients at high risk of cardiovascular complications who had not achieved their treatment goals on lower doses.

Interactions with other medicines

- Concomitant administration of simvastatin with gemfibrozil, cyclosporine, danazol and potent CYP3A4 inhibitors (such as itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) was contraindicated.
- Specific precautions (such as lower recommended simvastatin doses) also existed for patients taking moderate inhibitors of CYP3A4, amiodarone, the calcium channel blockers verapamil, diltiazem and amlodipine, fibrates other than gemfibrozil (which was contraindicated), niacin (≥1 g/day) and colchicine.

Information for patients

Patients should talk to their doctor if they were taking simvastatin, and they had:

• muscle pain, tenderness or weakness
• dark or red coloured urine
• unexplained tiredness (13).

All the foreign country health authorities took action about muscle related adverse effects of statins. The method of taking action can be withdrawal of the drug from the market, making changes to the Summary of Product Characteristics (SPC) or Patient Information Leaflet (PIL). Data for these two important actions can only be obtained from individual case report from post marketing experiences or clinical research data. Govermental health authorities should educate the doctors about the importance of spontaneous reports and should carefully follow up the safety of drugs available in the pharmaceutical market.

Statins and İEGM Warnings (Ministry of Health of Turkey General Directorate of Pharmaceuticals and Pharmacy for Turkey)

In Turkey, safety warnings are published in the internet site of İEGM (Ministry of Health of Turkey General Directorate of Pharmaceuticals and Pharmacy for Turkey). İEGM sends these warnings to Association of Research Based Pharmaceutical Companies and Pharmaceutical Manufacturers Association of Turkey. Local drug companies are members of Pharmaceutical Manufacturers Association of Turkey whereas international companies are members of Association of Research Based Pharmaceutical Companies. In local companies, these warnings are sended as circular. The warnings mentioned below are gathered from circular arhieve of Pharmaceutical Manufacturers Association of Turkey.

For other countries, muscle related warnings and dear doctor letter publications were focused. But for Turkey, all warnings published for statin drugs will be mentioned. Because there is not only warning specified for muscle related adverse effects, but also the main safety warnings had been focused by İEGM.

- In 2004, İEGM published another warning about atorvastatin. In this warning, products containing atorvastatin should add the interaction with St. John's wort and grapefruit juice to their Summary of Product Characteristics (SPCs).
- In 2006, İEGM published a warning about atorvastatin. In this warning, it was mentioned that in clinical trials 10 mg atorvastatin was found to be used in the primary prevention. So it should be corrected in the SPCs that 20 mg, 40 mg and 80 mg atorvastatin dosages are not used for primary prevention of cardiovascular diseases but are used for treatment of cardiovascular diseases.
- In 2009, İEGM published a warning about rosuvastatin. In this warning, it was mentioned that for the SPCs of products containing 40 mg rosuvastatin, it should be added that specialist should be controled performation for the dosages over 20 mg. Because adverse effects of 40 mg dose of rosuvastatin is higher than lower dosages, the final titration to 40 mg should only be done if enough response can not be taken with 20 mg and in patients with hypercholesterolemia and in high cardiovascular risk (homozygote and heterozygote patients with familial hypercholesterolemia and patients with familial combined hypercholesterolemia). These patients should be monitored

regularly. It should be advised that 40 mg dosage should be used under specialist control.

- Another warning published by İEGM about all statins (such as atorvastatin, fluvastatin, rosuvastatin, simvastatin, pravastatin) in 2010. In this warning it was mentioned that all statins should change their indications according to the indication specified below:

With diet;

- Is indicated to decrease cardiovascular morbidity and mortality in hypercholesterolemic patients but without clinical coronary heart diesease (fatal or nonfatal myocardial infarction, need of coronary revascularisation)
- Is indicated to decrease secondary events in hypercholesterolemic patients but with clinical coronary heart disease (fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, transient ischemic attacks, coronary revascularisation need and cardiovascular mortality)
- Is indicated to decrease lipid levels in hyperlipidemia with increases in total cholesterol, LDL-cholesterol, apolipoprotein B and triglyceride levels (Frederickson Type 2a, 2b, 3 and 4 hyperlipidemias)

- The last warning which is published by İEGM in 2012 covered all statins. In this warning it was mentioned that all statins should add the following warning to their Warnings Part of their SPCs.

As it was seen in other HMG-CoA reductase inhibitors, the patients treated with this statin (drug name) increases in HBA1c and serum glucose levels were observed. In patients with diabetes risk, an increase in diabetes incidence with this statin (drug name) was observed (14).

As it is mentioned above, İEGM tried to provide the safe use of statins. But there was not any warning related with the muscle related adverse effects of statins. Safety concerns regarding the use of statin treatment were heightened by the withdrawal of cerivastatin from the world market in 2001, owing to a rate of fatal rhabdomyolysis that, in postmarketing voluntary reports to the US Food and Drug Administration (FDA), was found to be much more frequent than with other statins. This isolated withdrawal of a previously approved statin drug suggests that the degree of risk of potential adverse

experiences (in this case rhabdomyolysis) varies between statins. These differences in safety risk are based on the marketed statin doses and the statin pharmacology profile such as bioavailability, metabolism, excretion rate and mode, as well as the patient population treated and the concurrent use of agents having a potential for drug interactions. The circumstance surrounding the withdrawal of cerivastatin also illustrates that even when early clinical trials suggest reasonable safety, independent postmarketing surveillance reports are critical to detect potential severe adverse experiences that may be revealed only after millions of patients have been exposed to the drug (15). For the other countries, there were many safety warnings related with statins. But unfortunately, there is not any warning about this issue in Turkey. This difference shows the need of more safety data publication by İEGM.

2. AIM AND METHOD

2.1. Aim

The aim of the thesis is to find out the cost of treatment of statin adverse effects especially the most serious and fatal adverse reaction of statins which is known as rhabdomyolysis. Rhabdomyolysis is thought as an important adverse drug reaction of statins. Direct cost of rhabdomyolysis for one patient in Turkey in case of the doctor or the patient does not realize that it is statin-induced has been calculated. In comparison, direct cost in case of the patient or the doctor realizes statin-induced muscle related complaints has been calculated. Because of lack of a standard treatment protocol of rehydration in this type of patients, in this thesis, a patient who has undergone rehydration treatment due to rhabdomyolysis in Turkey has been chosen as model and calculations have been done using this case. These two costs are to be discussed to show the payers (reimbursement agencies) and users (patients and physicians). Calculations have been done by payer's perspective.

2.2. Method

2.2.1. Literature Search

National and international literature search has been done and publicly available data in English by using the terms "*statins, HMG-CoA reductase inhibitors, adverse effects, rhabdomyolysis, meta-analysis, muscle toxicity"*. Publications discussing HMG-CoA reductase inhibitors effectiveness, safety, rhabdomyolysis, adverse effects and muscle toxicity were selected for review. The reference lists of relevant articles were examined for additional citations.

2.2.2. Search on the web

Web sites of different conuntries health authorities for warnings and safety alerts related to statins such as Health Canada (HC) for Canada, Therapeutic Goods Administration (TGA) for Australia, Food and Drug Administration (FDA) for USA, Medicines and Healthcare Products for Regulatory Agency (MHRA) for UK, European Medicines Evaluation Agency (EMEA) for European Union, Netherlands Pharmacovigilance Center (Lareb) for Netherlands and İlaç Eczacılık Genel Müdürlüğü

(İEGM) for Turkey were searched. These web sites are also followed regularly from marketing authorisation holders for safety alerts due to the Turkish Ministry of Health's demand. In case of any safety alert, marketing authorisation holders have to report it to Ministry of Health to draw attention for safety alerts.

2.2.3. Search

To calculate the total cost of the statins' muscle related adverse effect rhabdomyolysis for Turkey, TUFAM (Turkish Pharmacovigilance Center) for incidence of spontaneous reports data of statins and rhabdoymyolysis was asked for some information. But TUFAM denied providing the data of spontaneous reports of rhabdomyolysis because of the privacy policy.

IMS data was used to analyze the sales trends or use of the statins and other lipid lowering agents.

To calculate the direct cost of rhabdomyolysis, drug prices and laboratory test prices were needed. For the laboratory test prices, some data from Social Security Institution Health Application Announcement which was revised at the date of 03.07.2012. For the prices of drugs RxMediaPharma was used. In RxMediaPharma, the minimum price which constitutes the lowest value of price band that is reimbursed by Social Security Institution in March 2012 was chosen for each drug. The prices that are consistent with payer's perspective for both laboratory tests and drugs were used. In order to be sure about the prices in daily life, data related to the prices of laboratory tests was gathered from Kırklareli Public Hospital Counting House and Şişli Etfal Education and Research Hospital Counting House.

In addition, to evaluate the incidence of statin-induced rhabdomyolysis and to learn the details of acute tubular necrosis treatment, I made an interview with Prof.Dr. Mustafa Arıcı. Prof. Dr. Mustafa Arıcı is is a nephrologist in Hacettepe University Hospital. He is also the corporate affairs chairman of Turkish Hypertension and Kidney Disease Association. He is a key opinion leader.

Pharmacoeconomic analyses are generally performed due to assumptions and modellings. Generally, perspective effects the results of the study. In my study, I took account the direct costs and I used the costs gathered from the last updated Health

Application Announcement. By taking account the indirect costs, there may be different results.

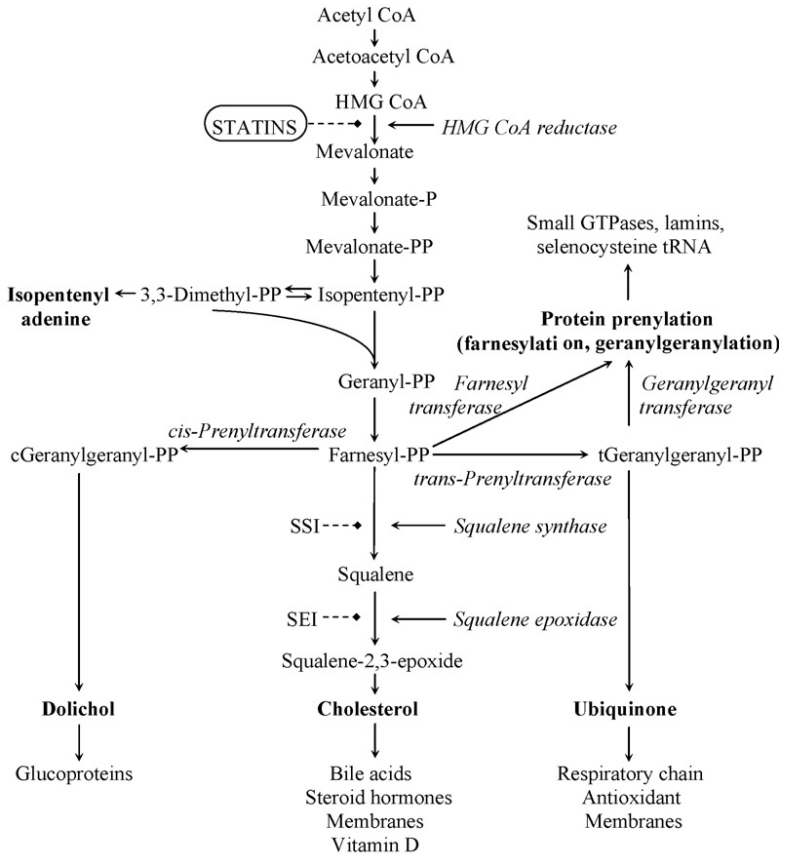
3. GENERAL INFORMATION

3.1. Biosynthesis and transportation of cholesterol and other co-metabolites

3.1.1. Biosynthesis

Cholesterol is a very important molecule as it is an essential component of all cell membranes and the precursor molecule for steroid hormones, vitamin D and bile acids. The body cholesterol pool has two origins, exogenous (dietary) and endogenous. Many tissues, in particular the liver and intestine can synthesize cholesterol from acetate (16).

Endogenous cholesterol biosynthesis occurs in the endoplasmic reticulum and cytosol and is shown in Figure 1. Sequential condensation of three molecules of acetyl CoA by thiolase and HMG CoA synthase leads to the formation of HMG CoA. The next downstream reaction, HMG CoA reduction to mevalonate by HMG CoA reductase, represents the principal regulatory step in cholesterol synthesis. Very important intermediates of this pathway are geranyl pyrophosphate (GPP) and farnesyl pyrophosphate (FPP). These are derivatives of common 5-carbon building blocks, isopentenyl pyrophosphate and its isomer dimethylallyl pyrophosphate, called isoprene units. Apart from the biosynthesis of cholesterol, FPP and GPP are involved in the post-translational modification (i.e. prenylation) of various cellular proteins, as well as serve as precursors for the biosynthesis of important compounds, such as dolichol, and ubiquinone (17).



PP=Pyrophosphate, **SSI**=Squalene Synthase Inhibitors, **SEI**=Squalene Epoxidase Inhibitors

Figure 1. Cholesterol Biosynthesis

3.1.1.1 Prenylated proteins

Post-translational prenylation of proteins occurs by the covalent addition of only two types of isoprenoids, FPP and geranylgeranyl pyrophosphate (GG-PP), to cysteine residues at or near the C-terminus. Prenylated proteins, such as small GTPases and lamins constitute up to 2% of total cellular protein (17). The lipophilic prenyl group enables these prenylated proteins to anchor to cell membranes, which in most cases is an essential requirement for their biologic function. Selenocysteine tRNA undergoes post-transcriptional prenylation, which is an important modification for its proper function (1).

3.1.1.1.1. Biologic role of prenylated small GTPase family of proteins

Small GTPase proteins are prenylated proteins that cycle between an inactive guanosine diphosphate (GDP) – bound and active guanosine triphosphate (GTP) – bound state, and they have crucial roles in controlling multiple signaling pathways (18).

Upon tyrosine kinase receptor activation, the farnesylated membrane bound small GTPase protein Ras becomes activated by binding to GTP. Ras serves as a signal transduction intermediary by initiating a cascade of events culminating in positive regulation of cell growth. Rab small GTPases are involved in organelle biogenesis and intracellular vesicular trafficking. More than 60 Rab small GTPase isoforms have been identified. Each has a specific intracellular localization and regulates a specific trafficking step. For example Rab1 is involved in the transportation of vesicles from the endoplasmic reticulum to the Golgi apparatus and Rab8 carries newly synthesized transmembrane proteins from the Golgi apparatus to the plasma membrane (19).

These are doubly geranyl geranylated, an important modification for their exquisite localization, which is in turn required for their proper function (20, 21).

3.1.1.1.2. Biologic role of prenylated lamins

Lamins are the main component of the intermediate filament lamina, which lines the inner nuclear membrane. Besides having a structural role, lamins have a role in chromatin organization as well, and there are several examples of lamin participation in gene expression (22).

According to a review article lamins B1 and B2 undergo farnesylation, whereas prelamin A, which is the precursor molecule of lamin A, undergoes prenylation dependent processing (1).

3.1.1.1.3. Biologic role of selenocysteine tRNA and selenoproteins

Selenocysteine tRNA was isopentenylated at adenosine 37, (A37) a commonly modified position immediately 3' at the anticodon (23). Selenocysteine tRNA decodes UGA, normally a stop codon, and inserts selenocysteine into nascent selenopeptides. The absence of tRNA isopentenylation was found to reduce the efficiency of the altered selenocysteine tRNA in decoding nonsense codons in bacteria and yeast (24).

Improper translational stop codon read-through may lead to premature termination of translation and production of truncated proteins. (1)

3.1.1.2. Dolichols

According to a review article published in 2009, dolichols were told as derivatives of F-PP and isopentenylpyrophosphate. Dolichols are polyisoprenols with typically 16–22 isoprene units, whose single chain varies in length both within cells and

between cell types and organisms. Dolichols mediate the N-linked glycosylation of nascent polypeptides by serving as carriers, as well as sites whereupon the core oligosaccharide unit for protein glycosylation is assembled. Glycosylation is an intricate modification that proteins undergo and is an integral component for proteins' proper biologic functioning (1).

3.1.1.3. Ubiquinone

Another article published in 2009 stated that ubiquinone was composed of a hexameric quinone ring (Q) and a ten isoprenyl unit side chain, hence the name coenzyme Q10 (CoQ10). It acts as a mobile component of the respiratory chain in mitochondria that collects reducing equivalents from the more fixed flavoprotein complexes and passes them onto the cytochromes further downstream the respiratory chain (1).

On the other hand, either low or high cholesterol concentration was associated with pathological conditions such as Smith-Lemli-Optiz syndrome (25) or atherosclerosis (26), respectively.

3.1.2. Transportation

Blood lipids (or blood fats) are lipids in the blood, either free or bound to other molecules. Blood lipids are mainly fatty acids and cholesterol. Cholesterol is minimally soluble in water; it cannot dissolve and travel in the water-based bloodstream. Instead, it is transported in the bloodstream by lipoproteins - protein molecular-suitcases that are water-soluble and carry cholesterol and triglycerides internally. The apolipoproteins forming the surface of the given lipoprotein particle determine from what cells cholesterol will be removed and to where it will be supplied.

The largest lipoproteins, which primarily transport fats from the intestinal mucosa to the liver, are called chylomicrons. They carry mostly fats in the form of triglycerides. In the liver, chylomicron particles release triglycerides and some cholesterol. The liver converts unburned food metabolites into very low density lipoproteins (VLDL) and secretes them into plasma where they are converted to intermediate density lipoproteins (IDL), which thereafter are converted to low-density lipoprotein (LDL) particles and non-esterified fatty acids, which can affect other body cells. In healthy individuals, the relatively few LDL particles are large. In contrast, large

numbers of small dense LDL (sdLDL) particles are strongly associated with the presence of atheromatous disease within the arteries. For this reason, LDL is referred to as "bad cholesterol".

High-density lipoprotein (HDL) particles transport cholesterol back to the liver for excretion, but vary considerably in their effectiveness for doing this. Having large numbers of large HDL particles correlates with better health outcomes, and hence it is commonly called "good cholesterol". In contrast, having small amounts of large HDL particles is independently associated with atheromatous disease progression within the arteries (27).

3.2. Cardiovascular risk

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for nearly 30% of the annual global mortality (28).

According to the report of American Heart Association in the United States, where the disease is highly prevalent, over one third of the population has one or more types of CVD. Coronary heart disease (CHD) affects nearly 18 million Americans. As the predominant cause of death from CVD, it is estimated that over one million individuals suffer from acute CHD events each year in the United States. Stroke, the second leading cause of death from CVD, has a prevalence of nearly 6.5 million, and over 600,000 new stroke cases are diagnosed annually in the United States (29).

Other forms of high-risk CVD conditions are common as well. Approximately 5 million Americans have been diagnosed with heart failure (HF), and around 8 million Americans with peripheral vascular disease (PVD). Diabetes mellitus, a major CVD risk factor and CHD-equivalent, afflicts approximately 5.5 million individuals in the United States (30).

Coronary artery disease is the leading cause of morbidity and mortality in the United States, and hyperlipidemia is a major risk factor. High blood cholesterol, or hyperlipidemia, is a common cardiovascular system problem. In the United States, 35.6% of adults have been told that they have hyperlipidemia. The causes of hyperlipidemia are multifactorial. Blood cholesterol tends to rise with age and body mass index. However, women tend to have lower blood cholesterol before menopause and higher blood cholesterol after menopause. Alcohol intake, race, and education have been associated with hyperlipidemia (31).

At this point, Chatzizisis Y.S. et al mentioned that atherosclerotic cardiovascular disease is the most frequent cause of morbidity and mortality in developed countries (32).

3.2.1. The relation of cardiovascular risk and blood lipids

The relationship between abnormal plasma cholesterol fractions and increased CVD risk was described up to 60 years ago, when the role of the different lipoproteins in atherosclerosis is being elucidated by Barr D.P. et al (33).

The modern concept of atherogenesis highlights the crucial roles these lipoproteins play in the atherosclerotic process. One of the earliest steps in atheroma formation involves the infiltration of the dysfunctional vascular endothelium by low-density lipoprotein cholesterol (LDL), the most atherogenic of the lipoproteins. The LDL in the vessel wall becomes oxidized and is taken up by macrophages forming the classic foam cells. This process further stimulates lipid deposition and incites the inflammatory cascade that leads to the formation of the atherosclerotic plaque. On the other hand, the highdensity lipoprotein cholesterol (HDL) promotes reverse transport of cholesterol from lipid-laden macrophages in the vascular wall, and has anti-inflammatory effects, thereby inhibiting the progression of atherosclerosis and potentially inducing regression of the atherosclerotic plaque (30). See the figure 2 below:

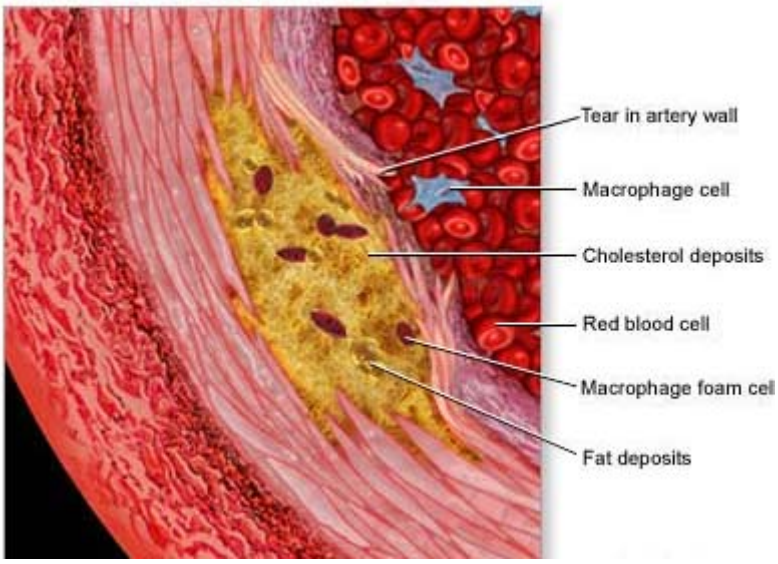


Figure 2. Atherosclerotic plaque formation

In various conditions where levels of LDL are abnormally high or levels of HDL are low, the atherosclerotic process is enhanced, increasing the risk of development of CVD (30).

Elevated low-density lipoprotein cholesterol (LDL-C) is recognized as a major risk factor for coronary heart disease (CHD) (34). Low-density lipoprotein cholesterol (LDL-C) reduction attenuates the progression of atherosclerosis and reduces the risk of cardiovascular events (32).

Accumulating evidence suggests that elevated triglyceride (TG) levels may also pose a significant independent risk. Elevated TG levels are thought to increase CHD risk through the atherogenic effects of TG-rich remnant lipoproteins, which are partially degraded, TG-rich lipoprotein remnants of hepatic and intestinal origin that have lost TG through the action of lipoprotein lipase and have picked up cholesterol ester through the action of cholesterol ester transfer protein. Specifically, chylomicrons are produced in the gut from dietary fat and are not thought to be atherogenic until their TG core is removed by lipoprotein lipase. It is the resulting chylomicron remnants that are atherogenic, perhaps because they are sufficiently small to infiltrate arterial walls Similarly, very low-density lipoprotein (VLDL) particles are produced in the liver from hepatic TG and become VLDL remnants after cleaving of the TG core (34).

According to Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of-High Blood Cholesterol in Adults (Adult Treatment Panel III) final report elevated TG levels, together with low levels of HDL-C and an increased prevalence of small LDL particles, constituted a lipid triad termed *atherogenic dyslipidemia* that was associated with premature CHD (35).

An elevated TG level (>150 mg/dL) is also one of the determinants of risk for the metabolic syndrome, a cluster of metabolic abnormalities related to insulin resistance and elevated free fatty acid levels that is associated with an increased risk for development of type 2 diabetes and premature CHD (34).

Also according to the results of The Lipid Research Clinics Coronary Primary Prevention Trials, in the past three decades, significant advances have been made in the understanding and management of lipid disorders. Epidemiologic data published in the 1970s identified an association between elevated levels of total cholesterol (TC) and

coronary heart disease (CHD), with low-density lipoprotein cholesterol (LDL-C) as the primary contributing factor (36, 37).

Known as the "lipid hypothesis," this association was further substantiated by the Multiple Risk Factor Intervention Trial (MRFIT), a large epidemiologic study that evaluated the relation between CHD and serum cholesterol, smoking status, and blood pressure in 361,662 middle-aged men. Published in the 1980s, the results of MRFIT show a steep curvilinear increase in the CHD death rate when TC levels exceed 200 mg/dl (38). See Figure 3.

Atherosclerosis regression trials published in the 1980s and 1990s show that lipid-lowering therapy can slow atherosclerosis progression and, in some cases, minimally reduce the size of existing lesions. Although generally not designed to detect a difference in clinical events, these trials also show a trend toward a reduction in cardiovascular risk (39).

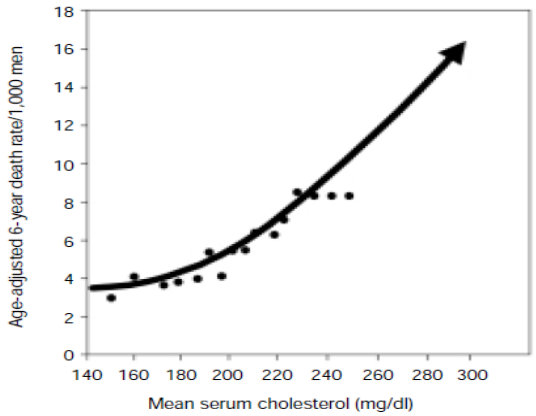


Figure 3. CHD death rate and TC levels

3.2.2. Populations at risk

It is well established that those with diabetes mellitus exhibit an increased risk of vascular disease, possibly owing to disturbances, not only in plasma lipoprotein levels but also other atherogenic pathways. Subjects with renal disease also have an unexplained increment in risk, with most patients dying of CHD rather than the primary disorder; chronic renal failure was found in studies, such as the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial, to be highly prevalent in the elderly and a predictor of risk and treatment benefit. Furthermore, diseases associated

with activation of the innate immune system, such as rheumatoid arthritis, are now recognized to carry a high burden of atherosclerotic vascular complications. Within Western countries, CHD exhibits a distinct demographic pattern, having a higher prevalence in those of lower socioeconomic status and, in the UK, in migrants from Pakistan and the Indian subcontinent. Rather, it is likely that adverse social circumstances (e.g., low wage, poor diet and housing) impact on a range of atherogenic pathways. The increased risk of vascular disease in British Asians is probably related to the higher prevalence of obesity and metabolic syndrome (40).

3.2.3. Conditions that can increase serum blood lipid levels

Elevated TG levels are associated with a number of conditions, including obesity, type 2 diabetes, renal disease, and the metabolic syndrome each of which is associated with increased morbidity and mortality due to CHD (34). See Table 3.

Table 3. Conditions that can increase blood lipids

Lifestyle factors
Excess caloric intake
High carbohydrate intake
Excess alcohol intake
Physical inactivity
Diseases and conditions
Insulin resistance
Metabolic syndrome
Type 2 diabetes
Chronic kidney disease
Chronic renal failure
Cushing's syndrome
HIV disease
Hypothyroidism
Nephrotic syndrome
Pregnancy
Medications
Atypical antipsychotics
β-Blockers
Corticosteroids
Estrogens
HIV protease inhibitors
Retinoids
Tamoxifen
Thiazide diuretics
Genetic factors
Familial combined hyperlipidemia
Familial dysbetalipoproteinemia
Familial hypertriglyceridemia

Obesity, defined as a BM1 >30 kg/m^2, is present in almost one third of the adult US population. The cardiovascular risks associated with type 2 diabetes, which affects 20.8 million adults, are so great that this condition was designated a CHD risk equivalent by the NCEP ATP lll. The prevalence of the metabolic syndrome increases with age, 5 affecting 44% of adults aged >50 years. Hypertriglyceridemia also occurs within familial syndromes. Familial combined hyperlipidemia is common, with an

estimated prevalence of 1% to 6% among Western populations. In this condition, patients have high levels of LDL-C and apolipoprotein (apo) B. In contrast, familial hypertriglyceridemia involves hypertriglyceridemia alone. Familial dysbetalipoproteinemia is characterized by excess chylomicrons and VLDL cholesterol (VLDL-C) remnants. Familial hypertriglyceridemia with chylomicronemia, or type V hyperlipoproteinemia, is characterized by very high TG levels (eg, >1000 mg/dL) and may be associated with eruptive xanthomas and/or pancreatitis. Familial chylomicronemia, a rare form of type 1 hyperlipoproteinemia in which extremely high TG levels are present from birth, is also associated with recurrent pancreatitis. Medications may also be associated with increases in TG levels (see Table 3). These include estrogen replacement therapy, oral contraceptives, tamoxifen, corticosteroids, β-blockers, and thiazide diuretics. Other medications that increase TG levels include retinoids, some antipsychotic agents, and immunosuppressants (34).

3.2.4. Methods of detection of atherosclerosis

Recognition of chronic activation of the innate immune system is central to the etiology of CHD has prompted an evaluation of the role of inflammatory markers in improving the discriminative power of prediction models. In this context, CRP has undergone intensive study as a potential biomarker of CHD risk. Observations suggest that elevated levels of CRP and IL-6 associate more strongly with the risk of fatal rather than nonfatal cardiovascular events. An alternative approach to identifying the individual at risk of a major coronary event is to use modern, noninvasive imaging techniques to examine the vascular bed and detect atherosclerotic changes. There are a number of modalities available, including ultrasound, computed tomography and MRI. Ultrasound investigation of the carotid arteries was tought as the most convenient and widely used method for assessing atherosclerosis in asymptomatic and diseased populations; two features of the artery wall are usually quantified, the intima-media thickness (IMT) and the number of plaques present. It is found noteworthy by Packard C.J. that, in employing this imaging strategy, the most frequent outcome was to move subjects to a lower-risk category than that assigned on the basis of traditional risk factors, thus potentially offsetting the cost of the investigation by savings on drug prescriptions (40).

3.2.5. Benefits of early detection of atherosclerosis

According to Klag et al., studies have shown that hypercholesterolaemia in young adults is associated with risk of subsequent onset of CHD, even though tracking of lipid values is not complete (41). Among children with familial hypercholesterolaemia, serum levels of LDL cholesterol are usually exceptionally high from birth and will persist without treatment (42).

According to Scientific Steering Committee on behalf of the Simon Broome Register Group, the relative risk of CHD by the fourth decade in this group is very high, but has been reduced subsequent to the advent of statins (43).

These observations, in addition to evidence from autopsy studies showing that lipoprotein levels are associated with the extent and prevalence of coronary atherosclerosis and with the development of plaques, indicate that lowering elevated serum cholesterol in children would be expected to prevent premature CHD (44).

Moreover, measurements of morphological and functional changes in arteries by high resolution carotid ultrasonography or brachial artery low-mediated dilatation have provided noninvasive data on the effects of hypercholesterolaemia in children (42).

Children with familial hypercholesterolaemia tended to have a thicker intimal-medial layer in the carotid artery than controls and the presence of carotid plaque was related to the cholesterol-years score and LDL cholesterol level (45, 46).

Increased level of LDL cholesterol is associated with an impaired capacity of the brachial artery to dilate in response to hyperaemia and, in adults, has been shown to be reversed following cholesterol-lowering treatment (47).

Studies have demonstrated that children with familial hypercholesterolaemia have brachial artery endothelial dysfunction compared with controls, particularly those with a family history of premature cardiovascular disease (48, 49).

These observations indicate that cholesterol-lowering in children may improve arterial function, thereby reducing future risk of atherosclerotic cardiovascular disease (42).

3.3. Guidelines and goals

Guidelines can be defined as recommended practice that allows some discretion or leeway in its interpretation, implementation, or use. For the prescription of statins,

every country has its own guideline. In this thesis "NCEP ATP guidelines" for foreign countries and "Diagnosis and treatment guideline" and "Social Security Institution Health Application Announcement" for Turkey were focused on. NCEP ATP guideline was prefered because it includes worldwide data for clinical use. In addition to this, in order to make a correct calculation Turkish guidelines have to be known well. So guidelines and the goals mentioned in these gudelines were categorized as "Other countries" and "Turkey".

Other countries

Adults

A number of recognized bodies act as national or international sources of guidelines on the prevention of CHD. These include the US National Cholesterol Education Program (NCEP), the Joint Task Force of European Societies, The Japan Atherosclerosis Society, and, in the UK, the NICE. The NCEP Adult Treatment Panel (ATP) guidelines are adopted by many countries with modifications to suit local circumstances and practice. Most guidelines agree that the principal aim of lipid-lowering treatment is a reduction in LDL cholesterol to specific target levels. In the case of patients with established CHD or other manifestations of vascular disease (secondary prevention), this is less than 2.0 mmol/l (<70 mg/dl), a more aggressive goal than the original less than 2.6 mmol/l (<100 mg/dl) in the NCEP ATP-III. Low HDL (<1.0 mmol/l; <35 mg/dl) is regarded as a risk factor (even if LDL is also low), but no goal has been set for elevation of this lipoprotein class and, as discussed previously. Plasma triglyceride is regarded as a risk marker, particularly if cholesterol-rich 'remnants' are present (a remnant is the partial hydrolysis product generated as a result of lipoprotein lipase action on chylomicrons or very-LDL). Elevated triglyceride level is an indication that more-aggressive lifestyle changes should be adopted to correct obesity or excessive alcohol intake. It is also a marker of Type 2 diabetes and further investigation is required to establish glucose tolerance status. The NCEP ATP-III introduced non-HDL cholesterol as a surrogate for apoB, and a measure of the total concentration of 'atherogenic' lipoproteins. The NCEP ATP-III proposed that non-HDL cholesterol be a secondary target for therapy with goals set 30 mg/dl above the LDL cholesterol target. In asymptomatic individuals (i.e., primary prevention), the first step is to engage in a

systematic program of risk assessment. Population groups may be targeted on the basis of age, attendance at a 'well-person' clinic or through family follow-up. All patients being screened for hypertension or diabetes should also have their coronary risk estimated. Guidelines recommend different thresholds for action but it is generally accepted that an estimated 10-year risk of 20% of a vascular event is high and mandates drug therapy when lifestyle changes have not yielded a satisfactory (as agreed by the patient and physician) response. Opinions vary as to the target LDL level in primary prevention. NICE recommends a 40-mg dose of simvastatin (or equivalent alternative) but no LDL goal, whereas the NCEP ATP-III sets targets according to the estimated 10-year risk (e.g., a risk of 20% is considered 'CHD equivalent' and has a goal of LDL reduction to <100 mg/dl, whereas for lower risk, the goals are <130 mg/dl and <160 mg/dl. It is debatable whether the goals of treatment should differ in primary and secondary prevention. Arguably, the higher risk in those with established vascular disease requires more-aggressive therapy. On the other hand, it is critically important to prevent the first event, since it may be fatal. Thus, there are grounds for suggesting that, once the decision is made, pharmacological agents should be used (statins alone or in combination with another drug), then an aggressive goal of less than 2.0 mmol/l should be pursued, regardless of the background risk or vascular status of the patient (40, 50).

The Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) recommends the use of lower cutpoints for the categorization of TG levels (normal, borderline high, high, and very high) than the ATP II guidelines, reflecting a growing awareness of the importance of even moderate TG elevations (34). See table 4 below:

Table 4. Comparison of serum TG levels from ATP II and ATP III

Serum TG Category	ATP II	ATP III	ATP III Treatment Goals
Borderline high	200–400 mg/dL	150–199 mg/dL	Achieve LDL-C goal
High	>400–1000 mg/dL	200–499 mg/dL	Primary: Achieve LDL-C goal Secondary: Achieve non–HDL-C goal (30 mg/dL above LDL-C goal)
Very high	>1000 mg/dL	≥500 mg/dL	Primary: Prevent pancreatitis Secondary: Prevent CHD

LDL-C = low-density lipoprotein cholesterol; non–HDL-C = non–high-density lipoprotein cholesterol; CHD = coronary heart disease.

Children

European recommendations do not include specific guidelines for the treatment of children; however, familial hyperlipidaemias are noted to increase the risk of CHD. While the US guidelines (National Cholesterol Education Program, 1992) did not support universal screening of serum cholesterol levels in children, the population strategy of maintaining lower cholesterol levels in all children through the diet was recommended. Targeted screening was recommended for children with a family history of premature cardiovascular disease or at least one parent with high cholesterol levels or for children for whom the family history is unavailable, particularly those with other risk factors. The panel further recommended that drug treatment be considered for children older than 10 years of age who, despite dietary modification for 6-12 months, had an LDL cholesterol level ≥4.91 mmol/L and no other risk factors or an LDL cholesterol level ≥4.13mmol/L and a positive family history of premature cardiovascular disease (before 55 years of age) or two other risk factors. Recognized risk factors included low HDL cholesterol levels (<0.9mmol/L), smoking, diabetes, obesity, or hypertension, if still present after vigorous attempts had been made to control them. Multiple measurements are recommended before diagnosing a child as hypercholesterolaemic (42).

Turkey

A "Diagnosis and treatment guideline" was published by Ministry of Health in 2003 in Turkey. According to this guideline hyperlipidemia was identified as disorders that are observed as an increase in total serum cholesterol levels as a result of lipoprotein metabolism disorder. Also a decrease in high density lipoprotein cholesterol can also accompany. Hyperlipidemia is the most important reason of atherosclerosis and other complications related to atherosclerosis. In our country total cholesterol levels are generally low in comparison with western society. Total cholesterol level is above 200 mg/dL and/or triglyceride level is above 150 mg/dL in %25 of adults at the age of over 30. High density lipoprotein cholesterol levels are below 40 mg/dL in %70 of men and %50 of women. It was shown that an increase in the total cholesterol/high density lipoprotein ratio is the best forecasting for future coronary events.

Hyperlipidemia can be classified as primary or secondary: In primary hyperlipidemia the most important factor is heritage also environmental factors may accompany. Secondary hyperlipidemia may be observed due to diabetes, chronic kidney and liver diseases, obesity, alcohol intake, hypothyroidis and drug use (steroid and steroid derived hormones, thiazide diuretics, retinoids, beta-blockers (risk/benefit evaluation should be performed to change/stop these drugs)).

It is not important why the patient applied to the hospital, in individuals that have at least one of the risk factors listed below, lipid levels should be measured, and all patients whose blood lipid levels were not measured but have the risk factors listed below should be advised to change their lifetsyles.

1. Healthy adults above the age of 45
2. Postmenopausal women (physiological or surgical)
3. Individuals that have hyperlipidemia, early coronary heart disease or early death history in their first degree relatives
4. Smokers
5. Obesity
6. Individuals with atherosclerotic vascular disease history
7. Individuals with secondary hyperlipidemia risk
8. Individuals with metabolic syndrome; at least 3 of the diagnostic tools should be found.

Metabolic syndrome diagnostic tools

Abdominal obesity waist circumference:	Men > 102 cm Women > 88 cm
Triglyceride	>150 mg/dL
HDL-C	Men < 40 mg/dL Women < 50 mg/dL
Blood pressure	130/85 mmHg
Blood sugar in fasting	110 mg/dL

Diagnosis

Symptoms and findings

Hyperlipidemia generally does not cause any symptom or finding. Detailed medical history of the patient should be taken and physical examination should be done.

Physical examination:

- Body mass index should be calculated. Body mass/(height)^2= kg/m^2
- Skin: Xanthelasma, xanthoma
- Cardiovascular: Arterial murmur and/or lack of pulse
- Cerebrovascular: Murmur or similar symptoms should be searched in carotid auscultation.

Diagnosis is made by measuring blood lipid levels.

For measuring triglyceride levels, blood samples should be taken after 12 hours of fasting.

Lipid levels classification

	Total cholesterol (TC)	**LDL-C**	**Triglyceride (TG)**
Optimal		< 100	
Normal	< 200	100-129	<150
High in limit	200-239	130-159	150-199
High	240	160-189	200-500
Very high		190	>500

HDL-C level that is below 40 mg/dL is accepted as low.

Treatment

Normalisation of lipid levels, in addition to the decrease in risks of coronary heart disease and stroke also decreases the cardiovascular system (CVS) deaths. Individuals with hyperlipidemia should be evaluated in respect to all other cardiovascular risk factors, follow-up and treatment should be done accordingly.

Aim of the treatment is to decrease LDL-C level below 100 mg/dL and TC/HDL-C ratio below 5 for patients with high coronary heart disease risk.

Patients with hyperlipidemia or patients whose blood lipid levels have not been checked but have the tisk factors should be advised for lifestyle changes.

Suggested life style changes:

- Avoid foods containing high saturated lipid and cholesterol levels; prefer foods with high fibre content and fish
- Quit smoking and alcohol
- Have the ideal body weight
- Regular exercise: 20 minutes walking or exercise minimum 4 times in a week

Drug treatment

Drug treatment should be started after the exclusion of secondary reasons.

Drug treatment goals are determined according to patient's risk group.

Risk groups in drug treatment

High risk	Atherosclerotic vascular disease (ASVD) and/or Diabetes mellitus (DM) and/or Metabolic syndrome + 50 year old men Metabolic syndrome + < 50 year old women + TC/HDL-C 5
Moderate risk	For coronary heart disease existence of 3 risk factor (absence of ASVD or DM) or metabolic syndrome + < 50 year
Low risk	Existence of maximum 2 risk factors (absence of ASVD, DM (glucose intolerance), metabolic syndrome)

Risk factors for coronary heart disease

Age	45 in men, 55 in women or in menopause (physiological or surgical)
Family history	Existence of coronary artery disease in first degree men relatives before 55 years of age and in first degree women relatives before 65 years of age
Smoking	Being a smoker
Hypertension	Blood pressure higher than 140/90 mmHg or having hypertensive treatment

Hypercholesterolemia	TC 200 mg/dL, LDL-C 130 mg/dL
Low HDL-C	Lower than 40 mg/dL
DM	Diabetes in addition to be a risk factor itself, also carries an equivalent risk with coronary heart disease

In high cholesterol levels statins, in high triglyceride levels fibrates are used. Cholestyramine can be used in patients only with high cholesterol in combination with statins or alone in patients that can not use statins.

Drugs that can be used in hyperlipidemia treatment

Drug*	**Dose**	**Adverse reactions**	**Contraindications**
Fibrates *Fenofibrate (micronized)* *Gemfibrozil*	200-250 mg/day Once 600-1200 mg/day Twice	Gastrointestinal system disorders, anxiety, increase in transaminases, skin rash, pancreatitis	Liver and kidney failure, gallstone, diabetic neuropathy, pregnancy, lactation
Bile acid sequestrants *Cholestyramine*	8-36 g/day Four times	Constipation and other gastrointestinal system adverse effects, decreases the absorption of lipid soluble vitamins and co-administered drugs	Biliary occlusion
Statins (HMG-CoA reductase inhibitors) *Atorvastatin* *Fluvastatin* *Pravastatin*	Single dose a day 10-80 mg/gün 40-80 mg/gün	Increase in transaminases,	Pregnancy, lactation, active or chronic liver disease,

Simvastatin	10-40 mg/gün 10-80 mg/gün	rhabdomyolysis, myositis	unexplained increase in transaminases, serious muscle trauma

*Drug names were written in alphabetic order.

Follow-up

In addition to blood lipid levels, serum transaminase levels should also be monitored before and after the treatment. These follow-up should be performed once in every 6 weeks in the first 3 months, then with 6 month interval in the first 3 years and in dose increases. This follow-up is especially important in patients with high serum transaminase levels or patients with alcohol intake. It may also be beneficial to know the creatinin kinase level at the beginning of the treatment. There is no need for routine creatinine phosphokinase control. Patients should be warned to apply to the doctor in case of muscle pain, weakness and severe malaise.

During the follow-up, adverse effect evaluation should also be done.

It is aimed to protect the target lifelong with these follow-up after treatment. In patients taking drug, LDL-C target should be achieved with the minimum dose avaliable.

Referral

- All risk groups if it is not possible for laboratory evaluation
- Patients in high risk group who do not respond to the treatment at the end of 6 weeks despite the life-style changes or drug treatment
- Patients with other systemic disorders
- Patients in moderate or low risk group who do not respond to life-style changes or eating habits
- Patients with familial hyperlipidemia
- Patients with TC level above 500 mg/dL
- Patients who have high cholesterol and triglyceride levels (mixed type), and do not respond to treatment without drug

- In moderate and low risk groups, in patient with life-style changes if the LDL-C level is 130 mg/dL and 160 mg/dL at the end of 3. And 6. months respectively should be referred (5).

According to Social Security Institution Health Application Announcement published in 2010 and revised in 07.03.2012, the principles of the use of lipid lowering agents was specified as follows:

a) Statins and other lipid lowering drugs other than statins

1) Patients without a lipid lowering drug history

a) Statins (including the combination with antihypertansives) can be used by relying on the specialist report in the cases in which LDL level is above 160 mg/dL (the level of LDL is 100 mg/dL in patients with diabetes mellitus, acute coronary syndrome, MI history, coronary heart disease, peripheral artery disease, abdominal aort aneurysm or carotid artery disease and level of LDL is 130 mg/dL in patients over 65 years with hypertension) and lipid lowering drugs other than statins (fenofibrate, gemfibrozil, cholestyramin) can be used in patients with triglyceride level above 300 mg/dL. (teh level of triglyceride is 200 mg/dL in patients with diabetes mellitus, acute coronary syndrome, MI history, stroke history, coronary artery disease, peripheral artery disease, abdominal aort aneurysm or carotid artery disease).

b) These drugs can be prescribed by all doctors relying on the specialist report. During the report, laboratory test results are not taken into consideration. In the first specialist report that determines the starting to the use of drug, laboratory test results are specified which were done in the last 6 months that shows blood lipid levels are high.

2) That group drugs are prescribed in 1x1 dosage. In the treatment with gemfibrozil (if the triglyceride level is above 1000 mg/dL), these drugs can be prescribed in 2x1 dosage by endocrinologists' reports which was prepared by the same doctors.

3) Preparations containing 40 mg rosuvastatin active ingredient can only be prescribed by cardiologists and endocrinologists relying on the specialist report which was prepared again by the same doctors.

b) Ezetimib (including the combinations with statins)

1) This drug can be prescribed by all doctors relying on the report of cardiologists, internal medicines specialists, neurologists or heart and vascular surgery specialists if

the LDL level is above 100 mg/dL despite the treatment with statins for 3 months by documenting this case.

2) This drug can be prescribed by all doctors relying on the report of cardiologists, internal medicines specialists, neurologists or heart and vascular surgery specialists if at least one of the hepatic enzyme levels (AST/SGOT or ALT/SGPT) are above the three times limit of normal or creatinin phosphokinase levels are above the two times limit of normal and so that the patient can not be treated with statins.

c) Niacin

1) This drug can be prescribed by all doctors relying on the report of endocrinologists, internal medicines specialists or cardiologists if HDL level is below 40 mg/dL in patients above 18 years of age.

d) Renewal of the report in patients with report

1) In patients with report in case of the renewal of the report, without taking account the new laboratory test results, it is enough to add the photocopies of previous report to the new report or to specify the treatment initiation and laboratory test results at this time in the report. But if the new laboratory test results are consistent with the results at the initiation of the report, it is reimbursed in 1x1 dosage without any need to the datas on the old report.

e) Test results

Laboratory test results must be print out and results which are hand-writing can not be taken into consideration (51).

In 19 March 2012, Social Security Instution of Turkey has published made a change in the prescription of statins. According to this change, prescription of statins as it was specified in 2. Section of A part, execution of "That group drugs are prescribed in 1x1 dosage. In the treatment with gemfibrozil (if the triglyceride level is above 1000 mg/dL), these drugs can be prescribed in 2x1 dosage." has been stopped.

3.4. Treatment of cardiovascular health diseases

3.4.1. Treatment of cardiovascular health diseases in adults

Cholesterol-modifying therapy has well-established benefits in the primary and secondary prevention of CHD and stroke (30).

Recognition of the role of elevated TG levels in CHD has prompted a need for more aggressive TG management. In the ATP III recommendations, TG management through the control of non-HDL-C (TC - HDL-C) levels is an important part of the algorithm for dyslipidemia (see table 5). The ATP III guidelines recommend treatment of elevated TG levels according to their severity and the levels of other lipids. For borderline high TG levels (150-199 mg/dL), the aim of therapy is to reduce LDL-C through lifestyle changes. Recommended lifestyle modifications include weight loss, regular physical activity, smoking cessation, restriction of alcohol intake, and avoiding a highcarbohydrate diet. When drug therapy is needed, agents that lower LDL-C (ie, statins) should be used first. If low HDL-C levels are present with normal LDL-C and borderline high TG levels, niacin or a fibrate may be used (34, 50).

Table 5. Algortihm for treatment of dyslipidemia

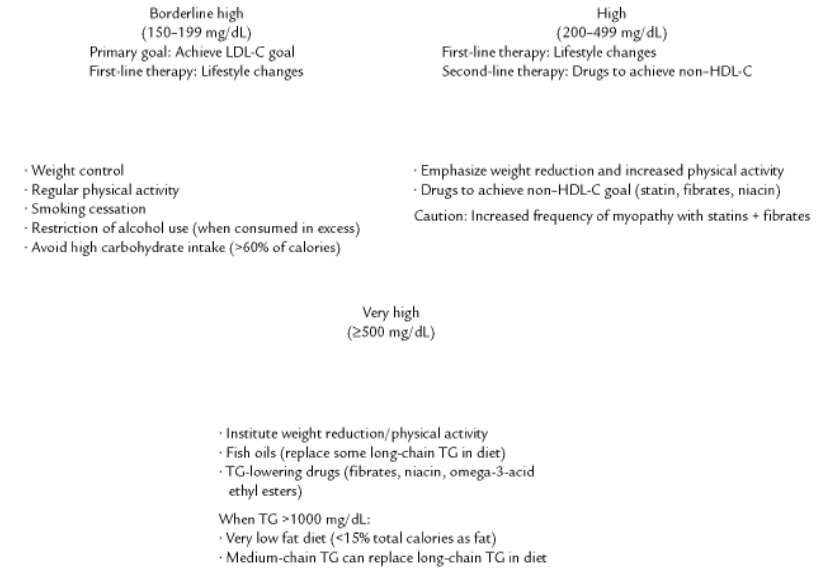


Figure. Treatment algorithm for elevated serum triglyceride (TG) levels.[3] LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

NCEP ATP III when TG levels remain high (200-499 mg/dL) even after the LDL-C goal is reached with lifestyle interventions, treatment with a hepatic hydroxymethylglutaryl coenzyme A-reductase inhibitor (statin) to reduce non-HDL-C is recommended. Determination of non-HDL-C does not require a fasting sample and is calculated as TC - HDL-C (non-HDL-C = TC - HDL). If the non-HDL-C goal (ie, 30

mg/dL higher than the LDL-C goal) is not achieved with statin therapy, treatment with niacin or a fibrate may be added. Use of niacin is also recommended for lowering non-HDL-C when LDL-C is not significantly elevated. When TG levels are very high (≥500 mg/dL), TG management to prevent pancreatitis is the primary goal of therapy; only after TG levels are <500 mg/dL should attention turn to lowering LDL-C levels. Use of drugs that increase TG levels and alcohol consumption should be discontinued. Weight loss and increased physical activity are also recommended, as is the use of a fibrate or niacin. In persons with elevated levels of fasting or 2-hour postprandial glucose, antihyperglycemic therapy should be started or adjusted. The ATP III also indicated that omega-3 fatty acids at relatively high doses (3-4 g/d) may be considered as an alternative to fibrates or niacin (34, 50).

To sum up; we can devide lipid lowering therapy into 2 subgroups such as lifestyle modifications and drug therapy.

3.4.1.1. Lifestyle modifications

Weight loss and increased exercise are the cornerstones of TG-lowering therapy. The ATP III guidelines recommend regular physical activity of moderate intensity (4-7 kcal/min). Table 6 lists the types and amounts of exercise that meet the requirements for CHD risk reduction (50).

Table 6. Lists of types and amounts of exercise

Brisk walking (3–4 mph for 30–40 minutes)
Swimming laps for 20 minutes
Bicycling 5 miles in 30 minutes
Volleyball (noncompetitive) for 45 minutes
Raking leaves for 30 minutes
Pushing a powered lawn mower for 30 minutes
Heavy housework (cleaning)
Basketball for 15 to 20 minutes
Golf (pulling a cart or carrying clubs)
Social dancing for 30 minutes

Incorporation of such lifestyle changes may have beneficial metabolic effects that include reduction of insulin resistance, a common physio logic basis for hypertriglyceridemia. There is known to be an association between insulin resistance and CHD. Insulin resistance is associated with increased free fatty acid flux from the

periphery and insulinstimulated lipogenesis, both of which drive hepatic secretion of TG-rich lipoproteins (ie, VLDL-C). Insulin resistance is also characterized by decreased clearance of TG from the circulation. With an increase in insulin sensitivity through weight loss and increased physical activity, these metabolic alterations are improved. To reduce TG levels, the NCEP ATP III recommends dietary modifications that involve consumption of fewer calories, with resultant weight loss, as well as reduced consumption of refined carbohydrates. Dietary guidelines from the American Heart Association recommend eating fish (particularly fatty fish such as mackerel, herring, and salmon) at least twice weekly (34, 50).

Weight loss of 10 lbs can lower LDL-C by 5–8%. Low-fat, low-carbohydrate, plant-based diets may provide an additional 5–10% LDL-C lowering over highcarbohydrate, low-fat diets. Sources of viscous fiber include oats, guar, pectin, and psyllium, with doses of 5 to 10 g lowering LDL-C by 3–5%. The primary dietary sources of plant sterol and stanol esters are fat-rich vegetables, including vegetable oils, fruits, and nuts. Several commercial products incorporate plant stanol and sterols, including margarines, cereals, and fruit juice. Stanol and sterols competitively replace cholesterol in bile salt micelles, resulting in reduced absorption of unesterified cholesterol from the small intestine. In doses ranging from 0.8 to 4.0 g daily, LDL-C concentration can be reduced by 10–15%. A dose of 50 g of isolated soy protein with isoflavones decreases LDL-C concentration on average by about 3%. Use of isoflavone supplements in food or pills is not recommended (52).

3.4.1.2. Drug therapy

The pharmacotherapeutic effects of most widely used TG-lowering agents are summarized in Table 7 (34).

Most commonly used antihyperlipidemic agents will be discussed more detailed below.

Table 7. Pharmacotherapeutic effects of TG-lowering agents

Drug	TC	LDL-C	HDL-C	TG
Statin	↓ 15%–60%	↓ 20%–60%	↑ 3%–15%	↓ 10%–40%
Resin	↓ 20%	↓ 10%–20%	↑ 3%–5%	↑ or neutral
Niacin	↓ 25%	↓ 10%–15%	↑ 15%–35%	↓ 20%–50%
Fibrate	↓ 15%	↓ 0%–15%	↑ 6%–15%	↓ 20%–50%
Fish oil	↑ or neutral	↑ or neutral	↑ or neutral	↓ 20%–50%
Ezetimibe	↓ 12%	↓ 18%	↑ 1%	↓ 8%

TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

3.4.1.2.1. Statins

Statins are widely used to manage hyperlipidemia. (53) Statin therapy is established as the cornerstone of CHD prevention in primary and secondary prevention settings (40).

The most commonly prescribed lipid-modifying therapies are the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, more commonly known as the statins **(53).** Commonly known as statins, 3- hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been shown to be the most successful class of lipid-lowering drugs for reducing risks associated with cardiovascular disease, while having an acceptable risk-benefit ratio (31). Lovastatin was the first of a novel class of therapeutic agents and was shortly followed by simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, and rosuvastatin (54).

Statins exert their LDL-lowering effect primarily through the inhibition of the HMG-CoA-reductase enzyme, which mediates the first committed step in the mevalonate pathway of cholesterol synthesis. To a lesser degree, these agents also decrease triglyceride levels, probably through inhibition of its synthesis in the liver and enhancement of lipoprotein lipase enzyme activity in the adipocytes (30).

Statins lower plasma LDL-C through intracellular cholesterol depletion and upregulation of the expression of LDL receptors in hepatocytes (32).

Statins also have modest HDL-raising properties, which are postulated to result from the activation of peroxisome proliferator-activated receptors, leading to Apo-A1 gene induction. It is also theorized in the publication that lipid-independent effects of statins contribute to some degree to their anti-atherothrombotic properties. A few of these purported pleiotrophic effects in this publication include modulation of inflammatory response, improvement of endothelial function, and inhibition of coagulation (30).

The IC50 (the concentration resulting in 50% inhibition of cholesterol synthesis) values for the inhibition of cholesterol synthesis by various statins are summarized in Table 8. In general, therapeutic doses of statins are in the range of 10 to 80 mg per day; however, cerivastatin may be used in much lower doses (in pg range). (16)

Table 8. IC_{50} Values for various statins in different cell lines

Cell Type	Lovastatin	pravastatin	simvastatin	fluvastatin
mouse lymphocytes	2	1354	3.6	NA
rat hepatocytes	3-146	5-500	3-50	1.7-52
rat spleen cells	3.5-4.5	158	5	62
human Hep G2	24-50	700-2650	345-150	30-43
human skin fibroblasts	4-188	452-9000	2.7-10	8.3

Statins are highly efficacious at lowering LDL-C, although there are differences in the extent of LDL-C lowering at therapeutic doses and in the maximal reduction achieved with each agent (see Table 9). Of the statins currently available, rosuvastatin is the most effective at lowering LDL-C, with reductions of up to 63% reported with a daily dose of 40 mg. Data from comparative trials confirm that on a milligram basis, rosuvastatin is the most efficacious statin for lowering LDL-C, followed by atorvastatin, simvastatin and pravastatin. Pitavastatin (2 mg/day) has been shown to reduce total cholesterol and LDL-C concentrations by 28 and 38%, respectively, and the lipid modifying efficacy of pitavastatin was considered to be similar to that of atorvastatin. Statins also increase HDL-C levels to varying degrees, although a predictable dose–response relationship is not always observed. It is told in an article that in a comparative study in patients with hypercholesterolaemia, rosuvastatin 10–40 mg increased HDL-C by 7.7–9.6%, compared with 2.1–5.7% for atorvastatin 10–80 mg, 5.2–6.8% for simvastatin 10–80 mg, and 3.2–5.6% for pravastatin 10–40 mg (53). Comparative efficacy of different statins on various lipid fractions is given in table 9.

Table 9. Comparative efficacy of different statins on various lipid fractions

	Atorvastatin	Cerivastatin[a]	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin	Pitavastatin
Serum LDL-C reduction (%)[b]	50	28	24	34	34	41	63	48
Serum HDL-C increase (%)[b]	6	10	8	9	12	12	10	-[c]
Serum triglyceride reduction (%)[b]	29	13	10	16	24	18	28	23

[a]Voluntarily withdrawn from clinical use; [b]this effect was elicited in patients with hypercholesterolaemia by a daily dose of 40 mg for atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin and rosuvastatin, 4 mg for pitavastatin and 0.3 mg for cerivastatin [60,73,74]; [c]no significant effect reported.
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

In comparison; it is mentioned in a publication that statin therapy reduced the risks of coronary heart disease (CHD) events for men without prior cardiovascular risk, but not for women in a comparison of sex-stratified primary prevention research. Total mortality was not reduced for either men or women (55).

Evidence to date suggests that treatment with statins is efficacious and well-tolerated and may be used in children at exceptional risk of CHD (42).

The detailed analysis of the efficacy and safety of statins is in part 3.5. Statins

3.4.1.2.2. Ezetimibe

Ezetimibe inhibits the absorption of dietary and biliary cholesterol at the brush border of the small intestine to selectively inhibit the absorption of cholesterol by blocking NPC1L1. Ezetimibe undergoes enterohepatic circulation with minimal systemic exposure. Although ezetimibe is extensively glucuronidated, it does not interact with statin metabolism (52).

3.4.1.2.3. Fibrates and Niacin

Although gemfibrozil has little effect on LDL-C, it has been shown to reduce cardiovascular events in hypertriglyceridemic men with coronary heart disease and low HDL-C and LDL-C levels. Fenofibrate will lower LDL-C by approximately 10%, but its cardiovascular benefits are less clear. Niacin at a dosage of 2 g daily is needed to reduce LDL-C by 15% (52).

3.4.1.2.3.1. Fibrates

Lipid lowering effect of clofibrate was detected, and this drug has been marketed since 1966. Other fibrates have been developed (e.g. fenofibrate, bezafibrate, ciprofibrate and gemfibrozil), also showing this lipid-lowering effect (56).

Fibrates (eg, fenofibrate, gemfibrozil) are agonists of peroxisome proliferator-activator receptors (PPARs), members of the nuclear hormone receptor superfamily of transcription factors involved in the regulation of various metabolic processes. Fibrates activate PPAR-α which leads to increased expression of the enzyme lipoprotein lipase, resulting in increased degradation of TG. PPAR- α induction also results in the inhibition of apo C-III gene transcription. Reduction of the apo C-III content of TG-rich lipoproteins increases the accessibility of these lipoproteins to lipoprotein lipase (34).

Helsinki Heart Study showed that the gemfibrozil treated group had a 43% reduction in TG compared with placebo and a 34% reduction in the incidence of CHD. Additional favorable lipid changes in the gemfibrozil-treated group included an 10% increase in HDL-C, with a decrease in LDL-C of similar magnitude. A subsequent analysis found a 71% reduction in CHD events in a high-risk group with TG levels >203 mg/dL and an LDL-C: HDL-C ratio >5 (57).

In the Coronary Drug Project, patients who had survived MI were randomized to receive either conjugated estrogens, clofibrate, dextrothyroxine sodium, niacin, or placebo. No significant effect was observed for the other active agents compared with placebo. When the data were stratified by serum TG levels, an 11.7% reduction in all cause mortality was observed in patients with baseline TG levels >150 mg/dL who had been treated with niacin compared with placebo. A 9.4% reduction in mortality was observed in niacin-treated patients with TG levels <150 mg/dL compared with placebo (58).

In Bezafibrate Infarction Prevention Study, patients with previous MI or stable angina and high TG levels and/or low HDL-C levels were randomized to receive bezafibrate 400 mg/d or placebo. By study end point, there was no overall difference in cardiovascular events between groups. However, among patients with TG levels ≥ 200 mg/dL, bezafibrate treatment was associated with a 39.5% reduction in the primary end point of fatal or nonfatal MI and sudden death (59).

In the Stockholm Ischaemic Heart Disease Secondary Prevention Study, patients with MI were randomized to receive clofibrate plus niacin or placebo for 5 years. Overall, combined treatment with clofibrate and niacin reduced TG levels by 19% and TC levels by 13%, and was associated with a 26% reduction in total mortality compared with placebo. However, the reduction in mortality with lipid-lowering treatment occurred only in patients with baseline TG levels ≥133 mg/dL (≥1.5 mmol/L). Moreover, mortality was reduced by 60% in the 44% of patients whose TG levels decreased by ≥30% (60).

Clinical outcome studies of the impact of ‘HDL raising’ on vascular events have generated mixed findings (40).

In VA-HIT study, patients with low HDL-C levels and CHD were randomized to receive gemfibrozil 1200 mg/d or placebo and followed for a mean of 5.1 years.

Gemfibrozil treatment was associated with TG levels that were a mean of 31% lower than those with placebo (115 vs 166 mg/dL). HDL-C levels were a mean of 6% higher in gemfibrozil-treated patients compared with those who received placebo (34 vs 32 mg/dL). These lipid changes were accompanied by a 24% reduction in the combined outcome of risk of death from CHD and nonfatal MI or stroke. The greatest benefit of gemfibrozil in terms of CHD risk reduction in this study was seen in patients with the highest insulin levels (61).

However, The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study evaluated the effect of 5 years of fenofibrate therapy (200 mg/d) on the incidence of CHD death or nonfatal MI in patients with diabetes. Patients treated with fenofibrate had an apparent 11% reduction in events compared with placebo, a statistically nonsignificant difference (62).

Fibrates do not have a place in CHD prevention in the general population or in Type 2 diabetics but these agents may have a role in treating patients with elevated plasma triglyceride and low HDL (40).

3.4.1.2.3.2. Niacin

Niacin (also known as vitamin B3, nicotinic acid and vitamin PP) is an organic compound with the formula $C_6H_5NO_2$ and, depending on the definition used, one of the forty to eighty essential human nutrients (27).

Niacin's putative mechanism of action in lowering TG involves inhibition of free fatty acid release from adipose tissue. The reduced mobilization of free fatty acids decreases their delivery to the liver, which, in turn, decreases their hepatic re-esterification and VLDL-C production; the VLDL particles that are secreted are smaller and contain less TG. The TG lowering action of niacin may also occur through direct inhibition of the hepatic synthesis or secretion of lipoproteins containing apo B (non-HDL-C) (34).

Niacin has been reported to lower TG levels by 20% to 35%. Niacin also has been associated with 5% to 25% reductions in LDL-C, 20% to 30% reductions in lipoprotein(a), and 15% to 35% increases in HDL-C (34).

In the Coronary Drug Project, niacin use was associated with a 28% decrease in recurrent nonfatal myocardial infarction (MI) at 6 years (63).

In the High-Density Lipoprotein Atherosclerosis Treatment Study, niacin in conjunction with simvastatin significantly reduced the progression of coronary atherosclerosis compared with placebo (0.7% vs 3.9% stenosis progression, respectively) and promoted the regression of coronary atherosclerosis (0.4% stenosis regression) (65).

In the Arterial Biology for the Investigation of Treatment Effects of Reducing Cholesterol (ARBITER)- 2 and -6 trials, it was found to reduce carotid atherosclerosis when administered in addition to statin therapy and, possibly, gave a benefit that was superior to that achieved with further LDL reduction with ezetimibe (40).

3.4.1.2.4. Bile Acid Sequestrants

Bile acid sequestrants bind bile acids in the intestine, thereby preventing enterohepatic recirculation of cholesterol. Use of the older bile acid sequestrants cholestyramine and colestipol is limited by significant gastrointestinal adverse effects and interference with absorption of a number of other drugs. Colesevelam has greater specificity for bile acids, eliminating most drug interactions and reducing the tendency for constipation. The usual dose of cholestyramine and colestipol of 2 scoops per day, and colesevelam of 6 caps per day, will lower LDL-C by about 15% when used as monotherapy or when added to statins. Higher doses of cholestyramine have been shown to reduce LDL-C by up to 30%. Colesevelam has also been shown to decrease hemoglobin A1c by about 0.5% in patients with diabetes. Trials involving cholestyramine and colestipol alone or in combination with other agents have shown beneficial effects on coronary disease. Although bile acid sequestrants have no systemic absorption, the occasional statin-intolerant patient will nonetheless report myalgias. Colesevelam does not appear to further reduce LDL-C in ezetimibe-treated patients (52).

3.4.1.2.5. Thiazolidinediones

Thiazolidinediones (eg, pioglitazone, rosiglitazone) are insulin-sensitizing agents approved for the treatment of type 2 diabetes. Like fibrates, thiazolidinediones are PPAR agonists, although receptor activation occurs mainly via PPAR-γ, which targets glucose homeostasis, with minor PPAR-α effects (lipid regulation). Although thiazolidinediones are believed to promote fatty acid uptake and storage in adipose

tissue, data are lacking on the mechanism underlying their TG-lowering effect in humans (34).

In the Prospective Pioglitazone Clinical Trial in Macrovascular Events, patients with type 2 diabetes who had evidence of macrovascular disease were randomized to receive oral pioglitazone (starting dose 15 mg/d, titrated to 45 mg/d) or placebo and observed for a mean of 34.5 months. Although results for the primary end point (composite of all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, surgical intervention in coronary or leg arteries, and amputation above the ankle) were not significant, pioglitazone was associated with a significant reduction in risk for the composite secondary end point (all-cause mortality, MI, and stroke) compared with placebo (66).

3.4.1.2.6. LDL Apheresis

Multiple clinical studies demonstrate an average reduction in LDL-C of 60% with LDL apheresis. Clinical outcome trials have confirmed the effectiveness of this therapy. LDL apheresis may be considered medically necessary when patients have failed previous treatment and meet one of the following criteria:

1) homozygous familial hypercholesterolemia (LDL-C>500 mg/dL),

2) functional heterozygous familial hypercholesterolemia with LDL-C≥ 200 mg/dL and documented coronary artery disease,

3) familial hypercholesterolemia with LDL-C≥300 mg/dL (52).

3.4.1.2.7. Red Yeast Rice

Red yeast rice, a dietary supplement, has been used as an alternative to statins. A major component is lovastatin, but plant sterols and isoflavones are also present. The product used in the trial is a unique formulation not sold in the United States and is not identical to other products sold as “red yeast rice.” Because dietary supplements are unregulated in the United States and the lack of consistency between different manufacturers is a major problem, caution should be used in recommending such products at this time (52).

In Turkey, these type of products are also not controlled by Ministry of Health but they are controlled by Ministry of Food, Agriculture and Livestock. So the dietary supplements are also unregulated in Turkey.

3.4.1.2.8. Omega-3 Fatty Acids

The effect of omega-3-acid ethyl esters on the lipid/lipoprotein profile--a decrease in circulating VLDL particles and a shift from dense to more buoyant LDL may be indicative of a less atherogenic profile relative to no treatment with omega-3-acid ethyl esters, as 2 important components of the atherogenic lipid triad--TG levels and small, dense LDL are affected. This potential benefit must be weighed against the high CHD risk associated with a predominance of small LDL particles in plasma (34).

The first prescription formulation of omega-3 fatty acids, omega-3-acid ethyl esters capsules, was approved by the US Food and Drug Administration (FDA) in November 2004 for use as an adjunct to diet to reduce very high (≥500 mg/dL) TG levels (67).

In a 4-month, randomized, double-blind trial treatment with omega-3-acid ethyl esters 4 g/d was associated with a 45% reduction in mean TG levels, compared with no effect with placebo. VLDL-C was reduced by 32%, and HDL-C and LDL-C were increased by 13% and 31%, respectively (68).

In a crossover study, 14 patients with familial combined hyperlipidemia received 8 weeks of either omega-3-acid ethyl esters 4 g/d or placebo. Compared with placebo, treatment with omega-3-acid ethyl esters was associated with a 27% reduction in TG and an 18% reduction in VLDL-C. Although LDL-C increased by 21%, separation of LDL subclasses by rate zonal ultracentrifugation indicated an improvement in LDL-C particle distribution (69).

A 1-year, randomized, double-blind study was conducted in 59 CHD patients with combined hyperlipidemia whose TG levels remained elevated despite treatment with simvastatin alone. Patients receiving omega-3-acid ethyl esters 4 g/d had a sustained 20% to 30% decrease in TG levels compared with placebo or baseline, respectively, as well as a 30% to 40% decrease in VLDL. (70)

3.4.1.2.9. Potential New Therapies

Apolipoprotein B (apoB) antisense agents inhibit messenger RNA to impair translation of apoB- 100. A potential advantage of antisense drugs is their increased specificity for the liver, such as apoB, and several other proteins important in lipid metabolism, such as apoCIII and lipoprotein (a). Mipomersen, a second-generation, antisense agent given subcutaneously approximately once a week, results in LDL-C

reductions of 50% at the highest doses. Another apoB-directed agent in development is the microsomal transfer protein inhibitor lomitapide. Microsomal transfer proteins play an important role in the lipidation of apoB and in the formation of chylomicrons and very low density lipoprotein. Lomitapide has been shown to reduce LDL-C by 35% when used as monotherapy and up to 66% when used in combination with atorvastatin. Adverse hepatic effects appear to include increased transaminase levels and hepatic fat accumulation, as well as decreases in HDL-C. Mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9) protease gene, which prevent the degradation of LDL receptors, are associated with lower lifetime levels of LDL-C. Although development of the cholesterol ester transfer protein (CETP) inhibitor torcetrapib was halted due to excess toxicity attributed to idiosyncratic blood pressure elevation, clinical trials evaluating the CETP inhibitors anacetrapib and dalcetrapib continue. Anacetrapib lowers LDL-C by approximately 15% in addition to raising HDL-C by more than 40% (52).

3.4.2. Treatment of cardiovascular disease in children

Children with familial hypercholesterolaemia have been treated with bile acid binding resins since the 1960s. Later, studies have focused on treatment with statins. All studies suggest that the efficacy and tolerability profiles of short-term statin use in children are similar to those reported in adults. However, all of the studies were underpowered for safety. In a study it was reported that treatment with pravastatin in the LIPIDS-study (long-term influence of pravastatin on intima-media diameter in childrenwith FH) for 2 years retarded progression of atherosclerosis in the carotid artery of children with familial hypercholesterolaemia. Discussion of contraception is imperative when statins are prescribed to girls with familial hypercholesterolaemia who may be sexually active. Small studies using probucol, fibrates and niacin to control dyslipidaemia in children have been performed. No data are available on the long-term efficacy and safety of these drugs for children. Ezetimibe is the first of a new class of cholesterol absorption inhibitors that inhibit dietary and biliary cholesterol absorption at the brush border of the intestine. The drug appears to have a similar safety profile to placebo and was effective and safe in lowering LDL cholesterol levels in children 12 years of age and adults with homozygous familial hypercholesterolaemia. No studies in

children with heterozygous familial hypercholesterolaemia have appeared to the date of mentioned literature (42).

3.5. Statins

3.5.1. Physicochemical Properties of Statins

A compound (ML-236A) from *Penicillium citrinum* with cholesterol-lowering properties in rats was isolated; it was found to inhibit HMG-CoA R. Since then, various other compounds (cholesterol metabolites, bile acids, ketoconazole and statins) had been shown to have inhibitory effects on HMG-CoA R activity (16).

In 1990, Duggan and Vickers defined the pharmacokinetic criteria for an ideal HMG-CoA reductase inhibitor, or statin, as a drug that is well absorbed, reaches the liver unchanged, is completely extracted by the liver, and is eliminated, in its active form, by direct excretion in bile (71).

Lovastatin, pravastatin and simvastatin are fungal derived inhibitors of HMG-CoA reductase, while atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin and rosuvastatin are fully synthetic compounds. The chemical structures of the different statins are shown in Figure 4. These structures can be broadly divided into three parts: an analogue of the target enzyme substrate, HMG-CoA; a complex hydrophobic ring structure that is covalently linked to the substrate analogue and is involved in binding of the statin to the reductase enzyme; side groups on the rings that define the solubility properties of the drugs and therefore many of their pharmacokinetic properties (53).

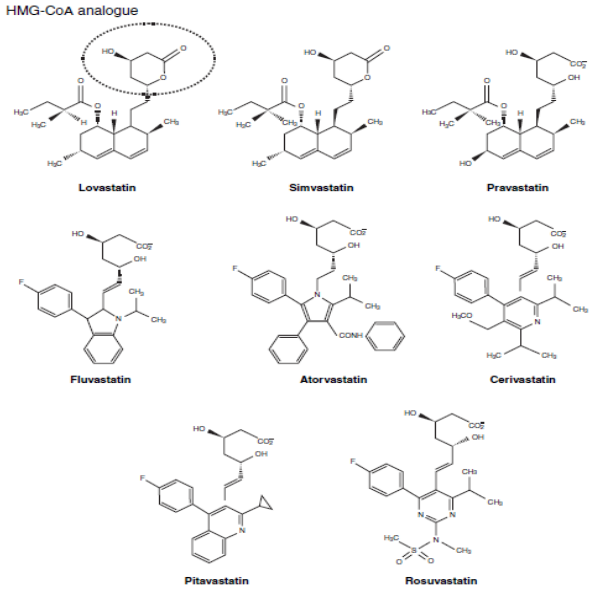


Figure 4. Chemical structures of different statins

Pravastatin, rosuvastatin and to some extent fluvastatin exhibit hydrophilic properties, as opposed to the lipophilicity of the other statin molecules (i.e. atorvastatin, simvastatin and lovastatin) (32).

Pravastatin and rosuvastatin are more hydrophilic as a result of a polar hydroxyl group and methane sulphonamide group, respectively (53).

The physicochemical properties of statins, which determine their bioavailability and thereby affect the risk of myopathy, are summarized in Table 10. Water solubility affects statin permeability through cellular membranes of non-hepatic (including muscular) cells and their ability to cross the blood-brain barrier (32).

Table 10. Physicochemical and pharmacokinetic properties of statins

Characteristic	Lovastastin	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin
Daily dosage (mg)	20–80	10–80	20–80	40–80	10–80	10–40
Origin	Fungi	Semisynthetic	Fungi	Synthetic	Synthetic	Synthetic
Prodrug	Yes	Yes	No	No	No	No
Solubility	Lipophilic	Lipophilic	Hydrophilic	Intermediate	Lipophilic	Hydrophilic
CNS permeation	Yes	Yes	No	No	No	No
Effect of food intake on absorption	Increased absorption	None	Decreased absorption	None	None	None
First-pass metabolism	CYP3A4	CYP3A4	Multiple ways	CYP2C9	CYP3A4	Limited CYP2C9
Protein binding (%)	95	95	50	98	90	90
Half-life (hours)	2–3	2–3	1–2	0.5–2	13–16	19
Hepatic excretion (%)	69	79	46	>68	Not available	63
Renal excretion (%)	30	13	60	<6	<2	10

CYP = cytochrome P450 enzyme.

All statins are competitive inhibitors of HMG-CoA reductase with respect to the binding of the substrate, HMG-CoA, but not for that of the co-enzyme NADPH,

suggesting that their HMG-CoA-like moieties bind to the HMG-CoA-binding portion of the enzyme active site. The structural mechanism for statin inhibition of HMG-CoA reductase has been elucidated by solving crystal structures of the catalytic portion of the enzyme bound to six different statins. The structures revealed that statins act by binding to the active site of the enzyme, sterically preventing the substrate from binding. The substrate-binding pocket of the enzyme also undergoes a rearrangement that enables the rigid, hydrophobic ring structures of the statins to be accommodated. Comparison of the six statin–enzyme complexes revealed subtle differences in their modes of binding. An additional hydrogen bond was demonstrated in the atorvastatin– and rosuvastatin–enzyme complexes along with a polar interaction unique to rosuvastatin, such that rosuvastatin has the most binding interactions with HMG-CoA reductase of all the statins. The full significance of these differences remains to be elucidated, but additional bonding properties of statins to the enzyme may account in part for increased potency (53).

The binding of the statins to the enzyme is reversible. The affinity of HMG-CoA R for statins is in the nanomolar while that for the natural substrate is in the micromolar range. Thus, the affinity of statins for the enzyme is approximately 3 orders of magnitude greater than that of HMG-CoA. Table 10 shows a comparison of the k (the dissociation constant for the inhibitor-enzyme complex) values for various statins (16).

Table 10. K_i (The dissociation constant for the inhibitor- enzyme complex) values for various HMG-CoA Reductase Inhibitors)

Substrate	K_i (M)
Lovastatin	$0.6x10^{-9}$
Pravastatin	$2.3x10^{-9}$
Simvastatin	$0.12x10^{-9}$
Fluvastatin	$0.3X10^{-9}$
Cerivastatin	$1.3X10^{-9}$

3.5.2. Pharmacokinetic Properties of Statins

3.5.2.1. Absorption

All members of this group of lipid-lowering agents are absorbed, to a varying degree, from the gut. It is told that lovastatin, pravastatin and simvastatin are absorbed primarily from the intestine and to a lesser degree from the stomach. Lovastatin and

simvastatin which are inactive pro-drugs are converted into their respective active (B-hydroxyacid) forms in the liver (16). Other statins are administered as the active hydroxy acid. (53)

3.5.2.2. Distribution

Equivalent doses of statins resulted in different distribution of the drug in the liver (via enterohepatic circulation) or peripheral tissues (via systemic circulation). Pravastatin was found in lower concentrations in the liver (about 50%) and in higher concentrations (300-600%) in the peripheral tissues, including kidney, spleen, testis, adrenal glands and non-glandular stomach as compared to lovastatin or simvastatin. Therefore, lipophilic pro-drugs (lovastatin and simvastatin) have greater selectivity for the liver, the major site of cholesterol synthesis (16).

Majority of statins are highly bound to plasma proteins, resulting in minimal systemic exposure of unbound, pharmacologically active drug (see Table 11) (72).

Table 11. Pharmacologic characteristics of statins

Parameter	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Absorption						
Fraction absorbed (%)	30	98	98	30	34	60–80
T_{max} (h)	2–3	2.5	0.5–1	2–4	0.9–1.6	1.3–2.4
C_{max} (ng/mL)	27–66	2	448	10–20	45–55	10–34
Bioavailability (%)	12	60	19–29	5	18	5
Effect of food	↓ 13%	0	↓ 15% to ↑ 25%	↑ 50%	↓ 30%	0
Distribution						
Fraction bound (%)	80–90	>99	>99	>95	43–55	94–98
Lipophilicity, *C* log *P* (octanol/water)	4.06 (1,482)	1.47 (29.51)	3.24 (1738)	4.27 (18,620)	−0.22 (0.60)	4.68 (47,86)
Metabolism						
Hepatic extraction (%)	>70	NA	>68	>70	46–66	78–87
Systemic metabolites	Active	Active	Inactive	Active	Inactive	Active
Clearance (L/h/kg)	0.25	0.20	0.97	0.26–1.1	0.81	0.45
Excretion						
$t_{1/2}$ (h)	15–30	2.1–3.1	0.5–2.3	2.9	1.3–2.8	2–3
Urinary excretion (%)	Negligible	30	6	10	20	13
Fecal excretion (%)	Major route	70	90	83	71	58

Based on a 40 mg oral dose, with the exception of cerivastatin (0.2 mg).
NA, No available data at present; $t_{1/2}$, terminal elimination half-life.

3.5.2.3. Biotransformation

Hepatic cytochrome P450 enzyme (CYP) system is responsible for the metabolism of many drugs, including statins to some extent with the exception of pravastatin. Lovastatin, simvastatin and, to a lesser extent, atorvastatin are metabolized by the CYP3A4 isozyme. Coadministration of the previously mentioned statins with medications or food that either inhibit or are substrates of CYP3A4 decreases the statins' firstpass metabolism, thereby resulting in increased bioavailability (32).

For atorvastatin, the major active metabolites are 2-hydroxy- and 4-hydroxy-atorvastatin acid, while for simvastatin the b-hydroxy acid and its 6'-hydroxy, 6'-hydroxymethyl and 6'-exomethylene derivatives are the major active metabolites. Fluvastatin is mainly metabolized by CYP2C9, and to a much lesser extent by CYP3A4 and CYP2C8, and consequently does not interact with CYP3A4 inhibitors. Pravastatin is metabolized through several pathways, including isomerization, sulfation, glutathione conjugation and oxidation, and only to a small extent (1%) by the CYP enzyme system. Rosuvastatin undergoes minimal metabolism via the CYP2C9 isoenzyme. Lipophilic drugs are known to be much more susceptible to oxidative metabolism by the CYP450 system. Statins metabolized by the CYP450 system are more likely to produce muscle toxicity because of the risk of drug interactions with many drugs that inhibit CYP450, notably the CYP3A4 isoform; drug interactions may increase plasma levels of statins, with a consequent increased risk of toxic effects (53).

The systematic bioavailability of statins is quite. All statins present a high affinity with blood proteins (95%), except pravastatin (approximately 50%). Atorvastatin and rosuvastatin are the two statins with longer half-lives (13–16 hours) and this property is most probably linked to their higher lipid-lowering efficacy (32).

3.5.2.4. Elimination

Predominant route of elimination for the majority of statins is via the bile after metabolism by the liver (53). Fluvastatin it is the only statin with a significant renal excretion (approximately 60% of the absorbed quantity), in keeping with its hydrophilic nature. Rosuvastatin is 90% eliminated as the parent compound in the faeces (32).

3.6. Mechanism of action of statins

HMG-CoA reductase catalyses the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol synthesis. Competitive inhibition of this enzyme by the statins decreases hepatocyte cholesterol synthesis (See figure 1). Associated reduction in intracellular cholesterol concentration induces LDL-receptor expression on the hepatocyte cell surface, which results in increased extraction of LDL-C from the blood and decreased circulating LDL-C concentrations. Statins also has been thought to have beneficial effects on other lipid parameters, including increases in high-density lipoprotein cholesterol (HDL-C) concentration and decreases in triglyceride

concentration. Statins also raise HDL-C by 5 to 15%, possibly by activating peroxisome proliferator-activated receptor α (PPAR-α), and lower triglycerides by 7 to 30%. Research has shown that the activation of PPAR-α induces apolipoprotein (apo) A-I, the major apolipoprotein of HDL. This appears to be a downstream effect of HMG-CoA reductase inhibition (39).

Secondary mechanisms by which statins may reduce levels of atherogenic lipoproteins include inhibition of hepatic synthesis of apolipoprotein B100 and a reduction in the synthesis and secretion of triglyceride-rich lipoproteins. In addition, statins may exert beneficial cardiovascular effects independent of their lipid-modifying properties. These pleiotropic properties may be explained by inhibition of synthesis of nonsteroidal isoprenoid compounds, which are also produced from mevalonic acid (Figure 1), and include improvement of endothelial cell function, modification of inflammatory responses, and reduction of smooth muscle cell proliferation and cholesterol accumulation. As it is mentioned in a publication, large-scale clinical trials have demonstrated that the statins substantially reduce cardiovascular-related morbidity and mortality in patients with and without existing CHD. Statins have also been shown to slow the progression or even promote regression of coronary atherosclerosis, resulting in fewer new lesions and total occlusions compared with untreated hypercholesterolaemic patients. This has been suggested to be a consequence of the shrinkage of the lipid core of the atherosclerotic plaque, avoiding plaque rupture that would otherwise trigger intramural haemorrhage and intraluminal thrombosis (53).

3.7. Efficacy of statins

3.7.1. Clinical Trials According to the End Points

Large number of clinical trials have now been conducted to show that statins are safe and efficacious, not only in lowering LDL, but in preventing vascular disease in those who are asymptomatic and in those who have had a vascular event (See Figure 5) (40).

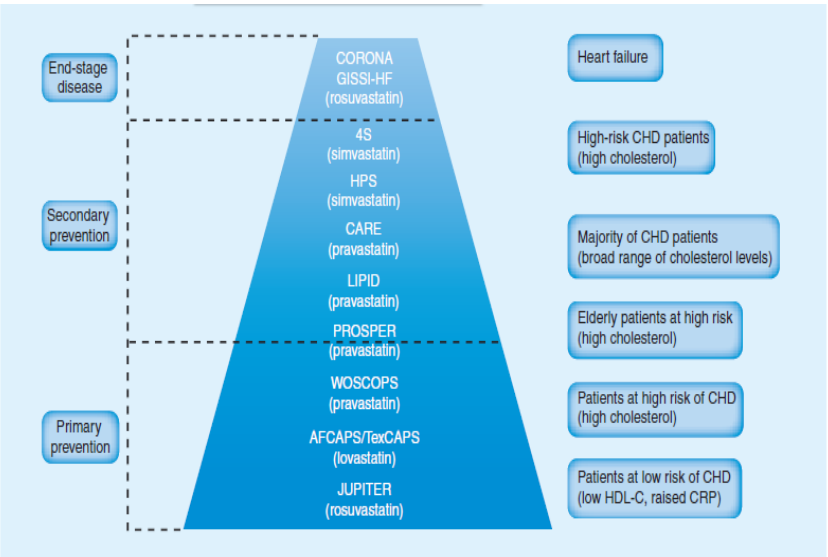


Figure 5. Placebo controlled trials of statin treatment

3.7.1.1. Primary Prevention Studies Performed with Statins

Primary prevention West of Scotland Coronary Prevention Study (WOSCOPS) found that over 4.9 years of follow-up, there was a highly significant relative risk reduction of 31% in nonfatal MI or CHD death, the primary combined endpoint. Other clinical benefits included significant reductions in nonfatal MI (31%) and coronary revascularizations (37%). A 22% decrease in overall mortality just missed statistical significance. In this trial, statin therapy lowered TC, LDL-C, and triglycerides by 20, 26, and 12%, respectively, and increased HDL-C by 5% (73).

According to primary prevention Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/Tex- CAPS) lovastatin 20 to 40 mg/day versus placebo produced a highly significant 37% reduction in the combined primary endpoint of fatal or nonfatal MI, unstable angina, or sudden cardiac death. There were also significant reductions in fatal or nonfatal MI (40%), unstable angina (32%), and coronary revascularizations (33%). At Year 1, LDL-C levels had decreased by 25%, to an average of 115 mg/dl, and there were reductions of 18 and 15% in TC and triglycerides, respectively; HDL-C levels had risen by 6%. (74).

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) found that treatment with the agent rosuvastatin led to a 54% reduction in MI and 20% mortality reduction in this group of low-risk

individuals. Lipid-lowering guidelines published before the completion of the JUPITER trial recommend that for primary prevention of CHD in low-risk patients, statin therapy should be started if LDL is above 190 mg/dL, and is only optional if LDL is 160 mg/dL. Pharmacologic treatment is otherwise not advocated for healthy individuals with LDL, 160 mg/dL, unless two or more CVD risk factors are present (50, 75).

In Collaborative Atorvastatin Diabetes Study (CARDS) over 2,800 diabetic patients with average cholesterol levels and without preexisting CVD, treatment with atorvastatin led to reductions in CHD events by 36%, stroke by 48%, and mortality by 27% (76).

In patients with elevated cholesterol levels but without prior history of MI or stroke, the benefit of treatment with statins in the primary prevention of CHD was also assessed by the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trial. With an aggregate sample size of over 14,500 people, in both studies it was demonstrated that pravastatin was associated with reductions in MI (48% in MEGA) and mortality (28% in MEGA) after 5 years of follow-up (77).

3.7.1.2. Secondary Prevention Studies Performed with Statins

3.7.1.2.1. Statins in the secondary prevention of CHD

Scandinavian Simvastatin Survival Study (4S) was the first large clinical trial to demonstrate such benefit (30). The 4S found that simvastatin 10 to 40 mg/day significantly reduced the relative risk for total mortality by 30%. The incidence of major coronary events (coronary death, acute MI, or cardiac arrest), the secondary endpoint, was significantly reduced by 34%. Other benefits included significant decreases in coronary death (42%) and coronary revascularizations (37%). In this trial, simvastatin reduced TC, LDL-C, and triglyceride concentrations by 25, 35, and 10%, respectively, while HDL-C level increased by 8% (78).

In Cholesterol and Recurrent Events (CARE) trial, pravastatin 40 mg/day reduced the risk for CHD death or nonfatal MI, the primary endpoint, with average cholesterol levels and prior acute MI. Compared with placebo, pravastatin significantly reduced the incidence of a primary endpoint event by 24%. In addition, there were significant reductions of 23% in nonfatal MI, 25% in fatal or nonfatal MI, and 27% in coronary revascularizations. A 37% decrease in the incidence of fatal MI was not

statistically significant. Pravastatin reduced TC levels by 20%, LDL-C levels by 28%, and triglyceride levels by 14%, while HDC-C levels rose by 5% (79).

The mortality benefit of statin therapy was unclear in the CARE trial, but this was definitively established by the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study of patients with unstable CHD. In this trial, pravastatin lowered the overall mortality by 14% and cardiovascular mortality by 24%, along with a 29% reduction in MI. The survival advantage of statin therapy was consistent, irrespective of baseline cholesterol level, as illustrated by the Heart Protection Study in high-risk patients with CVD. In this trial, simvastatin was associated with significant reductions in all-cause mortality by 13% and in cardiovascular mortality by 18%, across a wide range of initial LDL levels. High-dose statin therapy is associated with significantly greater reduction in the rate of progression of atherosclerosis compared to a moderate-intensity regimen in patients with CHD and elevated LDL (80).

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) included a follow-up arm that evaluated the effect of lipid lowering therapy (LLT) in patients with well-controlled hypertension, a subgroup underrepresented in earlier clinical trials. After 6 years of therapy, calculated LDL-C levels decreased by 30.1% with pravastatin and by 16.2% with usual care- a differential of 13.9% (mean LDL-C difference of 17.2 mg/dl). This contrasts markedly with the large statin trials, in which the placebo-controlled groups experienced little or no cholesterol reduction. After 6 years of follow-up, pravastatin produced nonsignificant reductions of 1% in total mortality, the primary endpoint, and 9% in CHD death plus nonfatal MI, a secondary endpoint. For the secondary endpoint of cause-specific mortality, there was a nonsignificant decrease of 1% in CHD death. The investigators conclude that the nonsignificant reduction in fatal and nonfatal coronary events is understandable given the modest differential in LDL-C levels between the pravastatin and control groups. This is likely the result of having patients under usual care as controls, almost one third of whom began taking lipid-lowering therapy at some time during the trial. By the study's end, 26% of subjects under usual care were taking a statin. Moreover, medication adherence had declined to 77% in the pravastatin group. Applying the estimation technique described in the HPS, it appears that the ALLHAT-LLT intention-to-treat analysis was based on approximately half of pravastatin-allocated patients

actually taking the study medication (i.e., 77 minus 26%). This trial was estimated to provide 84% power to detect a 20% reduction in mortality, of which CHD death was a component. The ALLHAT-LLT results support the need for statin therapy sufficient to produce adequate reductions in LDL-C levels and, consequently, coronary risk (81).

Incorporation of serial arterial wall imaging in clinical trials has been employed to evaluate the impact of statin therapy on the natural history of progression of atherosclerosis. Meta-analyses of studies using either quantitative coronary angiography or carotid intima-media thickness (IMT) demonstrated a direct relationship between the degree of LDL-C lowering and ability to slow disease progression. This benefit has been demonstrated in patients who would not typically meet criteria for use of statin therapy. The Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) study demonstrated that 40 mg/d of rosuvastatin was associated with halting of IMT progression in low-risk patients with modest hypercholesterolemia and evidence of some early thickening within the carotid artery wall (90th to 95th percentile) (82).

3.7.1.2.2. Statins in the secondary prevention of cerebrovascular disease

Statin treatment was associated with a 27% reduction in stroke in high-risk patients enrolled in the ASCOT-LLA primary prevention study. Among low risk patients, on the other hand, statin therapy was associated with a 51% reduction in ischemic stroke in the JUPITER primary prevention trial. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial found that treatment with high-dose atorvastatin was associated with significant reductions in the incidence of recurrent stroke by 16% and CVD events by 20%. In a large registry of patients with ischemic stroke, pretreatment with statins was associated with a 40% reduction in the odds of poor outcome after stroke in Whites. The same effect, however, was not demonstrated in Blacks. In elderly individuals with CVD, statin therapy reduced the incidence of TIA by 25% in the PROSPER trial, although the overall stroke risk was unaffected. TNT trial demonstrated a 25% reduction in fatal and nonfatal strokes in CHD patients treated with high-dose compared to low-dose atorvastatin. Also, in patients with ACS, a substudy of the MIRACL trial found that short-term treatment with atorvastatin was associated with a significant 50% reduction in fatal and nonfatal strokes (30).

3.7.1.2.3. Statins in the secondary prevention of heart failure

In patients with preexisting HF, statin therapy was also linked to a 19% reduction in mortality. A substudy of the Treating to New Targets (TNT) trial which enrolled patients with stable CHD demonstrated that high-dose statin therapy (atorvastatin 80 mg daily) resulted in a 26% risk reduction in hospitalization for HF compared to low-dose atorvastatin (10 mg daily). This effect was even more prominent (41% risk reduction) in people who had history of HF. In patients with known CHD and ischemic HF, analysis of data from the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) showed that those who used statin 90% of the time had a 35% lower incidence of ventricular arrhythmias or cardiac death compared to participants who took statins less often. In patients with nonischemic cardiomyopathy, on the other hand, a substudy of the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial found a 22% decrease in appropriate defibrillator shocks and an 84% reduction in arrhythmic sudden death in participants treated with a statin. However, large, prospective, randomized trials failed to corroborate these findings. For instance, in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study, patients with ischemic HF, found no significant beneficial effect of statin treatment with rosuvastatin on risk reduction of CVD events. Likewise, rosuvastatin treatment had a similar influence as placebo in terms of CVD outcomes in over 4,500 patients with ischemic and non-ischemic HF enrolled in the GISSI-HF trial. In this context, statin therapy should be utilized in patients with HF if there are any comorbid conditions requiring its use (30).

3.7.1.2.4. Statins and peripheral vascular disease

Heart Protection Study provided one of the earliest reliable data sets for the beneficial effects of statin therapy in PVD. In 6,700 patients with known PVD enrolled in the trial, statin therapy using simvastatin was found to be associated with a 22% reduction in CVD events and a 20% decrease in noncoronary revascularization, effects which appeared to be independent of baseline cholesterol levels. Small, non-randomized studies also showed that statin use in patients with PVD was linked to significant improvements in walk performance and overall leg function. Pleitrophic effects of statins have been postulated to be responsible for these effects, as the findings appeared to be independent of cholesterol-lowering. Randomized trials in which a small number

of patients with PVD and intermittent claudication were enrolled also demonstrated improvements in overall walking performance, anklebrachial pressure indexes, and symptoms of claudication with statin therapy. Short-term (6 months) treatment with statins, on average, increased pain-free walking distance by 90 meters and symptom-free exercise time by nearly 1 minute. Since this condition is considered a CHD-equivalent, existing guidelines recommend the use of statin therapy to prevent CVD events in all patients with PVD to achieve a target LDL, 100 mg/dL, or lower (70 mg/dL) in those with lower extremity PVD at very high risk for ischemic events. The role of lipid-lowering therapies for treatment of claudication symptoms, however, has yet to be established (30).

3.7.1.2.5. Use of statins in diabetes mellitus

the possibility of a beneficial effect of statins on CVD events in patients with diabetes. Meta-analysis of the LIPID, CARE, and 4S trials found that in diabetic patients, statin therapy was associated with a 28% reduction in coronary events and a 32% reduction in stroke, across a wide range of baseline cholesterol levels. The protection from CVD events seen with statins was greater for patients with diabetes than the non-diabetics. The Heart Protection Study provided the first direct evidence that statin therapy produces reductions in CVD events among people with diabetes. It was found that patients with known diabetes, treatment with simvastatin was associated with a 22% reduction in coronary events and strokes, irrespective of comorbid CVD conditions and baseline LDL levels. The effectiveness of statin therapy in the primary prevention of CVD in patients with diabetes was subsequently established by the Collaborative Atorvastatin Diabetes Study (CARDS). In this trial of over 2,800 diabetic patients with average cholesterol levels and without preexisting CVD, treatment with atorvastatin led to reductions in CHD events by 36%, stroke by 48%, and mortality by 27% (30).

3.7.1.2.6. Statins and chronic kidney disease

In the CARE trial with concomitant mild renal dysfunction, statin therapy using pravastatin was associated with a 28% reduction in coronary events. In a similar subset of patients in the 4S trial, simvastatin treatment was associated with decreases in CHD events by 33% and in mortality by 31%. Statin therapy did not appear to reduce the incidence of stroke in these studies of patients with mild CKD. Patients with moderate

CKD were shown to have nearly 50% higher risk of CVD events compared to those with normal renal function or mild CKD. In a subgroup analysis of the MEGA study, reduction in the incidences of CHD by 48%, stroke by 73%, and mortality by 51% were seen with pravastatin therapy in patients with moderate CKD. The prospective German Diabetes and Dialysis Study (GDDS) after 4 years of follow-up, no beneficial effect on CVD events or mortality was seen with atorvastatin therapy. Although statin therapy led to a modest 18% reduction in combined cardiac events, this was, however, negated by a 2-fold increase in the incidence of fatal stroke. In AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial, where rosuvastatin treatment showed no significant influence in terms of CHD, stroke, or mortality risk reduction in patients undergoing dialysis, despite a 43% lowering in LDL, it is thought that the initiation of lipid-lowering therapy in patients who already have end-stage renal disease may be too late to translate into consistent improvement of outcomes. The National Kidney Foundation guidelines classify all stages of CKD as CHD-equivalent, and recommend that all patients with CKD be treated to a target LDL, 100 mg/dL. Statin is the initial preferred agent if baseline LDL is above 130 mg/dL or in patients with Stage 5 CKD (kidney failure or clinical indication for dialysis or transplantation) (30).

3.7.2. Clinical Trials according to the dosage of statin

3.7.2.1. Trials performed to evaulate LDL cholesterol and risk reduction

The Atorvastatin versus Simvastatin on Atherosclerosis Progression in familial hypercholesterolemia (ASAP) and Arterial Biology for the Investigation of the Treatment effects of Reducing cholesterol (ARBITER) trials demonstrated the regression of carotid IMT in association with high-dose statin therapy in patients with familial hypercholesterolemia and dyslipidemia, respectively. Intravascular ultrasound (IVUS) has demonstrated a similar benefit of high-dose statin therapy on progression of coronary atherosclerosis. The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study directly compared the impact of 80 mg/d of atorvastatin or 40 mg/d of pravastatin on atheroma progression in 502 patients with angiographic coronary artery disease. Disease progression was observed in the moderately treated patients (on-treatment LDL-C of 110 mg/dL), whereas no change in atheroma burden was demonstrated in the intensively treated patients (LDL-C of 79 mg/dL). The benefit

of high-dose statin therapy was extended in A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound- Derived Coronary Atheroma Burden (ASTEROID), in which 40 mg/d of rosuvastatin for 24 months was associated with lowering of LDL-C to 60.8 mg/dL, raising of high-density lipoprotein cholesterol (HDL-C) by 14.7%, and unequivocal regression of coronary atherosclerosis. In patients with acute coronary syndrome (ACS), the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study showed that statin therapy using high-dose atorvastatin significantly lowered early recurrent ischemic events by 24% (30).

Pooled analysis of IVUS trials similarly demonstrates a direct relationship between lowering of LDL-C and disease progression. In the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study a 4% absolute reduction or a relative 17% reduction in cardiovascular events was observed in the intensively treated patients. The Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study investigated survivors of myocardial infarction. They were treated with either 80 mg/d of atorvastatin or 20 mg/d of simvastatin, with evidence of a 1.2% absolute reduction in nonfatal myocardial infarction or relative 17% reduction in patients treated with high-dose atorvastatin. Different doses of atorvastatin (80 mg vs 10 mg) were compared in patients with coronary heart disease and a LDL-C less than 130 mg/dL in the Treating to New Targets (TNT) trials. Achieving a lower LDL-C (77 mg/dL vs 100 mg/dL) was associated with a 2.2% absolute reduction or 22% relative reduction) in cardiovascular events in the highdose group. Intensity of LDL-C lowering has also been extensively investigated in patients with acute coronary syndromes. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy– Thrombolysis in Myocardial Infarction (PROVE ITTIMI 22) study, patients with an acute coronary syndrome were treated with either 80 mg/d of atorvastatin or 40 mg/d of pravastatin. A 2.3% absolute reduction or 16% relative reduction in cardiovascular events was observed in the atorvastatin-treated patients. Similarly, achieving a lower LDL-C (63 mg/dL vs 77 mg/dL) in patients treated with increasing doses of simvastatin (from 40 mg to 80 mg) in phase Z of the A to Z trial was associated with a 1.3% absolute risk reduction or 25% relative risk reduction in cardiovascular death. These findings

supported the use of high-dose statin therapy early in the setting of patients with acute ischemic syndromes (83).

According to an analysis performed by Cholesterol Treatment Trialists' (CTT) Collaboration in 2010 which analyses efficacy and safety of more intensive statin treatment, it was reported that the previous CTT meta-analysis of individual participant data from randomised trials showed that lowering of LDL cholesterol by about 1 mmol/L with standard statin regimens safely reduced the 5-year incidence of major coronary events, revascularisations, and ischaemic strokes by about a fifth. In the GISSI-HF trial of rosuvastatin versus placebo in patients with heart failure (which was included in this meta-analysis), as well as in the similar CORONA trial (which was not), most cardiac deaths were non-occlusive and there were no significant reductions in cardiac mortality. Nor were there significant reductions in cardiac mortality in the two statin trials among patients with renal disease, in which only about half of cardiac deaths were definitely due to coronary disease. By contrast, since most of the cardiac deaths that were coded as non-coronary in this meta-analysis occurred in patients with pre-existing coronary disease, some are likely to have been due to coronary occlusion (and, hence, reduced by statin therapy). These findings suggest that the absolute reduction in cardiac mortality produced by lowering of LDL cholesterol with statin therapy in a given population depends chiefly on the absolute risk of death due to coronary occlusion (84).

3.7.2.2. Trials performed to evaulate HDL cholesterol and risk reduction

Studies that have employed arterial wall imaging have demonstrated that intensive lowering of LDL-C slows progression of coronary atherosclerosis. In ASTEROID, the combination of very low levels of LDL-C (60.8 mg/dL) and raising HDL-C by 14.7% to 49 mg/dL was associated with coronary atheroma regression. A subsequent pooled analysis of four studies that employed IVUS demonstrated that raising HDL-C by an average of 7.5% was an independent predictor of slowing disease progression in statin-treated patients with coronary artery disease. The combination of raising HDL-C in addition to intensive LDL-C lowering resulted in the greatest likelihood of patients undergoing regression of coronary disease (83).

3.8. Safety of Statins

3.8.1. General terms and approval of statins

3.8.1.1. General terms

Safety and tolerability of pharmaceutical agents is thought perhaps as the most important consideration in their clinical use (*primum non nocere*, *or* "First, do no harm") (15).

Pharmaceutical manufacturers design and conduct large scale clinical development programs to examine both the effectiveness and the safety of new products. However, quite often, the efficacy and safety profiles and, therefore the benefit-risk profile of a drug, continue to be defined in the months and years following approval (85).

For a New Drug Application (NDA), the FDA generally recommends that approximately 3,000 patients be studied to expose an adverse event with an incidence rate of 1:1,000 with 95% confidence intervals. Therefore, rare events (eg, statin related myopathy) may not be well characterized, and very rare events (eg, statin-related rhabdomyolysis) may not occur in the patient population studied for approval (86).

In Turkey, Ministry of Health Turkish Pharmacovigilance Center (TUFAM) evaluates the risk-benefit ratio of drugs and publishes relevant warnings about drugs as mentioned in part 1. Introduction.

According to the circulation published by American Heart Association, after the withdrawal of cerivastatin, it is estimated that >200 000 patients with dyslipidemia discontinued statin therapy (87).

3.8.1.2. Approval histories of cerivastatin and rosuvastatin

3.8.1.2.1. Cerivastatin approval history

Cerivastatin approval process and postmarketing data is an excellent case study illustrating how rare, potentially serious adverse events can be missed in the approval process. The sequence of events with cerivastatin begins in June 1997, when the 0.2-mg and 0.3-mg doses were approved and the risk of rhabdomyolysis was added as a warning to the approved label in July. In August 1998 a supplemental NDA was submitted requesting approval of a 0.4-mg dose, and soon after the first case of a cerivastatin and gemfibrozil interaction associated with rhabdomyolysis was published.

A change was made to the 0.4-mg dose NDA in May 1999, adding a warning regarding concomitant use with gemfibrozil. The NDA for the 0.8-mg dose was submitted in September 1999, followed by a letter to practitioners in December warning of the contraindication for using gemfibrozil with cerivastatin. As with cerivastatin, sponsors often request approval of the lowest doses initially, and supplemental NDAs are submitted afterward to request approval of higher doses. Often the higher doses are studied in fewer patients. Of note, an increased risk of myopathy in thin, elderly women given the 0.8-mg dose was recognized and reported by an FDA medical reviewer but, in the final analysis, this was not considered significant enough to prevent approval. Cerivastatin was voluntarily withdrawn from the market in August 2001 by Bayer, Inc. because of a significantly higher rate of rhabdomyolysis than was observed with other statins. (86) The withdrawal history of cerivastatin is summarised in table 12.

Table 12. Withdrawal history of cerivastatin from the market

Date	Event
June 1997	NDA approved for cerivastatin 0.2 mg and 0.3 mg
July 1998	Label update: rhabdomyolysis added to warnings
August 1998	Supplemental NDA for cerivastatin 0.4 mg submitted
April 1999	First published case report of rhabdomyolysis with cerivastatin–gemfibrozil coprescription
May 1999	Supplemental NDA for cerivastatin 0.4 mg approved; label update: additional gemfibrozil warnings
September 1999	Supplemental NDA for cerivastatin 0.8 mg submitted
December 1999	Label update: gemfibrozil coprescription contraindication
July 6, 2000	FDA medical review of cerivastatin 0.8 mg supplement identified thin, elderly women at increased risk of CK elevation to >10 × ULN
July 11, 2000	Supplemental NDA for cerivastatin 0.8 mg approved
April 2001	Label update: cerivastatin starting dose should be 0.4 mg
August 2001	Cerivastatin withdrawn form US market

CK = creatine kinase; FDA = US Food and Drug Administration; NDA = New Drug Application; ULN = upper limit of normal.

3.8.1.2.2. Rosuvastatin approval history

Initial rosuvastatin NDA was submitted in June 2001 after the withdrawal of cerivastatin. The cerivastatin experience significantly increased the initial awareness of safety issues for all of the statins and rosuvastatin's NDA contained data on 3,903 patients. The FDA ultimately denied approval of the 80-mg dose because the lipid-lowering benefits were outweighed by the increased risks for renal toxicity and myotoxicity. With the denial, the FDA also requested more safety data on rosuvastatin 20 mg and 40 mg, because the initial NDA was heavily weighted toward the 10-mg and 80-mg doses. As a result, additional studies were completed, and 12,569 patients were

included in the revised NDA for rosuvastatin submitted in February 2003. Approximately 4,000 patients were treated with the 40-mg dose alone, a greater number of patients than for all doses of any other statin NDA. The rosuvastatin NDA provided a database of approximately 4 times the number of patients of any previous statin NDA, allowing for significantly beter characterization of adverse events. However, 1 year after approval of rosuvastatin in March 2004, a Public Citizen petition was submitted to the FDA requesting removal of rosuvastatin from the market. The petition was subsequently rejected by the FDA in March 2005, primarily because of the extensive database provided in the NDA. However, the FDA did recommend additional collection of postmarketing pharmacoepidemiologic data on rosuvastatin. In addition to the large number of patients in the rosuvastatin database, the additional patients more accurately reflected the population treated with statins. The mean age was 58 years, with >33% of these patients >65 years of age- much older than patients evaluated in other statin NDAs. Approximately 50% of the patients had renal impairment defined by their glomerular filtration rate using the Cockcroff-Gault equation. The patients had significant comorbidities, including hypertension (51%), cardiovascular disease (36%), and diabetes mellitus (16%). Drug exposure data were also greater in the rosuvastatin NDA, because 4,000 patients received the 40-mg dose for ≥1 year and 1,100 patients received it for 2 years (86).

3.8.2. Adverse Effects Related to Statins

Statins are the most widely used drugs in many countries (88). Accumulating evidence from controlled trials and clinical experience demonstrates that statins are well tolerated medicines with a good safety profile (32).

The most important adverse effects are associated with muscle and liver toxicity. However, with increased use and dose of statins and their over-the-counter availability in some countries more cases of other rare side effects may be seen in clinical practice (88).

So, we can categorize statin related adverse effects into 2 groups; 1. Most common adverse effects related to statins and 2. Other adverse effects related to statins.

3.8.2.1. Most common Adverse Effects Related to Statins

As it was specified in many authors, the most important adverse effects are associated with muscle and liver toxicity. So in this part, I will focus mainly on these 2 side effects.

3.8.2.1.1. Muscle Adverse Effects

Muscle symptoms (i.e. pain, soreness, weakness, and/or cramps) or signs (CK elevations) are among the most prevalent and important adverse effects associated with statin therapy (89).

Statins confer a small but definite risk of myopathy, a dose-dependent adverse effect associated with all statins (class effect). Muscular adverse effects are usually mild and reversible; however, these adverse effects may be a prelude to rhabdomyolysis, a very rare but potentially serious and even life-threatening clinical condition (32).

In addition according to The National Lipid Association's (NLA) Muscle Safety Expert Panel which was composed of a clinical cardiologist, an exercise physiologist and skeletal muscle expert and an expert in preventive cardiology believes that muscle adverse events are a class effect as demonstrated by the observation that muscle toxicity has been reported with all of the currently available statins as well as with cerivastatin, which was withdrawn from the US market in August 2003. The Panel could find no direct evidence relating intramuscular statin concentrations to myopathy, even though most experts consider intramuscular statin levels critical to the myopathic process. The Muscle Expert Panel also believes that a CK elevation, even in the absence of other symptoms such as myalgia or weakness, does represent muscle damage (90).

There has been significant inconsistency in the terminology used to describe muscle-related side effects. In an attempt to bridge these inconsistencies, the American College of Cardiology Cardiology/ American Heart Association/National Heart, Lung, and Blood Institute (ACC/AHA/NHLBI) came up with the definitions presented in Table 13 (1).

Table 13. Definitions of muscle-related side effects of statins

Condition	Definition
Myopathy	A general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life
Myalgia	Muscle ache or weakness without CK elevation
Myositis	Muscle symptoms with increased CK levels
Rhabdomyolysis	Muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal) and with creatinine elevation (usually with brown urine and urinary myoglobin)

CK: creatine kinase.

The American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute have defined 4 syndromes related to the use of statin drugs. They include (1) statin myopathy- any muscle complaints related to statin drug use; (2) myalgia- muscle complaints without serum creatine kinase (CK) level elevations; (3) myositis- muscle symptoms with CK level elevations; and (4) rhabdomyolysis- CK levels >10-times the upper level of normal (ULN) with elevated CK levels associated with creatinine level elevation (pigment-induced nephropathy). Statin-induced myopathy is a continuum from nonspecific myalgias to rhabdomyolysis. Myalgias are defined by a constellation of symptoms, including muscle pain and tenderness. The CK level may be normal or mildly elevated. There are no accepted standard CK level elevations to establish the diagnosis of clinically important myositis or rhabdomyolysis. Clinically important myositis has been defined in most studies as muscle pain with CK levels >10-times the ULN (72). The levels of CK elevations are summarized in table 14.

Table 14. Levels of creatine kinase elevations

Level	Definition
Mild CK elevation	<10x ULN*
Moderate CK elevation	10x < ULN < 50x
Marked CK elevation	≥50x ULN

Rhabdomyolysis, in its most severe forms, leads to myoglobinuria with resulting acute renal failure and death (72).

For the detailed definitions and reasons of rhabdomyloysis see part 3.9. Rhabdomyolysis.

Epidemiologic data

The incidence of statin-induced myopathy is significantly lower in randomized controlled trials of statin efficacy than in observational studies of real-world patients **(91).**

Complaints of muscle symptoms occur in 1.5–3.0% of clinical trial participants, while rates widely range between 0.3% and 33% in routine practice (32).

In these trials disease events are unlikely to have been missed as participants were followed closely. However, some patient groups prone to statin-induced myopathy have either been excluded from these trials, such as those with elevated creatine kinase (CK) levels, or have been underrepresented, such as patients above 75 years and those with renal, and most notably, hepatic insufficiency. In addition, in some studies, such as the most recent stroke prevention by aggressive reduction in cholesterol levels (SPARCL) study, subjects were allowed to take statins if indicated. This non-trial statin "drop-in" may have diluted the apparent risk. Consequently, these trials may underestimate the incidence when statins are used in large unselected populations followed with less precision. In addition, these trials provide limited data regarding higher doses of statins. On the other hand data from voluntary notifications to regulatory authorities of adverse events, although having the advantage of recording information from a very large pool, are plagued by under-reporting. It is universally recognized that the occurrence of muscle-related symptoms less severe than rhabdomyolysis is under-reported, as complaints like minor muscle aches following exercise are frequently dismissed; the incidence of those may be at the range of 5% or even more. Therefore, it is difficult to estimate accurately the incidence of statin-induced myopathy (1).

3.8.2.1.1.1. Epidemiologic data from clinical trials

Myotoxicity appeared to be an extremely rare adverse effect of statin therapy in the large clinical trials undertaken to assess the efficacy of the first generation HMG-CoA reductase inhibitors. See Table 15. The Prospective Pravastatin Pooling Project, which analyzed 112,000 patient years of pravastatin exposure from the Cholesterol and

Recurrent Events (CARE), Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID), and West of Scotland Coronary Prevention Study (WOSCOPS) trials, shows no increased rate of myositis or rhabdomyolysis with statin therapy. In the Scandinavian Simvastatin Survival Study (4S) trial, in which 4444 patients were given simvastatin or placebo, there were 6 cases (0.14%) of mild myositis and 1 case of nonfatal rhabdomyolysis. The Air Force/ Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS) examined lovastatin treatment in 6605 patients. This study showed no difference in the incidence of myopathy between treatment and control groups. With the pooling of the data of these clinical trials involving first-generation statin drugs, muscle associated adverse effects are extremely uncommon and occur at the same rate in both the statin and control groups (72).

Table 15. Toxic effects on muscle in major statin trials

	Myositis*		Rhabdomyolysis	
No. (%)	**Statin**	**Control**	**Statin**	**Control**
Pravastatin Pooling Project (CARE, LIPID, WOSCOPS) (n = 19,952)	3 (0.02)	7 (0.04)	0	0
4S (n = 4444)	6 (0.14)	1 (0.02)	1 (0.02)	0
AFCAPS/TEXCAPS (n = 6605)	21 (0.32)	21 (0.32)	1 (0.02)	2 (0.03)
MIRACL Study (n = 3086)	0	0	0	0
Total (n = 34,087)	30 (0.09)	29 (0.09)	2 (0.01)	2 (0.01)

In a large population-based study conducted in the United Kingdom, there were four cases of myopathy in a general population cohort of patients without hyperlipidemia (n = 50,000), compared with no cases in a cohort of untreated hyperlipidemic patients (n =28,974) and nine cases in a hyperlipidemic cohort receiving lipid-lowering therapy (n = 17,219). In this study, confirmation of myopathy required at least two of the following: clinical diagnosis by a general practitioner; muscle weakness, pain, or tenderness (two of these symptoms); and CK level above the reference limit. Although statin users had an 8-fold increase in relative risk for myopathy, the absolute risk was one case in 10,000 patients treated for 1 year. The PPP Project reported no cases of myopathy (i.e., muscle aching or weakness with CK elevations >10 xULN), and no confirmed cases of rhabdomyolysis. Moreover, the incidence of myalgia and myositis was similar in the pravastatin and placebo groups,

with no differences between older and younger subjects. In PROSPER, there were no reports of rhabdomyolysis, and the incidence of myalgia was similar with pravastatin (36 cases) and placebo (32 cases). The only formal laboratory assessment, at 3 months, found no evidence of CK levels >10 xULN. The 4S noted one case of rhabdomyolysis in a woman taking simvastatin 20 mg/day, but the patient recovered when treatment was stopped. Elevations in CK >10 xULN occurred in one patient receiving placebo and six patients receiving simvastatin, but the latter experienced no muscle pain or weakness, and the elevations did not occur in a repeat sample. In AFCAPS/TexCAPS, the incidence of CK elevations >10 xULN were similar with lovastatin 20 mg/day (0.7%), lovastatin 40 mg/day (0.6%), and placebo (0.6%). There were three cases of myopathy (i.e., muscle symptoms with CK elevations >10 xULN)—two in placebo-treated subjects and one in a lovastatin-treated patient following surgery for prostate cancer. The HPS found no difference between treatment groups in the incidence of unexplained muscle pain or weakness, and myopathy (i.e., muscle symptoms plus CK levels >10 xULN) was diagnosed in a nonsignificant excess of simvastatin-treated patients. In general, study treatment was continued and CK elevations diminished in these patients. Some myopathy cases progressed to rhabdomyolysis (CK levels >40 xULN), but none were fatal (39).

Nonspecific muscle aches and joint pain not associated with CK elevations are a common complaint that occurs at a similar rate (about 5%) with statin therapy and placebo in clinical trials. This suggests that the symptoms may not be drug related, particularly since statin therapy is commonly administered to middle-aged and older persons, a population in which muscle, joint, and tendon symptoms are fairly common (39).

3.8.2.1.1.2. Epidemiologic data from adverse event reporting systems

Cases of drug toxicities reported to the US Food and Drug Administration (FDA) before June 2001 confirm that fatal rhabdomyolysis associated with statin therapy is a very rare event. However, this toxicity appeared to occur more frequently with cerivastatin treatment. Bayer introduced cerivastatin to the US market in 1997 and to the Canadian market in 1998. In 1999, the first report of rhabdomyolysis and renal failure associated with the cerivastatin-gemfibrozil combination was reported (72).

Yasuo Oshima conducted a retrospective analysis of all drug-associated rhabdomyolysis cases reported to FDA between January 2004 and December 2009. He analysed the datas from U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS).There were 8,610 cases of drug-associated rhabdomyolysis in the database. According to this analysis lipid modifying agents, such as HMG-CoA reductase inhibitors were most frequently reported as a suspected cause of reported rhabdomyolysis. In a previous report, one hundred and twenty five cases (67.6%) out of 185 cerivastatin-associated rhabdomyolysis cases reported to AERS were prescribed concomitant gemfibrozil between September 1999 and July 2000. On the other hand, only 220 cases (8.7%) out of 2,523 HMG-CoA reductase inhibitor-associated rhabdomyolysis cases were prescribed concomitant fibric acid derivatives between January 2004 and December 2009. This reduced proportion of concomitant use may be due to the successful communication from regulatory health authorities and market authorization holders including the dear doctor's letter and prescribing information. Proportion of fatal outcome for HMG-CoA reductase inhibitor-associated rhabdomyolysis case with or without concomitant fibric acid derivatives were 5.5% and 9.7%, respectively. Thus, the proportion for fatal outcome appeared to be lower in fibric acid derivatives cotreated subjects (92).

As Gotto A.M. mentions in his publication, of the Food and Drug Administration (FDA), there were 772 reported cases of statin-associated rhabdomyolysis between October 1997 and December 2000—a marked contrast to the large number of statin users in the United States (approximately 12 million). These cases included 387 associated with cerivastatin, 52% of which resulted from combination therapy with a fibrate. In August 2001, the manufacturer voluntarily withdrew cerivastatin from the market to prevent further cases of rhabdomyolysis when the drug was prescribed with gemfibrozil, a practice that continued despite a contraindication issued by the manufacturer in December 1999. It must be noted that the AERS is a voluntary reporting system, and that physicians generally report just 1% of serious adverse events. For the five statins now available, AERS data through June 25, 2001 indicate that rhabdomyolysis mortality per 1 million prescriptions written was 0.04 to 0.19, compared with 3.16 for cerivastatin—approximately 16 to 80 times higher than that for each of the other statins. Of the 31 rhabdomyolysis deaths reported with

cerivastatin, 12 (39%) were attributed to combination therapy with gemfibrozil, leaving 19 deaths caused by cerivastatin monotherapy (1.9 per 1 million prescriptions written). Twelve of the 19 deaths occurred after use of the 0.8-mg dose. For atorvastatin, approved approved 6 months before cerivastatin, the reported incidence of fatal rhabdomyolysis was 0.4 per 1 million prescriptions (39).

3.8.2.1.1.3. Epidemiologic data from literature review

According to a meta-analysis performed by Silva M. et al, eighteen randomized controlled trials, including 71,108 persons, and 301,374 person-years of follow-up, published between the years 1995-2006 was involved. The MEDLINE/EMBASE and the Cochrane Collaboration databases were reviewed for prospective randomized primary and secondary prevention trials of statin monotherapy. The total occurrences of any AE were 1017 events in the statin group and 811 events in the placebo group, with a corresponding NNH of 197. Statin therapy increased the risk of any AE by 39% compared with placebo. There were 316 myopathy-related events, including myalgia, myopathy, or asthenia, in the statin group compared with 253 events in the placebo group.In the statin group, 81 cases of creatine phosphokinase (CPK) elevation were reported versus 64 cases in the placebo group. There were 609 instances of elevated LFTs (liver function tests) >3 times the upper limit of normal (ULN) in the statin cohort compared with 487 in those receiving placebo. Nine cases of rhabdomyolysis were observed with simvastatin from 3 trials (Atorvastatin to Zocor, Heart Protection Study [HPS], Scandinavian Simvastatin Survival Study) and 1 case was linked to lovastatin during the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). There were 3 cases of rhabdomyolysis observed in the placebo group of the HPS and 2 cases in the AFCAPS/ TexCAPS placebo group. The other 14 trials do not report rhabdomyolysis with any statin or placebo. Serious events (CPK >10x ULN or rhabdomyolysis) are infrequent, requiring 3400 people to be treated with a statin, rather than placebo, to observe a statin related myopathy and 7428 people to observe a statin-related rhabdomyolysis. It is told in the literature that in this analysis, side-by-side comparisons suggest that atorvastatin was associated with more AEs than other statins. Lipophilicity in atorvastatin metabolism may partially explain the increased likelihood of AEs. This meta-analysis suggests that treating 1000 individuals with any statin will prevent 37 cardiovascular events such as myocardial infarction,

revascularization, stroke, cardiovascular death, or all-cause mortality and generate 5 reports of statin induced AEs including myalgia, myopathy, CPK elevations and LFT elevations, alone or in combination. Myalgia and LFT elevations >3x ULN accounted for approximately two thirds of the AEs in that report (54).

Kashani A. et al published a review of 35 randomised clinical trials enrolling 74,102 patients to the review. According to this review, myalgias, reported in 21 studies (60%) including 48 138 patients, were not significantly more common among those treated with currently available statins. When myalgia was evaluated among individual statins, only atorvastatin had a significantly higher incidence RD compared with placebo. CK elevation, reported in 16 studies (46%) including 41 457 patients, was no more frequent in patients treated with statins. None of the atorvastatin trials reported CK elevations as an end point. Rhabdomyolysis, reported in 20 studies (57%) including 68 110 patients, was not more common in the statin group. When cerivastatin was compared with placebo, the risk of myalgias or discontinuation due to any adverse event was not significantly increased. There was a nonsignificant trend toward higher rates of CK elevations. There was a significant increase, however, in the incidence of rhabdomyolysis and transaminase elevations with cerivastatin use compared with placebo. Cerivastatin was the only statin demonstrating significantly higher rates of rhabdomyolysis with drug therapy. This study supports the rare incidence of rhabdomyolysis with currently available statins and a 12-fold increased risk with the withdrawn statin (cerivastatin). In ~60% of the total number of cases, statin-related rhabdomyolysis was found to be related to drug-drug interactions (87).

According to a meta-analysis of findings from 21 clinical trials providing 180,000 person years of follow-up, myopathy (defined as muscle symptoms + CK > 10xs ULN) occurs in 5 per 100,000 person-years and rhabdomyolysis in 1.6 per 100,000 person-years. He also mentioned that this compares with the reporting rate of 0.3 to 2.2 cases for myopathy and 0.3 to 13.5 cases of rhabdomyolysis per million statin prescriptions from the FDA's AYERS database and with 1.6 to 3.5 cases of hospitalized myopathy (including rhabdomylosis) per 10,000 person-years from an analysis of an administrative managed care claims database (89).

For statins other than cerivastatin, the incidence of rhabdomyolysis in 2 cohort studies was 3.4 (1.6 to 6.5) per 100,000 person-years, an estimate supported by data

from 20 randomized controlled trials. Case fatality was 10%. Incidence was about 10 times greater when gemfibrozil was used in combination with statins. Incidence was higher (4.2 per 100,000 person-years) with lovastatin, simvastatin, or atorvastatin (which are oxidized by cytochrome P450 3A4 [CYP3A4], which is inhibited by many drugs) than pravastatin or fluvastatin (which are not oxidized by CYP3A4). In persons taking simvastatin, lovastatin, or atorvastatin, 60% of cases involved drugs known to inhibit CYP3A4 (especially erythromycin and azole antifungals), and 19% involved fibrates, principally gemfibrozil. The incidence of myopathy in patients treated with statins, estimated from cohort studies supported by randomized trials, was 11 per 100,000 person-years (93).

Guyton J.R. mentiones in his publication that the only substantial, well-defined mortality risk with statin therapy is that of fatal rhabdomyolysis. From clinical trial and cohort data, Law and Rudnicka2 estimate the rate of all cases of rhabdomyolysis at 3 per 100,000 person-years during statin treatment. The case fatality rate is about 9%, giving a mortality risk from rhabdomyolysis of 0.3 per 100,000 person-years. (94)

Silva M. et al searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from *1995* to 2006 for prospective, randomized controlled trials comparing intensive-dose statin therapy with moderate-dose statin therapy for the reduction of secondary CV events in patients with ACS or stable CAD. The risk of rhabdomyolysis did not differ significantly between intensive dose and moderate dose statin therapy, but that finding should not be interpreted as meaning that rhabdomyolysis does not occur with intensive-dose statin therapy. It was also mentioned that statin-induced myositis can progress to rhabdomyolysis, which results in 1 statin-related death per 6.66 million statin prescriptions in the United States. (95)

3.8.2.1.2. Liver Adverse Effects

According to an article published in 2003, it is told that the ACC/AHA/NHLBI Clinical Advisory reports that statins are well tolerated by most, with dose-dependent liver enzyme elevations occurring in 0.5 to 2% of cases. Whether these elevations qualify as true drug-related hepatotoxicity has not been determined (39).

Persistent ALT elevations more than 3 times ULN are observed in ≤1% of statin-treated patients. Persistent transaminase elevations more than 3 times ULN are related to dose, with rates of less than 0.5% for moderate-dose statins and rosuvastatin at all

doses, and slightly higher rates of about 1% for 80 mg of atorvastatin and 80 mg of simvastatin. Liver failure has been reported at a rate of 1 case per 1 million patient-treatment years, the same as the reporting rate of liver failure in the population not taking a statin (52).

Elevations in alanine transaminase (ALT) and aspartate transaminase (AST) are generally reversed with statin dose reduction and tend not to recur with rechallenge or selection of another statin. Although cholestasis and active liver disease are contraindications to statin use, there is no specific evidence of exacerbation of liver disease by statins, and progression to liver failure attributable to statins is virtually nonexistent. Notably, statins do not appear to worsen outcomes in persons with chronic transaminase elevations caused by hepatitis B or C, and there is evidence that treatment of hyperlipidemia may improve transaminase elevations in patients with fatty liver (39).

3.8.2.2. Other Adverse Effects Related to Statins

With statins' prescriptions on the rise and with increasing pressure to become available over-the-counter, clinicians need to be aware that statin use may also be associated with other less well-known adverse effects.

3.8.2.2.1. Renal Adverse Effects

Renal damage with statin use is usually due to associated rhabdomyolysis causing acute tubular necrosis. According to Kiortsis D.N. et al's findings, there was no evidence of significant proximal tubular damage following rosuvastatin treatment. Tubular proteinuria is seen with all statins and directly relates to the potency of low-density lipoprotein (LDL) reduction at a given dose. The lipid-lowering potency of rosuvastatin together with its renal excretion may explain the proteinuria seen at higher doses of this agent (96).

In contrast, statins may actually reduce albuminuria. In normotensive type 2 diabetic patients simvastatin reduced the urinary albumin excretion rate. Statins have been shown to improve renal function. Also, atorvastatin can reduce serum uric acid concentrations. Of interest, statins may also result in a small but significant decrease in arterial blood pressure, which may be clinically relevant (88).

Kidney Expert Panel of the National Lipid Association's (NLA) Safety Task Force made up of 3 nephrologosits including Kaiske B.L. et al made an assesment about

the renal effects of statins. The Renal Expert Panel finds no evidence that statins cause ARF or renal insufficiency not associated with rhabdomyolysis. The Renal Expert Panel finds no association between renal tubular damage or proteinuria and statin use. There have been no case reports linking statins to renal tubular acidosis or other measures of tubular damage. Also they found no evidence that statins cause CKD or hematuria. In addition The Renal Expert Panel concludes that patients need not be routinely monitored for proteinuria and/or renal function while they are receiving a statin (97).

3.8.2.2.2. Gastrointestinal Adverse Effects

As it is mentioned in a review article that the most common gastrointestinal side effects associated with statin use include nausea, dyspepsia, abdominal pain, flatulence and diarrhoea or constipation. However, most patients continue treatment as these side effects are mild and transient. More serious rare adverse events have been occasionally reported, such as cholelithiasis, cholecystitis or cholestatic jaundice. Furthermore, fatal ulcerative colitis possibly related to simvastatin treatment has been reported in one case. Also they mentioned that there are many reports of statin-associated acute pancreatitis in the literature. A published case–control study, which included 2576 first-time admitted cases of acute pancreatitis and 25,817 age- and gender-matched controls from the general population, did not confirm an association between statin use and pancreatitis development (88).

3.8.2.2.3. Skin Adverse Effects

Statin-related dermatologic adverse reactions include: alopecia, rash, cheilitis, lichenoid eruption, dermographism, chronic urticaria and toxic epidermic necrolysis (88).

According to Lareb database reports on June 9, 2004 the database of the Netherlands Pharmacovigilance Centre contained three reports concerning lichenoid eruptrion associated with the use of HMG-CoA-reductase inhibitors. Two reports involved simvastatin and one atorvastatin. In addition Lareb received one report of lichenification associated with the use of atorvastatin, but it is not sure whether this reaction concerned a lichenoid eruption. In two of the four patients the symptoms appeared within two weeks after starting with the HMGCoA- reductase inhibitor and in one patient the symptoms disappeared after discontinuation of the HMG-CoA-reductase

inhibitor. This supports a causal relationship between the use of HMG-CoA reductase inhibitors and lichenoid eruptions (98).

3.8.2.2.4. Sensory Organ Adverse Effects

There are two reports of possible statin associated cataract development in humans. However, human studies have shown that even the long-term use of statin does not increase the risk of developing cataract. Furthermore, there is evidence that statin use may actually reduce risk of developing nuclear cataracts (99). There are 95 case reports possibly associating statin use and ocular haemorrhage submitted to the World Health Organization, the Food and Drug Administration, and the National Registry of Drug-Induced Ocular Side Effects. In the literature there is one report of nasal polyposis associated with statin treatment. Nasal polyps resolved after statin withdrawal (88).

According to Lareb database report On June 5, 2004 the database of the Netherlands Pharmacovigilance Centre Lareb contained 21 reports of taste disorders associated with the use of HMG-CoA-reductase inhibitors. Four reports refer to taste loss, five reports to a 'bitter taste', two reports to a metallic taste, five reports mention the sensation of non-specified altered taste perceptions (parageusia), five reports mention non-specified taste disorders. Only one report also mentions a smell disorder. From the reports of taste disorders, seven concerned simvastatin, three pravastatin and six atorvastatin, three fluvastatin and one cerivastatin. In four cases the suspect HMG-CoA-reductase inhibitor has been discontinued and in these cases the patient (partially) recovered (100).

3.8.2.2.5. Central Nervous System (CNS) Adverse Effects

In the early 1990s, some lipid-lowering clinical trials found a significant decrease in cardiovascular mortality but also an increase in non-cardiovascular mortality. This change in non-cardiovascular mortality was mainly due to an increase of suicides and violent deaths. The mechanisms for the CNS adverse effects of statins were not clear. However, all the primary and secondary prevention trials (e.g., the Heart Protection Study), a meta-analysis of 14 large randomized clinical trials as well as a meta-analysis of randomized clinical trials that assessed the association of cholesterol lowering and non-cardiac mortality did not show an increased incidence of suicide in patients receiving statins compared to those receiving placebo. As Kiortsis D.N. et al mentions, most of the trials with statins and dietary counselling did not demonstrate any

adverse effects on psychological well-being. These data notwithstanding, there are reports in the literature of depression associated with the use of simvastatin and pravastatin. In addition, there have been a number of reports of sleep disturbances and insomnia associated with statins. Furthermore, atorvastatin (as monotherapy) and simvastatin (in combination with metoprolol) have been reported to cause nightmares. Some studies also found disturbances of objective sleep measurements with simvastatin and lovastatin but not with pravastatin (88).

According to Lareb database reports, until March 4, 2008 the Netherlands Pharmacovigilance Centre Lareb received 18 reports of nightmares and nine reports of abnormal dreaming associated with the use of HMG-CoA-reductase inhibitors. Of the 18 reports of nightmares, only one report originated from a consumer, the majority or reports came from general practitioners. 11 patients recovered after withdrawal of the suspected drug. In five of these patients reintroduction of the suspected drug took place, resulting in a recurrence of symptoms (positive rechallenge). Two of these patients finally switched from simvastatin to atorvastatin without complaints. In another patient simvastatin was not discontinued, but the dose was reduced, after which symptoms diminished; dose increase resulted in worsening of symptoms. Finally simvastatin was discontinued. Of the 18 reports of nightmares, in eight cases a beta-blocker was used as concomitant medication, of which six times metoprolol was used (101).

3.8.2.2.6. Peripheral neuropathy

A number of reports indicated that statins may cause peripheral neuropathy. A disorder resembling Guillain–Barre syndrome on initiation of simvastatin has also been reported. The mechanisms underlying statin-induced peripheral neuropathy are unknown. It appears to be a drug class effect, as it has been observed with several statins. These drugs inhibit synthesis of the key mitochondrial respiratory chain enzyme, ubiquinone. This may disturb neuron energy utilization and thereby induce neuropathy (88).

According to Lareb database report on 8 March 2004, the database of the Netherlands Pharmacovigilance Centre Lareb contained ten reports of neuropathy, expressed as neuropathy, peripheral neuropathy or polyneuropathy, in association with the use of HMG -CoA-reductase inhibitors. In addition to these reports the database contained 26 reports of paraesthesias, one report of sensory loss, 22 reports of muscle

weakness and no reports of hyperaesthesias, conditions that might be a symptom of neuropathy. From the ten reports of neuropathy, five concerned simvastatin, three pravastatin and two atorvastatin. In four cases the suspect HMG-CoA-reductase inhibitor has been discontinued and in these cases the patient (partially) recovered. The mean time to onset is 25.5 months (range 0.75 to 72 months). Lareb concluded that long-term exposure to HMG-CoA-reductase inhibitors increases the risk for neuropathy (102).

3.8.2.2.7. Erectile dysfunction (ED)

Patients treated with statins have many vascular risk factors, and therefore they may have an increased risk for ED. Case reports suggested that statins may be associated with ED. In the Scandinavian Simvastatin Survival Study (4S) study, 37 of 1814 patients on simvastatin developed ED, as did 28 of 1803 on placebo, a difference which was not significant. Thus, the suggestion that statins cause ED was challenged (88).

Conversely, in a case- control study, Bruckert et al. investigated the prevalence of ED in 339 patients attending a lipid clinic compared with matched controls **(103).** Treatment with both fibrates and statins were independent predictors of ED. Halkin et al. suggested that ED is a class effect of statins (104). Furthermore, statin use has been associated with decreased libido (88).

According to Lareb database report, Lareb received a report of a decrease in testosterone levels and loss of libido in suspected association with the use of pravastatin. This 54-years -old male developed loss of libido shortly after starting pravastatin indicated for hypercholesterolaemia. During therapy his testosterone level was 5.8 mmol/l (morning value). Pravastatin was discontinued after seven months, where after the man's libido quickly returned to normal. Four months later, his testosterone level was determined again and had risen to 22.8 mmol/l (morning value). Lareb received four additional reports of decreased libido or impotence in suspected association with the use of pravastatin and a total number of 33 reports of decreased libido, impotence or decreased erection in suspected association with the other HMG -CoA-reductase inhibitors The reports in the Lareb database indicate that sexual dysfunction may be an adverse drug reaction of the HMG-CoA-reductase inhibitors. Moreover, this might be the result of a decrease in testosterone levels (105).

3.8.2.2.8. Gynecomastia

Very few data exist regarding the effect of statins on mammary gland. Gynecomastia was attributed to pravastatin in one case (88).

3.8.2.2.9. Blood effects

Simvastatin treatment depresses blood clotting by means of reduction of prothrombin activation, factor Va generation, fibrinogen cleavage and factor XIII activation as well as increase of factor Va inactivation. Statin use has been associated with thrombocytopenia and thrombotic thrombocytopenic purpura. In these cases there was a rapid recovery after discontinuation of the drug. The underlying mechanisms possibly involve drug hypersensitivity reaction or immune complex-mediated reaction related to cross-reactivity to previous antigen exposure (88).

In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, patients who had an acute myocardial infarction within 12 h of onset were prospectively randomized to receive balloon angioplasty with or without abciximab versus stenting with or without abciximab. Acquired thrombocytopenia was significantly associated with the presence of non-insulin-dependent diabetes mellitus, previous statin administration, and use of abciximab (106).

3.8.2.2.10. Autoimmune disorders

Treatment with statins has been rarely associated with autoimmune disorders. There is a number of reports of statin-induced lupus erythematosus, arthralgia, dermatomyosits and polymyositis. Also, autoimmune hepatitis associated with the use of atorvastatin and rosuvastatin has been described. Moreover, hypersensitivity pneumonitis has been linked to statin use. In most cases histological findings and positive antinuclear and antihistone antibodies confirmed the diagnosis. Statin-induced lupus was usually reversible on drug withdrawal (88).

Trial of Atorvastatin in Rheumatoid Arthritis (TARA), 116 patients with rheumatoid arthritis were randomized to receive 40 mg atorvastatin daily or placebo for 6 months as an adjunct to existing disease modifying antirheumatic drug therapy. Disease activity score (DAS28), C-reactive protein, erythrocyte sedimentation rate as well as swollen joint count improved significantly more with atorvastatin compared to placebo. These data show that statins can mediate modest but clinically apparent

antiinflammatory effects together with modification of vascular risk factors in autoimmune disorders, such as rheumatoid arthritis (107).

3.8.2.2.11. Cancer

In the pravastatin in elderly individuals at risk of vascular disease (PROSPER) study, there was an imbalance in new cancer diagnosis, which was 25% more frequent in the pravastatin group. Two large meta-analyses of major placebo-controlled double-blinded prospective statin trials found no association between statin use and overall risk for fatal or non-fatal cancer. There is evidence that statins may reduce colorectal risk cancer. In a case controlled study of nearly 4000 patients, statin use was associated with a 47% relative risk reduction for colon cancer incidence, even when controlling for other known risk factors. On the other hand, in a meta-analysis including 6662 incident cancers and 2407 cancer deaths, statins did not reduce the incidence of cancer or cancer deaths. No reductions were noted for any individual cancer type, suggesting that statins have a neutral effect on cancer incidence and cancer death risk in randomized controlled trials (88).

In comparison; in the large randomized secondary prevention study Cholesterol and Recurrent Events (CARE) Trial, among patients with average cholesterol levels, women randomized to pravastatin therapy exhibited a huge and unexplained increase in breast cancer incidence, some of which were recurrences. Subsequently, cancer was an exclusion criterion in randomized statin trials. The secondary analysis of the Treating to New Targets (TNT) study reported the effects of aggressive lowdensity lipoprotein (LDL) cholesterol lowering in women with stable coronary heart disease. In women randomized to high-dose atorvastatin (80 mg daily) therapy compared to the women randomized to low-dose (10 mg daily) atorvastatin there was a large excess in cancer mortality. Alarmingly, annualized cancer mortality was 1 in 1000 patients in the low-dose atorvastatin group and 4 in 1000 patients in the high-dose group. Furthermore, there was a trend towards increased all-cause mortality in the high-dose compared to the low-dose atorvastatin group, neutralizing any benefit in cardiovascular mortality (55).

3.9. Rhabdomyolysis

First historical reference to rhabdomyolysis is probably a passage in the Bible (Old Testament, Book of Numbers, 11:31) describing an acute devastating illness in Israelites who had eaten quail (that had probably fed on hemlock seeds). Nevertheless,

clinical rhabdomyolysis was long considered uncommon. A major cause of rhabdomyolysis is crush injury, which was first described in victims of the World War II bombing blitz in London and subsequently reported in victims of natural catastrophes and in individuals subjected to severe exertion (108). It is mentioned in a study that in 1941; Bywaters and Beall focused on the relation between skeletal muscle injury (Crush) and acute tubular necrosis (ATN) (109).

Many other causes of rhabdomyolysis have been identified, generating considerable interest in clinical investigations capable of determining the mechanism of rhabdomyolysis. Such investigations are crucial, as rhabdomyolysis is life-threatening unless the pathogenic process is controlled promptly. In addition, appropriate treatment is needed to prevent recurrences (108).

3.9.1. Definition

Rhabdomyolysis is the necrosis of skeletal muscle fibers with release of the fiber contents into the blood and urine (108).

Muscle cell content is formed by myoglobin, creatine phophokinase (CPK), aldolase, lactate dehydrogenase (LDH), serum glutamic-oxalacetic transaminase (SGOT) and potassium (K) (109).

Muscle fiber necrosis can occur as a primary disorder related to inherited or structural abnormalities of the muscle cells. In most cases, however, the necrosis is secondary to an infection, a toxic agent, an injury, or another external cause. Typically, rhabdomyolysis manifests as muscle fatigue, pain, cramps, and weakness, sometimes with an increase in muscle size. Reddish-brown urine indicating myoglobinuria is highly suggestive. Laboratory tests show a greater than fivefold increase above normal in serum creatine kinase (CPK) combined with high urinary levels of myoglobin. In older patients, however, high CPK levels without myoglobinuria may indicate rhabdomyolysis. In normal individuals, the MM isoform of CPK, which is derived from skeletal muscle fibers, contributes 95% of the total CPK activity. Several assays are available for measuring total CPK and each of the three CPK isoforms; normal values vary across laboratories (from 17 to 148 IU/l in males and 10 to 79 IU/l in females for total CPK). Rhabdomyolysis can cause death via several mechanisms. High serum potassium levels may induce fatal heart rhythm disturbances. Intratubular obstruction may cause acute renal failure with oliguria. Other abnormalities include hyperthermia,

tubular necrosis related to myoglobin deposition, volume depletion, leukocytosis, metabolic acidosis caused by release of intracellular sulfate and phosphate, early hypocalcemia related to precipitation of calcium carbonate within the damaged tissues (with a further rise in serum potassium levels), hypercalcemia in patients with chronic rhabdomyolysis, hyperphosphatemia, anemia, and disseminated intravascular coagulation (108).

Rhabdomyolysis is usually associated with symptoms such as muscle pain, weakness and brown urine, myoglobinuria, acute kidney injury, and markedly elevated creatine kinase levels. Acute kidney injury in myoglobinuria is caused by tubular injury resulting from excessive quantities of myoglobin (92).

3.9.2. Pathophysiology of rhabdomyolysis

Muscle fiber lysis (see figure 6) can be caused by damage to the sarcolemma or by metabolic disturbances related to a biochemical or genetic abnormality (108).

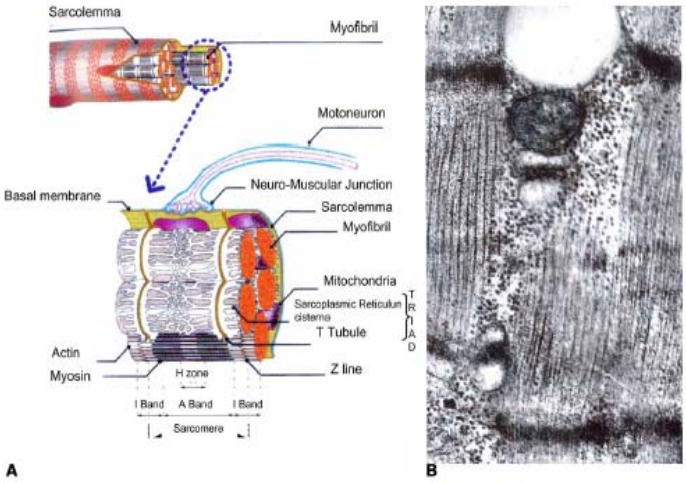


Figure 6. Muscle fiber lysis

Regardless of the initiating mechanism, the crucial factor in the genesis of rhabdomyolysis is elevation of intracellular free calcium levels. In the normal muscle cell, several mechanisms contribute to maintain calcium levels within the normal range. See figure 7.

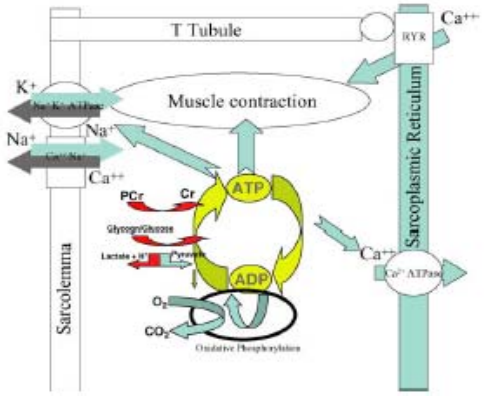


Figure 7. Diagram illustrating calcium transport within the muscle

In the sarcoplasmic reticulum (where calcium is stored), ryanodine and dihydropyridine receptors release calcium into the cytosol in response to cell membrane depolarization, and subsequently the enzyme calcium-ATPase pumps the calcium back into the sarcoplasmic reticulum sacs (See figure 7). Calcium transport across the sarcolemma is ensured by two pumps working concomitantly, the Na+/K+ pump and the Ca+/Na+ exchanger. The Na+/K+ pump keeps the intracellular sodium level low (10 mEq/l), thereby generating a strong gradient between intracellular and extracellular levels that promotes passive diffusion of sodium into the cell. This regulates the intracellular calcium content via sodium–potassium exchange. Thus, calcium homeostasis is in jeopardy when intracellular sodium levels change, whether the reason is ion pump dysfunction, membrane damage, or depletion of energy stores (most of the pumps involved in calcium homeostasis are dependent on ATP provided by glycolysis and mitochondrial respiration) (See figure 7). According to this article, disruption of calcium homeostasis results in activation of proteases and phospholipases, which break down the proteins that make up the contractile apparatus, cell membrane, and cytoskeleton (108).

3.9.3. Reasons that may cause rhabdomyolysis

There are many reasons of rhabdomyolysis. These reasons can be exercise-related, Crush syndrome, toxic agents, alcohol and medications, and infections for acute or sucacute rhabdomyolysis. Muscle dystrophies, ion disturbances, metabolic muscle disorders and other miscellaneous reasons (for example epilepsy, Lou Gehrig's disease, head injuries, acute psychotic disorders, Reye syndrome, bowel ischemia, graft-versus-

host disease, eosinophilic fasciitis, central core myopathy, or multiminicore myopathy) are the reasons of chronic rhabdomyolysis. Among these reasons exposure to toxic agents, including alcohol and medications, accounts for up to 80% of rhabdomyolysis cases in adults (See Table 16) (108).

Table 16. Substances of abuse, medications and toxic agents known to induce rhabdomyolysis

Substances of abuse
Alcohol, opiates (heroin, methadone), cocaine, amphetamines, LSD, Ecstasy
Toxic agents
Isopropylene alcohol, carbon monoxide, ethylene glycol, toluene, organophosphates (insecticides [malathion], herbicides [tribufos], arsenic, ingested metals, inhaled metal fumes, iron, mercury)
Biological toxins
Tetanus toxin, staphylococcal toxin, venom (snake venom [Viperides such as rattle snakes and vipers], Hymenoptera [bees and wasps], Diptera [flies and mosquitoes], Arachnids [spiders and scorpions], Reef fish poisoning [ciguatera, stonefish], Hemlock poisoning [by eating quail that fed on hemlock seeds], Kava extract, [Piper methysticum]), contaminated vegetable oil
Analgesics and antiinflammatory drugs
Salicylates, acetaminophen, propoxyphen, opiates, pethidine, NSAIDs (ibuprofen, diclofenac, niflumic acid, phenylbutazone), glucocorticoids
Antibiotiand related agents
Fluoroquinolones, pyrazinamide, trimethoprime + sulfamide, amphotericin B, Itraconazole, levofloxacine
Cholesterol-lowering drugs
Fibrates: bezafibrate, ciprofibrates, fenofibrates, gemfibrozil
Statins: fluvastatin, atorvastatin, pravastatin, simvastatin
Cytotoxic agents
Vincristine, cytarabine, mitoxantrone
Immunosuppressants
Cyclosporine A, alpha interferon, IL2, azathioprine, tacrolimus
Antithyroid drugs
Carbimazole
Anesthetics and neuromuscular blocking agents
Propofol, halogenated compounds, suxamethonium chloride, glutethamide, ketamine, succinylcholine
Antiviral agents
Zidovudine, ritonavir, didanosine
Benzodiazepines
Diazepam, temazepam
Neuroleptics and psychotropic agents
Haloperidol, risperidone, thioridazine, loxapine, naltrexone
Antidepressants
All classes
Antiulcer agents
Famotidine, cimetidine
Beta-blockers
Oxprenolol, labetolol
Miscellaneous
Chloroquine, hydroxychloroquine, amiodarone, colchicine, D-Penicillamine, sulfazalazine, vitamin A (etretinate), B3,B6 (pyridoxine), insulin, nifedipine, thioridazine, BCG vaccine, sodium valproate, antihistamines, emetine, tryptophane, streptokinase, laxatives, diuretics, methylxanthines (caffeine, theophylline, thiazides), levodopa, lithium, terbutaline, fenoverine, lypressin, vasopressin, naltrexone, podophyllin, glycyrrhizin, amino-caproic acid, radiotherapy to the chest (including the heart)

According to a review article published by Guis S. et al, substance abuse including acute or chronic alcohol abuse is the leading cause of rhabdomyolysis. After acute inebriation, CPK elevation is noted in 40–80% of cases, together with low serum sodium and phosphate levels and with hepatic P450 cytochrome induction responsible for the production of toxic metabolites. Alcohol can cause impairments in calcium, sodium, and potassium transport mechanisms, as well as alterations in membrane fluidity. Drug-induced rhabdomyolysis has also been reported in patients with muscle

disease. For instance, zidovudine can trigger mitochondrial myopathy, chloroquine and amiodarone can precipitate lysosomal myopathy, colchicine can induce microtubule abnormalities, and D-penicillamine can generate muscle disorders related to autoimmunity. Lipid-lowering drugs, including statins and fibrates, have been reported to induce rhabdomyolysis. Among patients on statin therapy, 3–5% exhibit CPK elevation and 0.04–0.2% experience rhabdomyolysis. The risk of rhabdomyolysis is highest with cerivastatin, which has been removed from the market as a result, and lowest with fluvastatin; since the removal of cerivastatin, simvastatin has contributed most of the cases. Only four cases of statin-induced myopathy have been reported. Among patients with statin-associated rhabdomyolysis, 55% were also taking other compounds such as fibrates, cyclosporine, mibefranil, macrolides, digoxin, warfarin, diltiazem, imidazole antifungal agents, and a number of substances of abuse. The muscular toxicity of statins seems dose-dependent and may be potentiated in patients with abnormalities in cytochrome systems (most notably P450) and/or in muscle cell calcium channels. In addition, specific clinical patterns associated with medications have been described, such as neuroleptic malignant syndrome, a condition of hyperthermia, dehydration, and muscle hyperactivity reported with butyrophenones, phenothiazine, thioxanthene, metoclopramide, and clozapine. Tricyclic antidepressants or antiparkinson agents are widely used to treat patients with malignant neuroleptic syndrome. Two clinical variants have been described in the mentioned review such as central anticholinergic syndrome with dopaminergic system inhibition and serotonin syndrome related to overactivation of the 5 HT1A and 5HT2 receptors. In serotonin syndrome, mental status abnormalities are present in addition to the classic clinical picture. Serotonin syndrome can be caused by antidepressants that selectively inhibit serotonin reuptake, the risk being greater with concomitant monoamine oxidase inhibitor therapy, or by selective norepinephrine reuptake inhibitors (108). Among all these medications, I will focus on statins.

3.9.4. Mechanism of action of statin-induced myopathy

The precise mechanism underlying statin-induced myotoxicity has not been clearly delineated. Several hypotheses exist in the literature about the exact mechanism of myotoxicity: (1) depletion of secondary metabolic intermediates; (2) induction of apoptotic cell death; and (3) alterations of chloride channel conductance within the

myocytes. Individual susceptibility appears to be dependent on the statin drug used, drug interactions, and the coexistence of factors predisposing patients to myotoxicity (72).

3.9.4.1. Depletion of secondary metabolic intermediates

By inhibiting HMG CoA reductase, statin drugs cause a secondary depletion of metabolic intermediates formed during cholesterol synthesis. With the inhibition of the HMG CoA reductase enzyme, levels of mevalonic acid also fall. (See figure 1) The subsequent administration of mevalonic acid, the precursor of cholesterol, reverses or ameliorates most of the toxic effects of cerivastatin. This observation suggests that the toxic effects are related to the statin drugs' inhibitory effects on cholesterol biosynthesis and not to intrinsic toxicity. Each related toxic effect was reversed or prevented by the administration of mevalonate, the immediate product of HMG CoA reductase activity. As also mentioned in the literature, other studies suggests that depletion of the mevalonate metabolites (ie, farnesol and geranylgeraniol), not cholesterol, participates in statin-induced myotoxicity (72).

Reduction of prenylated proteins can result in dysprenylation of proteins, including lamins and small guanosine triphosphatases, thereby causing an imbalance in the intracellular signalling cascades and enhancing apoptosis. Sarcolemmal cholesterol deficiency, as a result of the dynamic equilibrium between membrane and plasma lipids, may adversely modify membrane physical properties, integrity and fluidity, thus resulting in membrane destabilization. Inhibition of dolichol synthesis has been implicated in defective N-linked glycosylation of plasma membrane proteins and impaired response to growth factors (32).

Another enzyme that decreases as the result of HMG CoA reductase inhibition is coenzyme Q10, or ubiquinone. Coenzyme Q10 (CoQ10) is a steroid isoprenoid enzyme that assists in the oxidation of nutrients within cells to create adenosine triphosphate (ATP). Its main function is to serve as a lipid-soluble electron carrier in the membrane-bound electron transport chains of the mitochondria. CoQ10 is important for skeletal and cardiac muscle function. It has been suggested that statin drugs cause intracellular ubiquinone deficiency. Specifically, statin drugs are thought to block farnesyl pyrophosphate, an intermediary required for CoQ10 production (See figure 1). Furthermore, CoQ10 is transported in LDL particles. With statin drugs having a proven

effect on lowering LDL levels, CoQ10 levels would subsequently decrease as well. A reduction in CoQ10 levels results in decreased oxidative phosphorylation, which is needed for normal cellular respiration in muscle (72).

3.9.4.2. Induction of apoptotic cell death

Apoptosis, or programmed cell death, is a critical mechanism designed to assist in the remodeling and maintenance of tissue structure. When inappropriately activated, however, apoptosis can produce pathological conditions. Atorvastatin, lovastatin, and simvastatin produce a dose-dependent increase in apoptosis in vascular smooth muscle cells (VSMCs). This effect is reversed by mevalonate, farnesyl pyrophosphate, and geranylgeranyl pyrophosphate, but not by ubiquinone or squalene. Treating VSMCs with statin drugs sensitizes the myocytes to apoptotic agents, which leads to the conclusion that statin drugs enhance apoptosis, at least in VSMCs. Other studies have indicated that some HMG-CoA reductase inhibitors provoke apoptotic cell death of a muscle cell-derived cell line, specifically L6 myoblasts. The mechanism by which statin therapy may induce apoptosis is unclear. As depicted in Figure 1, prenylation of certain proteins is decreased by blocking the action of farnesyl pyrophosphate as a consequence of statin therapy. This leads to decreased activation of certain important regulatory glutamyl transpeptidase-binding proteins such as Ras, which attenuate apoptosis and promote cell growth and maintenance. Nevertheless, additional work is required to demonstrate whether an increase in apoptosis produces the myotoxicity of statin therapy (72).

3.9.4.3. Alterations of chloride channel conductance

Another hypothesis of statin-induced myopathy implicates chloride channels. Chloride channels in muscle are responsible for muscle cell hyperpolarization and therefore, for muscle relaxation. Myotoxicity caused by fibrates has been attributed to the blocking effect on chloride channels with resulting unopposed muscle contraction and rhabdomyolysis. However, in the case of HMG-CoA reductase inhibitors, this form of muscle toxicity is more elusive. Changes in the ratio between cholesterol and phospholipids, as induced by HMG-CoA reductase inhibitors, may lead to clinically significant alterations in membrane properties. An electrophysiological evaluation of rats that were given pravastatin and simvastatin failed to show any difference in

electromyographic activity with pravastatin, but demonstrated a 20% chloride conductance reduction with simvastatin. This finding is likely caused by simvastatin's ability to penetrate the muscle membrane because of its lipophilicity. By penetrating the muscle membrane, simvastatin may have a blocking effect on the chloride channel, leading to muscle cell contraction with resulting muscle cramping and myalgias (72).

The equilibrium between intramuscular statin transport and efflux may be a critical regulator of intramuscular drug concentration and consequently the risk of myopathy. Organic anion transporting polypeptide (OATP) 2B1, a recognized hepatic uptake transporter for statins, has also been identified in skeletal myofibres, and the OATP inhibitor estrone sulphate protected the skeletal myofibres against pravastatin and fluvastatin-induced toxicity. Furthermore, isoforms -1, -4 and -5 of the multidrug resistance associated protein (MRP), a well characterized statin efflux transporter, are highly expressed in skeletal muscle, and the inhibition of MRP with probenecid precipitates skeletal muscle toxicity in rats treated with rosuvastatin, implying that MRP-1 may be involved in statin efflux at the myocyte level (32).

3.9.5. Diagnosis of rhabdomyolysis

Many methods are used to diagnose rhabdomyolysis. Laboratory tests, electrophysiological studies, imaging studies, muscle biopsy, noninvasive metabolic investigation, ischemic forearm test and molecular biology test are the investigation methods that are used to diagnose rhabdomyolysis. Among these investigation methods laboratory tests, imaging studies, muscle biopsy and noninvasive metabolic investigation are the ones that are used to diagnose statin-induced myotoxicity.

3.9.5.1. Laboratory tests

Laboratory tests serve both to confirm the diagnosis of rhabdomyolysis and to help determine the cause. Serum CPK and urinary myoglobin levels provide information on the severity of rhabdomyolysis. Additional laboratory tests should be done as indicated by the clinical features and suspected cause (e.g., serum TSH in patients with suspected hypothyroidism or anti-JO1 antibodies in those with symptoms of polymyositis or dermatomyositis) (108).

3.9.5.1.1. Creatine kinase levels, liver function testing, and myoglobin levels

Historically, CK levels have been used to assist in the diagnosis of statin-related myopathy. Utilizing CK levels as the sole marker to identify the presence of myopathy may be misleading. Elevated CK levels can occur without myopathic effects and often are seen as a result of exercise (31).

Clarkson et al monitored several indicators of muscle damage, including CK, myoglobin, LDH, and other measures of renal function, following an eccentric exercise protocol. No subjects with moderate to marked increases in CK levels had signs or symptoms of renal failure. The results of this study confirm that large increases in CK and myoglobin as a result of exercise in individuals who are healthy are not sufficient to induce renal damage (110). In the presence of statin therapy, therefore, clinicians using a strength program for their patients should exercise caution when evaluating the presence of elevated CK levels. Simply maintaining adequate hydration in the presence of these elevated serum concentrations is adequate in preventing renal compromise. Because the onset of myopathy can be multifactorial, the need for more judicious monitoring of patients using statins, as well as more nontraditional screening methods, is indicated (31, 110).

Efficacy and cost-effectiveness of liver function testing for patients using statins has been discussed by several experts. Elevated transaminases, as regularly seen with statin use, in the absence of muscle symptoms and increased bilirubin are not indicative of serious risk to the patient. It has been suggested that transaminase elevations may be a normal and transient pharmacological effect of the reduction of cholesterol within the hepatocytes and that the costs of screening and monitoring would be staggering. Elevated myoglobin is thought as another marker used to identify damage to myocytes and often accompanies elevated circulatory CK levels. The release of myoglobin from damaged cells can instigate renal failure via accumulation in the renal tubules. Researchers have shown that despite elevations in myoglobin and CK levels after an eccentric exercise protocol, evidence of renal compromise was not evident (31).

3.9.5.1.2. Phosphodiesters

Several procedures previously suggested as efficacious testing measures to identify the presence of statin-related myopathy have been re-evaluated. Glycerophosphocholine, the primary phosphodiester in skeletal muscle, is a key factor

in cell membrane turnover as a result of lipid layer breakdown. Evaluation of this metabolite can give valuable information to researchers exploring the energetic mechanisms of physiological stresses. Elevation of phosphodiesters has been reported in other muscle disorders, including muscular dystrophies. It is thought that the elevation of this metabolite and associated myopathy are present with statin use due to accelerated myocyte membrane turnover or reduction in cholesterol synthesis. Researchers also found that even in the presence of statin induced elevated levels of phosphodiesters, muscle symptoms were absent. Testing of phosphodiesters may assist physicians in identifying those patients who may have adverse effects due to statin use (111).

3.9.5.2. Imaging Studies

In difficult cases with little or no physical findings or focal abnormalities, imaging studies (magnetic resonance imaging [MRI], computed tomography [CT], and ultrasonography) can provide diagnostic orientation. Scintigraphy has been suggested mainly for evaluating the extent of the lesions. MRI is the best method, as it is extremely sensitive. On T2-weighted sequences, the subcutaneous fat and the superficial and deep muscle fascias generate high-intensity signals. In addition, high-intensity signals are visible within the muscle at sites of edema or of necrosis with small hemosiderin deposits. The extent of the lesions can be determined fairly easily on MRI scans. The areas of high signal resolve in parallel with the clinical manifestations. MRI may help to identify muscle groups with massive edema requiring emergency decompression. Although nonspecific, these images further support the diagnosis of rhabdomyolysis in patients with suggestive symptoms. Ultrasonography can be helpful in doubtful cases by showing multiple hyperechoic foci. A major advantage of ultrasonography is the ability to rapidly image several muscle groups; the main disadvantages are the lack of specificity and highly operator-dependent nature of the abnormalities. In general, it is reasonable to consider that patients with acute rhabdomyolysis may benefit from imaging studies if they have symptoms suggestive of compartment syndrome or if their lesions seem sufficiently extensive to cause devastating renal damage. Later in the course of rhabdomyolysis, in chronic forms and, above all, in recurrent forms, imaging studies are useful for supporting the diagnosis, evaluating the extent of the lesions, and guiding muscle biopsies (108).

3.9.5.2.1. Muscle Biopsy

Two methods can be used to obtain muscle biopsies. Open surgical biopsies allow for a more detailed evaluation of the lesion and therefore increase the likelihood of making the correct histological diagnosis. Needle biopsy is less invasive but less likely to provide the diagnosis. Muscle biopsies can be used for morphological, histoenzymological, and ultrastructural studies. In patients with hyperthermia or exercise-related rhabdomyolysis, a large fragment of the biceps or quadriceps should be obtained by open surgical biopsy to allow in vitro contraction tests aimed at characterizing the profile of sensitivity to halogenated compounds (108).

Evaluation of skeletal muscle composition and function has been used to assess the presence of myopathy in statin users as it was told in an article published in 2010. Muscle biopsies are an invasive procedure that may be used in research to assess histochemical and morphological changes but are not clinical tests for muscle myopathy (31).

Phillips et al used muscle biopsies in a small sample of statin users to confirm the presence of myopathy in the absence of elevated CK levels. Four of the initial 21 patients were able to identify statin therapy versus placebo treatment based on the presence or absence of their reported muscle symptoms. Although different statins were used by each subject, biopsies showed myopathic effects, including diffuse lipid droplet accumulation vacuoles, cytochrome oxidase-negative myofibers, and an increased number of ragged red fibers. These findings were verified as myopathic effects by absence of carnitine deficiency and thyroid dysfunction (112).

3.9.5.2.2. Noninvasive metabolic investigation

In addition to MRI, which mainly provides structural information, nuclear magnetic resonance (NMR) spectroscopy with phosphorus provides direct and strictly noninvasive images of high-energy compounds present within the muscle cell, as well as measurements of intracellular pH. Thus, 31P-NMR spectroscopy is a noninvasive means of monitoring ATP-producing reactions within muscle cells in order to determine whether inadequate energy supply is the cause of the rhabdomyolysis (See figure 8) (108).

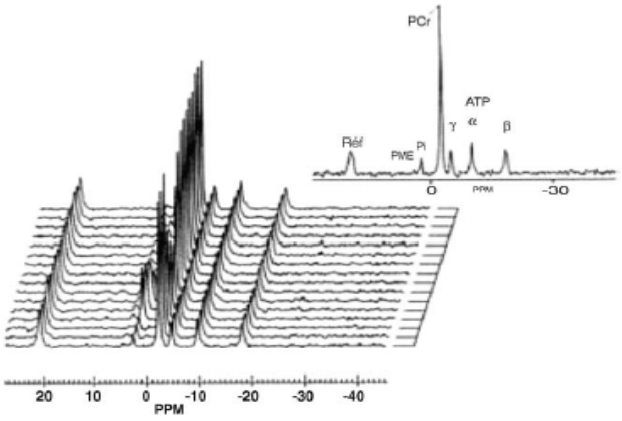


Figure 8. 31P-NMR Spectrum

Most studies of energy metabolism in patients with mitochondrial dysfunction disorders showed impaired recovery after exercise; in contrast, considerable variation occurred in energy utilization and acidosis after exercise, in keeping with the substantial phenotypic variability of these disorders. In addition to these genetic disorders, the effects of toxic agents responsible for rhabdomyolysis have been investigated by 31P-NMR spectroscopy. Fluoroquinolones cause disruptions in pH homeostasis that may be ascribable to alterations in calcium homeostasis. Cholesterol lowering agents capable of causing rhabdomyolysis have received considerable attention. Although no data on the energetic aspects of these toxic effects are available to date, preliminary investigations by in vitro contraction testing of muscle biopsies from patients with statin-induced rhabdomyolysis suggest calcium homeostasis disruption. Fenoverine, which is used to treat gastrointestinal disorders, has been reported to induce rhabdomyolysis. Metabolic studies using 31P-NMR spectroscopy suggested underlying muscle dysfunction, although no specific profile of metabolic abnormalities was identified (108).

3.9.6. Risk Factors that may precipitate drug induced myopathy

When administering statins, physicians should take into consideration a series of factors that potentially increase the risk of myopathic events. As summarized in figure 9, a constellation of factors are associated with the risk of statin associated myopathy development, including (i) patient characteristics (demographic characteristics, co-morbidities, genetic factors); (ii) drug properties (specific statin molecule, dose, pharmacokinetic properties); and (iii) concomitant interacting medications. Systemic exposure is considered to play a pivotal role in statin associated myopathy, and risk

factors that enhance the respective risk may do so, at least partly, by increasing either statin systemic bioavailability or the sensitivity to increased statin blood levels (32).

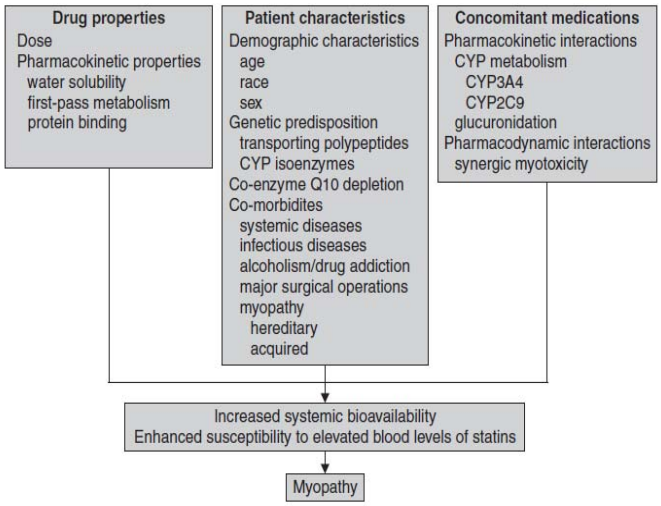


Figure 9. Risk factors for statin-induced myopathy

3.9.6.1. Patient Characteristics

3.9.6.1.1. Demographic Characteristics

Certain demographic characteristics have been associated with an increased risk of statin induced myopathy. It has been observed epidemiologically that advanced age (particularly >80 years), female sex, small body frame and frailty increase the myopathic effect of statins (32).

Increased age of users of statin therapy was associated with a significantly elevated risk for rhabdomyolysis, with individuals greater than 65 years having four times the risk of hospitalization for this disease compared to those under 65 years of age. Also they found that although the association did not reach statistical significance, they observed a higher than twofold increase in risk for rhabdomyolysis among females (113).

Myopathic symptoms may be hard to differentiate from muscular complaints commonly experienced in elderly patients. Polypharmacy and age-related impairment of renal function may in part account for the increased risk of myopathy among elderly individuals. A greater risk has been attributed to Chinese or Japanese descent, although this concept is inadequately supported by current evidence. Typically, Asians achieve

similar benefits to Caucasians at lower statin doses. Plasma levels of rosuvastatin in particular have been shown to be 2-fold higher in Asian than in Caucasian individuals receiving similar rosuvastatin doses. The smaller body mass index in Asians has been postulated as the underlying cause of the differences in drug response in some but not all comparable studies (32).

3.9.6.1.2. Genetic Factors

Knowledge of genetic variants associated with statin side effects may provide insight into the mechanism of statin myopathy (114). There may be genetic variants and genetic diseases associated with statin therapy.

3.9.6.1.2.1. Genetic factors affecting statin concentration

Steady state blood levels of statins are affected both by their extensive first-pass uptake in the liver and their rate of catabolism. The myopathic effect of statins increases with increasing doses of the drug and with factors that increase their blood concentration, although plasma drug levels do not entirely predict risk for statin myopathy. Consequently, genetic factors affecting statin concentration should affect the frequency of statin myopathy. Genetic variants in both hepatic uptake and statin catabolism have been associated with myopathy (114).

3.9.6.1.2.1.1. Genetic variants in SLCO1B1

The strongest association between genetic factors has been documented with genes affecting statin hepatic uptake. Statins are transported into hepatocytes by the organic anion transporting polypeptide C (OATP1B1), which is encoded by the gene SLCO1B1. Pravastatin, atorvastatin, rosuvastatin, simvastatin, and lovastatin are known to be transported by this mechanism. The only currently available statin not transported by OATP-C is fluvastatin. Fluvastatin may cross the hepatocyte membrane easily because of its lipophilicity or it may utilise other transporters. The pravastatin area under the plasma concentration curve (AUC) in patients with single nucleotide polymorphisms (SNPs) in the SLCO1B1 gene is 130% higher than in those without the polymorphism (114).

3.9.6.1.2.1.2. Genetic variants in the cytochrome P enzyme system (CYP)

CYP enzyme system is the most important enzyme system associated with phase 1 metabolism of various statins and has more than 30 known isoenzymes. CYP3A4 and

CYP2D6 catalyze the majority of CYP-mediated drug metabolism in humans. CYP3A4/5, CYP2D6, and CYP2C9 have genetic variants, which can affect their rates of metabolism. CYP2D6 plays a major role in the metabolism of simvastatin. More than 50 mutations of CYP2D6 gene have been described. Based on these mutations, patients can be classified into extensive metabolizers, poor metabolizers and ultra rapid metabolizers with significant interracial variability in the distribution of the allelic variants. Poor metabolizers should theoretically have higher plasma levels of the statin and are at higher risk of adverse effects. 5–10% of Caucasians are poor metabolizers compared to 2% of Blacks and <1% of Asians. Two factors may reduce the importance of CYP in statin myopathy. The CYP statin metabolic pathway appears most important with concomitant medications which, if metabolized by the same CYP isoenzymes as the statin, could inhibit statin metabolism (114).

3.9.6.1.2.2. Genetic variants affecting vascular function

Statins can affect vascular function via mechanisms not mediated by lipid changes. Apoptosis, or programmed cell death, participates in vascular remodelling. Atorvastatin, lovastatin, and simvastatin produce a dose dependent increase in apoptosis in vascular smooth muscle cells (VSMCs). Statin-induced apoptosis could limit atherosclerotic plaque growth by reducing VSMC proliferation, but apoptosis in skeletal muscle cells with statins could contribute to statin myopathy. There is not to knowledge any evidence that statin myopathy is related to changes in vascular function. Nevertheless, among 102 statin-treated patients, CK values were strongly associated with genetic variations in the angiotensin II Type 1 receptor (AGTR1) and with nitric oxide synthase 3 (NOS3). Neuronal nitric oxide on the sacrolemma may reduce muscle fatigue after exercise. Such results suggest that changes in NO itself or in vascular function may contribute to statin myopathy (114).

3.9.6.1.2.3. Genetic variants affecting pain perception

Myalgia is the most common presenting symptom of statin myopathy but some patients have asymptomatic CK elevation raising the possibility that individual differences in pain perception affects the frequency of myopathic complaints. The neurotransmitter serotonin influences pain perception and has been implicated in the pathogenesis of pain syndromes. Serotonin receptors have also been associated with rheumatic conditions, clinically characterized by muscle weakness and pain (114).

The relationship between variants in the 5alpha-hydroxtryptamine receptor (HTR) and serotonin transporter gene (LDC6A4) were examined in 195 patients treated with atorvastatin, simvastatin, or pravastatin. Results suggest that serotonergic genes variants may contribute to the severity of myalgia in statin-treated patients (115).

3.9.6.1.2.4. Inherited diseases of muscle energy production

3.9.6.1.2.4.1. Glycogen storage disorders

Both muscle phosphorylase deficiency (McArdle disease) and alpha-glucosidase deficiency (Pompe's disease) have been associated with statin myopathy. McArdle disease is an autosomal recessive deficiency of muscle phosphorylase and typically presents in the first two decades of life with exercise intolerance and chronic muscle cramps, with severe cases presenting with rhabdomyolysis and myoglobinuria (116).

3.9.6.1.2.4.2. Carnitine palmitoyl-2 (CPT-2) deficiency

CPT-2 deficiency is the most common inherited disorder of lipid metabolism usually manifesting in adulthood with recurrent myalgia, rhabdomyolysis and myoglobinuria, precipitated by heavy exercise, cold exposure, infection, emotional stress or fasting. CPT-2 is an enzyme attached to the inner mitochondrial membrane allowing acyl Co-A into the mitochondrial matrix for β-oxidation of fatty acids which is the major energy source for sustained skeletal muscle exercise. Biochemical studies have shown that patients with CPT-2 deficiency have an increased excretion of acylcarnitine and an elevated acylcarnitine/carnitine ratio in the plasma. Results suggest that statins can both provoke and worsen symptoms in individuals with diagnosed or occult CPT-2 deficiency (114).

3.9.6.1.2.4.3. Myoadenylate deaminase (MADA) deficiency

Myoadenylate deaminase converts adenosine 5 monophosphate (5 AMP) to inosine monophosphate (IMP) thus playing an important role in regulating ATP levels in the skeletal muscle. MADA deficiency is an autosomal recessive disorder of skeletal muscle associated with a mutation in AMP-D1 gene (114). Interestingly, Verzijl et al. showed that there was no increase in the frequency of AMP-D1 mutations in patients with neuromuscular disease compared to controls nor was the frequency of AMP-D1 mutations higher in patients with exercise intolerance compared to asymptomatic controls (117).

Consequently, the finding of increased prevalence of AMP-D1 genetic defects among patients with statin myopathy suggests that statins could act to uncover the symptoms in otherwise asymptomatic patients (114).

3.9.6.1.2.5. Mitochondrial myopathies

Mitochondrial myopathies are caused by maternally transmitted, mitochondrial DNA (mt DNA) mutations that affect enzymes in the oxidative phosphorylation pathway. As it is mentioned such mutations produce symptoms in organs with high obligate energy requirements including muscle and neurological tissues. Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke like episodes (MELAS) is a mitochondrial disorder resulting from genetically confirmed mutations, of A3243G, T3271C, and A3260G and manifesting as encephalopathy, stroke like episodes, ataxia, optic atrophy, and fixed proximal muscle weakness. There are at least three reports of MELAS developing after initiation of statin therapy in previously asymptomatic patients suggesting that statins may produce symptoms in MELAS carriers who were previously asymptomatic. (114).

3.9.6.1.2.6. Genetic variants in CoQ10 production

CoQ10 is produced via the mevalonate pathway. Statins inhibit the production of mevalonate from β-hydroxy-β-methylglutaryl CoA and thereby could reduce CoQ10 production. Statins do lower blood CoQ10 concentrations, but CoQ10 is transported in lower density lipoproteins and adjusting the decrease in serum CoQ10 for the decrease in serum cholesterol suggests that most of the decrease in serum CoQ10 levels is due to reduction in CoQ10 transport capacity. Evidence that muscle CoQ10 levels are decreased is less conclusive, although among 132 patients with statin myopathy, 50% had muscle Q10 levels 2 times less than normal (114).

3.9.6.1.2.7. Muscular dystrophies (MD)

The MDs are a group of inherited muscle diseases that cause progressive muscle weakness. Most patients with MDs including Duchenne, Becker, limb girdle, facioscapulohumeral and myotonic dystrophy have the onset of symptoms in childhood to early adulthood but some MDs including, oculopharyngeal and certain forms of limb girdle muscular dystrophies, can present later in life. Newly diagnosed patients with inherited myopathies have been reported to have a higher exposure rate to statins (mean exposure time was 33 months) than statin-exposed normal controls (statin exposure time

up to 3 months). The age of the myopathic patients was above 60 years which suggests that statin provoked the symptoms in these otherwise asymptomatic patients (114).

3.9.6.1.2.7. Calcium homeostasis

Normal regulation of calcium (Ca2+) release and reuptake is critical for normal excitation-contraction coupling in the skeletal muscle. The initial increase in intracellular Ca2+ in response to the action potential is mediated by L-type Ca2+ channels. This increase in Ca2+ opens the ryanodine receptors (RYR1) located in the sarcoplasmic reticulum which markedly increases intracellular Ca2+ and initiates muscle contraction. Ca2+ is pumped back into the sarcoplamic reticulum via Ca2+ATPase to terminate contraction. Simvastatin, cerivastatin and clofibric acid respectively have been shown to cause massive Ca2+ release from the sarcoplasmic reticulum in cultured myoblasts, mouse and rat skeletal muscle fibres, and skinned muscle fibres. Lovastatin decreased sarcolemmal Na+ K+ ATPase density and pump current in skeletal and cardiac muscles. This leads to excess intracellular Na+ and activation of Na+/Ca2+ antiport in the cell membrane causing an increase in intracellular Ca2+. Also statins cause decreased Ca2+ ATPase activity further contributing to increased sarcoplasmic Ca2+ (114).

3.9.6.1.2.7.1. Malignant hyperthermia susceptibility (MHS)

MHS is a subclinical autosomal dominant pharmacogenetic trait, that produces malignant hyperthermia (MH) episodes characterized by hyperthermia, skeletal muscle rigidity, metabolic acidosis and rhabdomyolysis on exposure to commonly used volatile anesthetic agent such as halothane or depolarising muscle relaxants such as succinylcholine (114). Two cases of previously asymptomatic men who developed muscle cramps, fatigue and CK elevations on statins were also subsequently shown by IVCT to have MHS (118).

3.9.6.1.2.7.2. Rippling muscle disease (RMD)

RMD is a skeletal muscle disorder first described in 1975 that presents as muscle hyperexcitability, myoedema and visible rippling in response to mechanical stimulation (114).

There is only one report of previously undiagnosed RMD presenting in a 54-year-old patient treated with statins. Symptoms resolved with discontinuation of simvastatin but reoccurred on statin rechallenge (119).

3.9.6.1.3. Co-Morbidities

The incidence of statin-induced rhabdomyolysis may be higher in patients with existing myopathies, either hereditary (e.g. carnitine palmityl transferase II deficiency, McArdle's disease and myoadenylate deaminase deficiency) or acquired (e,g. postpolyomyelitis syndrome). Statins have also been implicated in the potential aggravation of myasthenia gravis. Furthermore, an underlying metabolic predisposition consisting of biochemical abnormalities in mitochondrial or fatty acid metabolism in myocytes may render some apparently healthy individuals more susceptible to the development of statin induced myopathic outcomes than others. As it was also mentioned in the same publication that underlying chronic systemic diseases may serve as non-modifiable risk factors that decrease statin metabolism and excretion, and thereby increase their systemic bioavailability. These factors render some patients more susceptible to myopathy and increase the probability of adverse muscle events, which may ensue at any time during the administration of a statin. Although limited data suggest a beneficial cardiovascular effect of statins in patients with moderate renal impairment, coexisting renal failure increases the risk of statin-induced myopathic events. Diabetes mellitus constitutes a further myopathic risk factor in patients receiving statins, particularly combined with advanced age and chronic renal failure, although there is no consensus of opinion. It was mentioned that enhanced risk of statin-induced myopathy with excessive alcohol consumption cannot be conclusively supported by data from randomized trials as alcoholism is an exclusion criterion in most trials. However, increased alcohol intake per se confers a myotoxic potential and alcohol abuse could raise the blood levels of statins. Untreated hypothyroidism is considered to increase the risk of statin myopathy, and statins may aggravate the muscle symptoms and CK elevation caused by occult hypothyroidism. Liver dysfunction has been considered in the publication as a risk factor for statin myopathy, mainly due to the involvement of the hepatobiliary system in the metabolism and excretion of most statins. Although it is mentioned in the publication that hepatic dysfunction has been associated with statin-induced rhabdomyolysis in reports by regulatory authorities, the exclusion of patients with hepatic failure from randomized controlled trials prevents the establishment of a direct link between impaired liver function and heightened risk of myopathy. Furthermore, acutely acting factors predispose to myopathy independently, and may trigger the development of severe myopathy, even rhabdomyolysis, in statin-

receiving individuals. Such precipitating conditions include the use of addictive drugs (e.g. amfetamines, cocaine, heroin, LSD, ecstasy), serious viral or bacterial infection, major trauma and intense muscle activity. Statins can exacerbate exercise induced skeletal muscle injury, as reported in an observational study in patients receiving highdose statins and as suggested by the greater CK response to exercise in statin-compared with placebo-treated patients. Statin-related myopathy has been reported in the setting of extensive surgical operations; therefore, a short-term withdrawal of statins during hospitalization for major surgery is recommended. In the case of vascular surgery in particular, including coronary bypass procedures, it is told that statins should not be discontinued in light of their beneficial plaque stabilizing effect, with the exception of preoperative muscular symptoms, marked perioperative tissue compression or prolonged postoperative energy deprivation (32).

In addition to this, advanced age, severe electrolyte disturbances, surgery and hypoxia were thought to be predisposing factors. Certain genetic disorders, such as disorders of glycolysis, glycogenolysis, defects in fatty acid oxidation, and mitochondrial dysfunction, do not allow appropriate use of carbohydrates or lipids as energy substrates and was thought as predisposing factor. Patients with these enzymatic defects may be at increased risk of myotoxicity when exposed to statin drugs. Enzyme defects are found in 23% to 47% of adult patients with rhabdomyolysis (72).

3.9.6.2. Statin Properties

3.9.6.2.1. Dose-Dependent Effects

In a meta-analysis which covers approximately >108000 patients, Silva Matthew reported that more intensive strategy for the reduction of LDL-C was associated with more adverse events (95).

While the therapeutic benefit from statin therapy is related to the achieved LDL-C reduction, the risk of adverse muscular events appears to be a dose-dependent adverse effect regardless of the degree of LDL-C decrease. However, there does not appear to be a linear relationship between plasma levels achieved by a certain drug dose and the risk of adverse muscular events. Increased myopathic risk has been demonstrated with higher than marketed doses of simvastatin (160 mg) and pravastatin (160 mg). It is told in the same publication that an increased incidence of myopathy has also been shown in patients with acute coronary syndromes receiving simvastatin 80 mg daily compared

with placebo or simvastatin 20 mg. A higher incidence of statin-related myalgia was attributed to atorvastatin 80 mg compared with simvastatin 20 mg but notably this did not occur when atorvastatin 80 mg was compared with either atorvastatin 10 mg or placebo (32).

3.9.6.2.2. Physicochemical Properties of Statins: Lipophilicity versus Hydrophilicity

In vitro research data indicate that pravastatin, which is water soluble, is less myotoxic in relation to lovastatin and simvastatin. Moreover, pravastatin was 100-200 times (in an inversely dose-dependent mode) less myotoxic. Overall, different statins seem to exert diverse dose-dependent effects on the HMG CoA reductase activity of non-hepatic cells in vitro. The decreased myotoxicity of pravastatin appears to be related to its decreased penetration of the cell membrane and thus uptake by extra-hepatic tissues, presumably associated with the hydrophilicity of the molecule. Pravastatin is taken up by the hepatic cells via a sodium-independent bile acid transporter, the OATP, which, along with sodium-dependent taurocholate cotransporting polypeptide, also mediates the active hepatic uptake of the hydrophilic rosuvastatin molecule. The lipid-rich membranes of non-hepatic cells, such as muscle cells, lack OATP so that they function as a barrier to hydrophilic statins while allowing passive diffusion to lipophilic statins. However, the hydrophilicity of some statins per se has not been proven to offer clinically significant muscular protection and no clinical evidence supports a direct association between the degree of lipophilicity and the myotoxic potential since cases of rhabdomyolysis have also been attributed to hydrophilic statins (32).

Cytotoxicity of pitavastatin is examined using a prototypic embryonal rhabdomyosarcoma cell line (RD cells). To compare the cytotoxicities of statins, they examined the effects of all statins on RD cell viability. As shown in Figure 10 (a), lipophilic statins, cerivastatin, simvastatin acid, fluvastatin, atorvastatin, lovastatin acid and pitavastatin, significantly reduced cell viability in a concentration dependent manner.

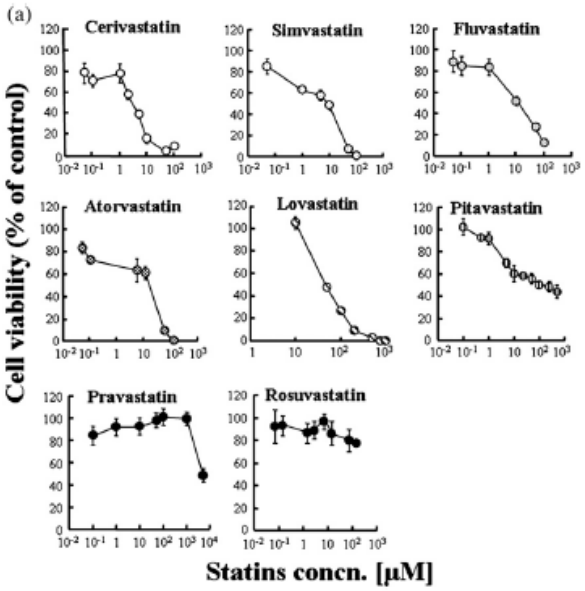


Figure 10 (a). Effects of statins in RD cells.

On the other hand, the effects of hydrophilic statins, pravastatin and rosuvastatin were very weak. As shown in Figure 10 (b), statins induced the reduction of cell viability correlated with these partition coefficients (120).

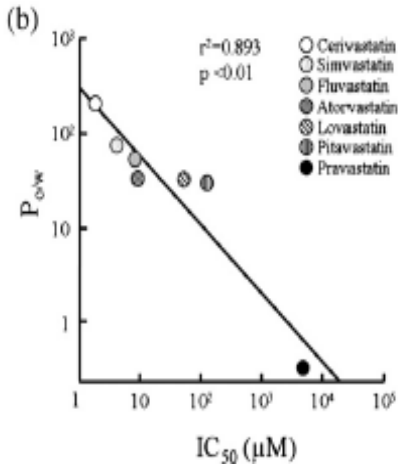


Figure 10 (b). IC_{50} concentration of statins

3.9.6.3. Statin-Drug Interactions

In general, DIs result from a change in the concentration of either or both drugs in the body (pharmacokinetic interaction) or from a change in the relation between drug concentration and the response of the body to the drug (pharmacodynamic interaction). Pharmacokinetic interactions can involve alterations of normal absorption, distribution, metabolism, or excretion of the substrate drug. Clinically significant DIs with statins are thought to result from altered pharmacokinetics, primarily metabolism, as these drugs are highly selective inhibitors of HMG-CoA reductase with no known effects on other receptors, making pharmacodynamic interactions less likely. For adverse events reported within the first year of marketing of each statin, overall 60% were in the presence of interacting drugs (121).

3.9.6.3.1. Mechanisms of statin drug interactions

Majority of reported cases pertain to competition at the level of hepatic metabolism, considering that over half of currently available drugs are metabolized by the CYP3A4 isoenzyme; inhibition of the CYP activity by coadministered drugs increases the risk of myopathic events. Simvastatin and lovastatin appear to be more susceptible to the inhibiting effect of other CYP3A4 substrates than atorvastatin. Similarly, the interaction between fluvastatin and CYP2C9 inhibitors or competitive substrates may be of clinical importance, whereas CYP450 isoenzymes are minimally involved in rosuvastatin clearance. (32). Inhibition of the liver P-450 system, other sites of potential statin DIs include inhibiting metabolism by intestinal P-450 isoenzymes, preventing P-glycoprotein (PGP) transfer across the intestinal wall, blocking organic anion transporting polypeptide (OATP)–mediated hepatic uptake, and decreasing renal elimination of hydrophilic metabolites. Each of the marketed statins differ in their pharmacokinetic profile, which affects the potential mechanisms and sites for DIs. In addition, genetic variability results in individual differences in expression of specific cytochrome P-450 isoenzymes, which can significantly alter drug disposition, affecting efficacy and risks of ADRs and DIs (121).

Drugs that has interaction with statins are listed in the table below:

Table 17. Substances that may precipitate statin induced myopathy

Non-hypolipidaemic medicines
Ciclosporin
Macrolide antibacterials (erythromycin, clarithromycin)
Azole antifungals (itraconazole, ketoconazole, fluconazole)
Calcium channel antagonists (diltiazem, verapamil)
Nefazodone
HIV protease inhibitors (ritonavir, nelfinavir, indinavir)
Warfarin
Histamine H_2 receptor antagonists (cimetidine, ranitidine)
Omeprazole
Amiodarone
Hypolipidaemic medicines
Fibrates (gemfibrozil > bezafibrate, clofibrate, fenofibrate)
Niacin
Other substances
Grapefruit juice
Over-the-counter medications (Chinese red rice fungus)

3.9.6.3.2. Interactions with Non-Hypolipidaemic Agents

3.9.6.3.2.1.Pharmacokinetic Interactions with Cytochrome P450 Enzyme (CYP) 3A4 Inhibitors and Competing Substrates

Inhibitors of CYP3A4 isoenzyme decrease statin metabolism and thus increase their serum levels and the likelihood of myopathy. Such enzymatic inhibitors include azole antifungals (itraconazole, ketoconazole, fluconazole), macrolide antibacterials (erythromycin, clarithromycin), calcium channel antagonists diltiazem and verapamil, the antidepressant nefazodone and the consumption of grapefruit juice exceeding approximately 1L daily (32). Other antidepressants such as fluoxetine, fluvoxamine, sertraline are also be thought to cause drug interactions especially with atorvastatin, lovastatin and simvastatin (52). In addition, concomitant use of neomycin and lovastatin cause rhabdomyolysis with or without renal impairment (16). Also grapefruit juice contains 60,70-dihydroxybergamottin, which acts as an inhibitor of the intestinal CYP3A4 isoenzyme resulting in decreased metabolism and thereby enhanced bioavailability of statins (32).

Oral bioavailability of drugs including statins that are metabolized by intestinal wall CYP3A4 is thought to increase with grapefruit juice ingestion due to a loss of this isoenzyme function within the intestinal epithelium (121).

HIV protease inhibitors (ritonavir, nelfinavir, indinavir) are recognized CYP3A4 inhibitors and this property renders the myotoxic potential of their combination with statins high risk, in particular those statins that rely to a large extent on the CYP3A4

isoform for their metabolism. Of clinical interest is the adverse effect of HIV protease inhibitors on the lipid profile, which may increase the risk of cardiovascular disease and- pancreatitis and often requires the administration of lipid-lowering agents. Statins are the most effective medicines for the treatment of hypercholesterolaemia in patients who have undergone transplantation, and their immunomodulatory properties appear to provide general protection for the graft. However, ciclosporin (cyclosporine) inhibits both intestinal and hepatic CYP3A4 activity and can therefore lead to increased bioavailability of statins metabolized by this cytochrome. The more lipophilic the statin and the greater the systemic exposure to unbound active statin compound, the greater the potential for myopathy. Pravastatin and fluvastatin are less likely to interact with ciclosporin on a pharmacokinetic basis. However, ciclosporin has been reported to increase serum levels of pravastatin. Competition at the level of biliary clearance resulting in reduced pravastatin removal through the bile duct and prevention of the P-glycoprotein transfer are considered the main pathomechanisms, indicating that CYP3A4 is not the only site involved in clinically relevant ciclosporin-statin interactions (32). In addition to these mechanism of actions, third mechanism of action was to inhibit multidrug resistance protein 2 (MRP 2) which is believed to transport hydrophilic agents (72).

Combination of statins with warfarin is likely to increase the serum levels of warfarin, thereby potentiating its anticoagulant effect. Regular anticoagulation control and possibly warfarin dose adjustment may thus be required. However, the potentiating effect of warfarin on statin levels has not been studied sufficiently. A hypothesis has been articulated that as warfarin constitutes the substrate of CYP2C9, and partly of CYP3A4, it could compete with statins in their enzymatic conversion (32).

When statins used concamitantly with colchicine, varying degress of myopathy including rhabdomyolysis may occur (31).

Combination of propranolol with either pravastatin or lovastatin has resulted in a small decrease in bioavaliability of the lipid lowering agents possibly due to their increased first-pass hepatic clearance caused by propranolol-induced increase in hepatic blood flow. In contrast, propranolol had no apparent effect on pharmacokinetic properties of fluvastatin. Co-administration of cerivastatin with either magnesium/aluminum hydroxide or cimetidine antacids resulted in no drug-drug

interaction. Simvastatin was showed to have no effect on the efficacy and pharmacokinetics of ramipril when they were used concomitantly (16).

3.9.6.3.2.2. Pharmacokinetic Interactions with CYP2C9 Inhibitors and Competing Substrates

Azole antifungal agents are recognized inhibitors of CYP2C9, as well as the previously mentioned CYP3A4. This necessitates a higher index of suspicion when they are administered in patients receiving fluvastatin. For example, fluconazole has been reported to increase fluvastatin bioavailability, although no cases of rhabdomyolysis attributable to such a combination are known. Furthermore, histamine H2 receptor antagonists cimetidine and ranitidine, and the proton pump inhibitor omeprazole, which are also substrates of CYP2C9, enhance fluvastatin's systemic exposure, but without particular clinical significance. Of note, omeprazole also appears to possess a CYP3A4 induction capacity, potentially increasing the biotransformation and thus decreasing levels of statins that are substrates of the CYP3A4 isoenzyme (32).

Fluvastatin is a statin which one is metabolised by cytidylyltransferase 2C9 (CYP2C9) isoenzyme and has been shown to singnificantly increase the concentration of diclofenac, indicating fluvastatin is a potent inhibitor of CYP2C9. Other drugs metabolized by CYP2C9 with documented increased effect when concomitantly administered with fluvastatin include warfarin and phenytoin (121).

3.9.6.3.3. Interactions with Other Hypolipidaemic Agents

3.9.6.3.3.1. Fibrates

In many cases of mixed dyslipidaemia, in diabetic patients or in patients with high triglycerides despite the achievement of the desirable LDL-C goal, the coadministration of statins with fibrates is an attractive therapeutic option (32). Because of their modest effect on lowering LDL cholesterol levels, howerever, fibrates fail as monotherapy to achieve complete resolution of dyslipidemia. As a result, fibrates are often used with statin drugs (72).

Combination of any statin with fibrates increases the risk of myopathy, which is usually observed within the first 12 weeks by the initiation of treatment (32). In an analysis of 20 combination fibrate/statin studies undertaken in the last 5 years (N=516), clinically apparent myopathy occurred in approximately 1% of cases (122).

Statin-fibrate interaction can occur at different levels. Fibrate drugs may impair liver function, which may result in a diminished hepatic extraction of statin drugs, leading to higher plasma drug levels. Patients with impaired liver function should therefore not be receiving combination therapy. There may also be an increased risk of myopathy with renal dysfunction because fibrate drugs are primarily renally excreted (72).

Increased risk of myositis (moderate CK levels as per the NLA's Muscle Expert Panel) with statins, fibrates, and other patient-related variables. These researchers showed that the average time to the onset of myositis was ≤2 years with both statin-fibrate combination therapy and statin use alone. Statins, fibrates, pre-existing renal disease, and hepatic disease are all significantly associated with myositis (123).

A significant increase in the risk of myopathies and myalgias with prolonged statin exposure at both 26 and 52 weeks and that the risk for myopathy for all statins and fibrates increases significantly after 12 months of use (124).

Even if most reports involve gemfibrozil, other fibrates (bezafibrate, clofibrate, fenofibrate) have also been implicated in cases of rhabdomyolysis when used alone and have an additive myotoxic potential when combined with statins. The presence of gemfibrozil in most cases of rhabdomyolysis is partly explained by its wider clinical use than other fibrates; however, the differential safety profile of fibrates seems to remain even after correction for the wider prescription of gemfibrozil (32). Selection of gemfibrozil over fenofibrate for combination statin lipid-lowering therapy can result in a significant increase in risk, as gemfibrozil is a potent inhibitor of several components of statin metabolism (conjugation and biliary excretion), while fenofibrate does not appear to interact with statins through these mechanisms (121).

Since fibrates do not interfere with CYP mediated statin elimination, the additive adverse effect when combined with statins appears to have a predominantly pharmacodynamic basis (synergy) (32). Hypothetical mechanism of pharmacodynamic interaction is that these medications lead to increased sarcolemmal fluidity and muscle membrane destabilization (72).

Concomitant use of gernfibrozil and atorvastatin may increase risk of myositis and rhabdomyolysis (16).

3.9.6.3.3.2. Niacin

Addition of niacin in a statin-receiving patient can yield complementary benefits in achieving a comprehensive lipid control. The concomitant administration of statins with high doses of niacin has been associated with rhabdomyolysis in a limited number of anecdotal reported cases through a mechanism that remains unknown but appears to be unrelated to statin serum levels. Niacin is not implicated as a strong precipitating factor for statin-induced myopathy, and the combination of statin and niacin is considered to carry a lower risk than statin-fibrate coadministration. Based on the evidence, no excessive risk of myopoathy as a result of a statin-niacin combination, compared with that expected by adding one agent to the other, can be supported (32).

3.9.6.3.3.3. Ezetimibe

Combined inhibition of intestinal cholesterol absorption mediated by ezetimibe and hepatic cholesterol synthesis via statins has emerged as a challenging therapeutic option. An enhanced lipid-lowering effect and comparable safety profile was shown when ezetimibe was added to statins in patients with hypercholesterolaemia. According to the same article, the incidence of muscle-related events was not higher in patients taking simvastatin alone than the combination of simvastatin plus ezetimibe according to pooled data from 17 relative randomized clinical trials. Overall evidence cannot support enhanced risk for statin-related myopathy by the coadministration of ezetimibe (32).

3.10. Compliance to statins in the real world

Despite the well-established benefits and abundance of clinical management guidelines strongly advocating statin use in high-risk cardiac conditions, long-term adherence to statin regimens in patients who are appropriate candidates has generally been poor, and continued use of statins drops substantially over time. It was thought that the causes for noncompliance are multifactorial. One of the major reasons is the unfounded fear by patients and physicians alike regarding the toxicity of lipid-lowering agents. A major contributor to this anxiety is the glut of information on the Internet on the adverse effects of statins. Another explanation for the nonadherence of patients to statin therapy is thought as the lack of education and awareness about the long-term benefits of treatment, especially since they do not feel better right away. Younger age, female gender, black or hispanic ethnicity, higher comorbidity, and lower median

income were some of the patient-related predictors of nonadherence to prescribed statin regimen. Among physician-related factors, it was found that patients were more likely to comply if the statin was prescribed by a cardiologist or a primary care doctor (30).

3.11. Management of patients with statin intolerance

There are 3 ways for management of patients with statin intolerance.

3.11.1. Decreasing Statin Dose

After muscle symptoms resolve and patients are rechallenged, many will tolerate a lower dose of the same or another statin. In general, a lower dose of a statin of similar efficacy would be the next choice. Approximate comparable efficacy can be obtained from 5 mg of rosuvastatin, 10 mg of atorvastatin, 20 mg of simvastatin, 40 mg of pravastatin or lovastatin, and 80 mg of fluvastatin. Fluvastatin, although less efficacious per milligram than other statins, has been recommended by some experts because of its relatively low incidence of myalgia compared with other statins. The extended-release formulation of 80 mg alone or in combination with ezetimibe has been shown to be an effective and well-tolerated lipid-lowering option. Fluvastatin is not a cytochrome P450 3A4 or glucuronidation substrate and has relatively low lipophilicity, which may contribute to a slower rate of passage into muscle cells. The slow-release formulation delays absorption from the gastrointestinal tract and increases first-pass hepatic uptake, avoiding hepatic saturation and thereby decreasing peripheral blood concentrations while maintaining the efficacy of higher doses (52).

3.11.2. Intermittent Statin Dosing

In addition to decreasing statin dose, less frequent dosing intervals can also be effective. For example, 2.5 to 20 mg of rosuvastatin once a week has been shown to decrease LDL-C by 25% and be tolerated by up to 70% of statin-intolerant patients. Twice and alternate-day regimens of rosuvastatin and atorvastatin alone or with ezetimibe have also been well tolerated in patients with muscle symptoms as well as transaminase elevations (52).

3.11.3. Change in drug therapy

Patients requiring additional LDL-C lowering on their tolerated statin dose, or who have been shown to be intolerant to all statins at any dose, may still tolerate other

LDL-C-lowering therapies. Alternative drug therapies other than statins can be used in the treatment of patients with statin intolerance. These include ezetimibe, bile acid sequestrants, fibrates and niacin, LDL- Apheresis, red yeast rice and other potential new therapies. Ezetimibe and bile acid sequestrants appear to be the best tolerated alternative to statins, although the occasional statin-intolerant patient may tolerate a fibrate or niacin (although generally not in doses that can lower LDL-C). Details of the mechanism of action of these drugs were given in part 3.4.1.2. Drug Therapy. In addition to these drugs; patients can also be given the drugs mentioned below for the control of statin induced side effects or statin intolerance (52).

3.11.3.1. Vitamin D Deficiency and Supplementation

Correction of vitamin D deficiency has been proposed to treat statin intolerance on the basis of anecdotal reports and nonrandomized studies. Randomized clinical trials are needed to evaluate efficacy, dosing, and safety before vitamin D supplementation is routinely administered to statin-intolerant patients (52).

3.11.3.2. Coenzyme Q10

Statins reduce coenzyme Q10 levels in serum and that supplementation of coenzyme Q10 increases these levels. However, the effect of statin therapy on coenzyme Q10 levels in muscle is inconsistent, and randomized trials of coenzyme Q10 supplementation have been conflicting, with only one study demonstrating improvement in muscle symptoms. Some have suggested that a dosage of coenzyme Q10 of 100 to 200 mg daily is needed. Coenzyme Q10 may be of value for its placebo effects in some patients (52).

4. RESULTS

In order to calculate the cost of muscle adverse effects for one patient, management of the muscle adverse effects should be carefully understood. As it is mentioned in part 1. Introduction, majortiy of statin-induced myopathy cases are asymptomatic. The Muscle Expert Panel which was composed of a clinical cardiologist, an exercise physiologist and skeletal muscle expert and an expert in preventive cardiology who also examined skeletal muscle complications of statin use does not advocate routinely measuring or monitoring creatinin kinase (CK) levels in asymptomatic patients because marked, clinically important CK elevations from statins alone are rare; most CK elevations during statin therapy are benign and related to such factors as recent physical exertion, and there is no evidence that the added cost of such monitoring improves medical care (90). So, the patients who are symptomatic will be focused on.

In this thesis, calculations are done according to two different scenarios. In the first scenario, the patient or the doctor is aware of the statins' muscle related adverse effects. In the second scenario, the patient and the doctor is not aware of the statins' muscle related adverse effects. In addition patients who are under general health insurance will not pay for the costs that will be mentioned below. So all these costs are paid by the government. In these two scenarios, direct medical costs and calculate the total cost for each from payer's perspective will be evaluated.

First scenario:

In the first scenario, a 55 year old, 70 kg patient has been prescribed statin. As the patient continues to take him/her drug, he/she realizes persisting muscle related complaints such as pain or weakness. Because of the muscle related pain, patient was expected to visit an orthopedist in a public hospital. According to a review published in 2011, the first thing that should be done is to perform a detailed physical examination. After that many laboratory examinations are performed to evaluate the reason of muscle related complaints. Details of the analysis are given below:

Physical examination

Examination of patients with possible statin-induced myopathy begins with a general assessment for signs of hypothyroidism or excess alcohol consumption. Ankle-

brachial indices are used to exclude significant peripheral vascular disease. The musculoskeletal examination focuses on muscle atrophy, tone, and strength but also excludes tendinopathies, arthropathies, and myofascial pain syndromes, which are often confused with muscle pain. Precise dynamometric measurements are tracked at subsequent visits and are helpful in following recovery from myopathy as well as in tracking strength during subsequent statin rechallenges. Routinely look for hyperreflexia, fasciculations, extensor-plantar responses, and decreased heel-to-shin movement, which would suggest myelopathy. Reflexes and a sensory examination including vibration and temperature sensation help exclude radiculopathy and peripheral neuropathy (91).

Laboratory evaluation

After physical examination, physician offers many tests to understand the main cause of the pain. In every patient with possibly statin myopathy, physician should measure:

• The serum CK level (preferably more than 72 hours after exercise)

• The 25-hydroxy vitamin level

• The thyroid-stimulating hormone level.

Further laboratory evaluation depends on the findings and will often be directed by subspecialists. For example, the sedimentation rate, anti-Ro and anti-La antibodies, and the myositis panel in patients with elevated CK whose other findings suggest an autoimmune or inflammatory process can be assesed. Serum carnitine levels (free, total, and esterified), fasting serum lactate levels, and serum cortisol in those with findings suggestive of metabolic myopathy can be tested. But because the latter tests are not necessary to detect statin induced myopathy, it will not be involved in the calculation. In the laboratory examination, the patient was found to have approximately 10 fold the upper limit of normal serum creatinine and creatine phoshokinase levels. Also patient's potassium level was above the normal interval. Patient's plasma bicarbonate level was 11.2 mEq/L.

Ultimately, a muscle biopsy may be necessary to exclude inflammatory or necrotizing myopathies in patients whose CK remains elevated despite withdrawal of statins. It may also be helpful when other findings suggest a metabolic myopathy. When

a biopsy is needed, magnetic resonance imaging of the affected limb may identify an affected muscle for biopsy (91).

Among all the imaging tests, muscle biopsy is the most widely used as I mentioned in part 3.9.5.2.1. Muscle Biopsy. In order to make a logical biopsy, it is beneficial to detect the right limb in which the muscle sample will be taken. So, I will take into account the cost of Magnetic Resonance Imaging too.

Direct cost of scenario 1

Costs of the examination, laboratory tests or other diagnostic tools were specified in Health Application Announcement as "processing score". Also it was mentioned in Health Application Announcement revised 03.07.2012 that "1" processing score equals to 0.593 TL. So, I will calculate the cost of the examination, tests and diagnostic tool by multiplying each one's processing score with 0.593 TL.

Examination cost

Visit an orthopedist or a nephrologist: Cost of a visit was specified in Health Application Announcement revised in 03.07.2012 as 26.14 processing score. So, visit an orthopedist or a nephrologist equals to 26.14x0.593= 15.50 TL

Laboratory tests cost

Thyroid test (TSH level): Cost of this test was specified in Health Application Announcement revised in 03.07.2012 as 7.59 processing score. So, cost of this test equals to 7.59x0.593= 4.5 TL

CK test: Cost of this test was specified in Health Application Announcement revised in 03.07.2012 as 2.36 processing score. So, cost of this test equals to 2.36x0.593= 1.4 TL

25-hydroxy vitamin test (Vitamin D test): Cost of this test was specified in Health Application Announcement revised in 03.07.2012 as 43.00 processing score. So, cost of this test equals to 43.00x0.593= 25.5 TL

The Muscle Expert Panel recommends a clinical approach to treating and evaluating myopathic patients. This clinical approach includes cessation of statin therapy, observation for symptom and CK resolution, and possible repeat challenge to determine whether symptoms reappear (90). In order to understand if the muscle symptoms related with statin or not, patient has to visit doctor twice. In order to follow up CK level, doctor will perform this test again in the second visit. Only CK level will

be tested again because other tests (25-hydroxy vitamin and thyroid) are indicative of other disorders and it is enough to measure them once to eliminate other factors that may cause muscle symptoms.

If the doctor suspects from statin-induced myopathy at the end of the second visit, he/she will perform muscle biopsy. And to determine the exact region of muscle damage, he/she may want to perform magnetic resonance.

Diagnostic methods cost

Muscle biopsy: Cost of this method was specified in Health Application Announcement revised in 03.07.2012 as 70.15 processing score. So, cost of method equals to 70.15x0.593= 41.6 TL

Magnetic resonance: Cost of this method was specified in Health Application Announcement revised in 03.07.2012 as 109.61 processing score. So, cost of method equals to 109.61x0.593= 65 TL

Total of direct costs:

Examination: Visit a doctor (twice)= 15.50x2= 31 TL

Laboratory tests: Thyroid test- 4.5 TL

25- hydroxy vitamin test (D vitamin test)= 25.50 TL

CK test (twice)= 1.4x2= 2.8 TL

Diagnostic methods: Muscle biopsy= 41.6 TL

Magnetic resonance= 65 TL

TOTAL: 170 TL

Second scenario

In the second scenario, same patient has muscle related complaints and visits his/her doctor. In this scenario, patient is not aware of the muscle related adverse events of statins. That means his/her awareness was not raised enough by his/her doctor and pharmacist. In addition to this, the doctor may also miss the point that the complaints of the patient may be directly related with statin drug. As it was told in a review article, if both the patient and the doctor miss the signs and symptoms of statin-induced myopathy, the patient was expected to have rhabdomyolysis which leads to acute tubular necrosis. Symptomatic treatment should be instituted immediately in patients with acute rhabdomyolysis. Rehydration is the first step (108). According to my expert Prof. Dr. Mustafa Arıcı's suggestions, there is not a standard treatment protocol for rehydration. The patient is given the rehydration fluids and the urination of the patient is observed. If the patient can urinate, rehydration treatment is repeated. But if the patient can not urinate, rehydration treatment is stopped. Renal impairment is suspected in these patients and the patient may undergo hemodialysis. So according to Prof. Dr. Mustafa Arıcı, it is not possible to say a standard rehydration treatment protocol period. Also it is specified by my expert that, it is not possible to tell an exact time interval (such as it may change from 6 hours to 4 days). It may change according to patient co-existing diseases or risk factors such as heart failure (109).

Izotonic saline infusion (1,5 L/hour and than 2.5mL/kg/hour infusion), sodium bicarbonate and furosemide (100 mg/day) treatment should be applied to the patient. Also CPK, Cr and K levels should be measured to prevent further complications (110). Dialysis is required in patients with severe metabolic disturbances and severe renal dysfunction related to myoglobinuria (108).

In this scenario, the patient applies to the hospital supposibly with dark urine. Or he/she visits her doctor but his/her doctor does not suspect from statin-induced rhabdomyolysis so that the case gets complicated. As mentioned above, the patient should be performed CPK, Cr and K tests to mesure the level of kidney damage. Patient will be treated with saline infusion, sodium bicarbonate and furosemide. But because of his/her syptoms supposibly will not be corrected by this treatment, he/she will undergo dialysis. Hemodialysis with bicarbonate is preferred (126).

Direct cost of scenario 2

Examination cost

Visit a doctor because of muscle complaints: Cost of a visit was specified in Health Application Announcement revised in 03.07.2012 as 26.14 processing score. So, visit an orthopedist or a nephrologist equals to 26.14x0.593= 15.50 TL

Apply to the emergency clinic of the hospital: Cost of an application to the emergency clinic of the hospital was specified in Health Application Announcement revised in 03.07.2012 as 26.14 processing score. So, visit an orthopedist or a nephrologist equals to 26.14x0.593= 15.50 TL

Stay in hospital: Cost of an application to the emergency clinic of the hospital was specified in Health Application Announcement revised in 03.07.2012 as 50.59 processing score. So, staying at hospital for one night equals to 50.59x0.593= 30 TL

Laboratory test cost

CK test: Cost of this test was specified in Health Application Announcement revised in 03.07.2012 as 7.59 processing score. So, cost of this test equals to 7.59x0.593= 4.50 TL

Cr test: Cost of this test was specified in Health Application Announcement revised in 03.07.2012 as 2.36 processing score. So, cost of this test equals to 2.36x0.593= 1.40 TL

K test: Cost of this test was specified in Health Application Announcement revised in 03.07.2012 as 1.85 processing score. So, cost of this test equals to 1.85x0.593= 1.10 TL

Drug cost

Isotonic saline solution: Cost of this drug was specified as 3.93 TL/1000 mL solution according to RxMediaPharma at the date of March 2012. Name of the relevant product is "PF® %0.9 Izotonik Sodyum Klorür Solüsyon". This price constitutes the lowest price of the price band and is reimbursed by Social Security Institution. According to literature data, isotonic saline solution amount should be 1,5L/hour and than 2.5 mL/kg/hour infusion should be given for rehydration (110). 1,5 L isotonic saline solution equals to 3.93x1.5= 5.9 TL. For the remaining 23 hours the patient will be given 2.5 mLx70 kgx23h= 4025 mL isotonic saline solution. Cost of this infusion is 4.025Lx3.93TL= 16.2 TL. Total cost of isotonic saline solution for one day equals to 5.9 TL+16.2 TL= 22.1 TL

Sodium bicarbonate solution: Bicarbonate value that is necessary to be given the patient is calculated by using the following formula: (15mEq/L- level of the patient's plasma

bicarbonate level)xpatient's weightx0.5. According to this calculation the amount of sodium bicarbonate level that must be given to the patient equals to (15mEq/L-11.2mEq/L)x0.5x70kg=133 mEq/L. Cost of this drug was specified as 6.10 TL/box (10 ampoules/box) according to RxMediaPharma at the date of March 2012. Name of the relevant product is "Drogsan® Sodyum Bikarbonat Ampul". This means 1 ampoule is 0.61 TL. This price constitutes the lowest price of the price band and is reimbursed by Social Security Institution. 1 mEq sodium bicarbonate equals to 1 mL sodium bicarbonate solution. 1 ampoule contains 10 mL solution that equals to 10 mEq. For 133 mEq, approximately 13 ampoules should be given to the patient. So, cost of this drug for one days equals to 0.61x13= 7.93 TL

Furosemide: Cost of this drug was specified as 1.72 TL/box (5 ampoules/box) according to according to RxMediaPharma at the date of March 2012. Name of the relevant product is "Furomid® IM/IV Ampul". This means 1 ampoule is 0.344 TL. This price constitutes the lowest price of the price band and is reimbursed by Social Security Institution. According to the literature data, furosemide amount should be 100mg/day (110). 1 ampoule contains 20 mg furosemide. Totally, the patient should be given 5 ampoules to reach 100 mg for one day. So, cost of this drug for one day equals to 1.72 TL.

Dialysis treatment cost

Hemodialysis in emergency: Because of the patient will probably apply to the hospital in emergency, he/she will have dialysis on emergency service. Cost of hemodialysis in emergency department was specified in Health Application Announcement revised in 03.07.2012 as 85.83 processing score. So, cost of hemodialysis in emergency service equals to 85.83x0.593= 50.90 TL

In addition to this cost, if the patient's kidney damage can not be corrected, the patient will probably be exposed to dialysis lifelong. So this will bring an enormous cost. For the year 2012, cost of one dialysis is specified as 244.52 processing score. Cost of one dialysis equals to 244.52x0.593= 145 TL

According to a study performed in 2010 by Duman S. et al, cost of hemodialysis for one patient annually equals to 28.384 TL. This study was performed taking account 100 patients from 26 different hemodialysis centers in İzmir. The total cost shows the real cost of hemodialysis for Turkey for the year 2010 (127).

The patient was assumed to be at the age of 55 in the calculations. According to the OECD (Organization for Economic Cooperation and Development) Report for 2011-2012, the average human life was determined as 73.8 for Turkey (128). As an assumption, that means the patient will have hemodialysis for 73.8-55= 18.8 years. So, total cost of lifelong hemodialysis will be equal to 18.8x28,384 TL= 533,619.200.

Total of direct costs:

Examination: Visit a doctor= 15.50 TL

Apply to the emergency service of hospital= 15.50 TL

Stay in hospital= 30 TL (for one night)

Laboratory test: CK test= 4.50 TL

Cr test= 1.40 TL

K test= 1.10 TL

Drug: Isotonic saline solution= 22.1 TL

Sodium bicarbonate solution= 7.93 TL

Furosemide= 1.72 TL

Dialysis: First dialysis in the emergency department= 50.90 TL

Other dialysis treatments (1 for the year 2012)= 145 TL

Other dialysis treatments (lifelong)= 533,619.200

TOTAL: 295.65 TL (one dialysis)

533,769.850 TL (lifelong dialysis)

4.1. Limitations of thesis

The most important restriction of the thesis may be exclusion of indirect costs. Cost of a doctor or nurse to the hospital, cost of hospital attendants for the second scenario can be thought as indirect costs. In addition, patient satisfaction has not been included in calculation.

Also, there may be extra costs due to complications of acute kidney impairment. In addition, hemodialysis will also bring extra costs such as the cost of insertion catheter, atrioventricular shunt or canules for hemodialysis. For the calculation of life long hemodialysis, real cost of dialysis was taken into account for the year 2010. Because there were not any real data available for the year 2011 or 2012. So the cost of lifelong hemodialysis should be expected to be higher than the calculated.

Also in the calculation, it is assumed that the patient does not have any other disease or patient's co-existing diseases are not affected by the adverse effect. If the patient has co-existing disease, this may bring an extra cost.

Another restriction may be about life expectancy of the patient. Life expectancy was determined as 73.8 according to OECD report. But this number may be higher or lower.

5. CONCLUSION AND DISCUSSION

Prof. Dr. Mustafa Arıcı who was a nephrologist and a key opinion leader was asked for evaluating the incidence of rhabdomyolysis in Turkey from his clinical experience and wanted to categorize this incidence in a scala from 1 to 10. According to his opinion, this number is too small so he can not categorize between 1 to 10. He thinks that there are many rhabdomyolysis patients in Turkey and some of them are taking statin so he thinks that the number of statin-induced rhabdomyolysis cases are greater than the number mentioned in the literature. But in order to understand the exact relation beetween statins and rhabdomyolysis in the patients, a detailed evaluation should be done by doctors for each patient. He adds that in order to have an idea about the statin-induced rhabdomyolysis cases in Turkey, pubmed can be searched by using the key words: “rhabdomyolysis and Turkey” (109). According to this search in the literature, there are 6 individiual case reports related with statin induced rhabdomyolysis in Turkey. Among these case reports, first was one was about a 56 year old woman patient who was taking 20 mg pravastatin and 200 mg fenofibrate daily for the treatment of coronary artery disease. The patient was diagnosed with severe rhabdomyolysis-induced acute renal failure resulted from use of the pravastatin plus the fenofibrate. The pravastatin and the fenofibrate were discontinued. Although adequate fluid resuscitation and forced alkaline-mannitol diuresis, metabolic acidosis developed and the patient undergo hemodialysis (129). The second case was a 56 year old man who was taking atorvastatin for hyperlipidemia. He had no familial or prior personal history of thyroid disease or muscle disorders. He had no previous history of muscular toxicity with statin or fibrate use. The diagnosis was rhabdomyolysis secondary to the additive effect of hypothyroidism and atorvastatin. Atorvastatin was stopped, intravenous fluids were started immediately and L-thyroxin (100 μg/day) was given after confirming the diagnosis of hypothyroidism. His symptoms progressively improved in a few days (130). Third case was a 56 year old man who had started combination therapy with fluvastatin 80 mg/day and gemfibrozil 1200 mg/day one month before. She was not using any other medications. She had no history of smoking, alcohol consumption, or illicit drug use. There was no other considerable morbidity, such as diabetes mellitus, hypertension, chronic kidney disease, or hepatitis, in her

medical history. The patient was diagnosed with acute hepatocellular injury and rhabdomyolysis, causing acute renal failure secondary to the combination fluvastatin–gemfibrozil antihyperlipidemic therapy. The antihyperlipidemic drugs were immediately discontinued and the patient was treated with intravenous hydration along with close monitoring of vital signs, serum electrolytes, and urinary output. The patient recovered (131). Fourth case was a 45 year old man who was prescribed 10 mg/day atorvastatin for hypercholesterolemia. Rhabdomyolysis was diagnosed on clinical and biochemical grounds, including a more than 50-fold increase in creatine kinase concentration and accompanying myoglobinuric acute oliguric renal failure. Concomitant use of colchicine and atorvastatin was thought to be the cause. After withdrawal of colchicine and atorvastatin, creatine kinase and myoglobin levels gradually decreased, and the patient's muscle strength improved. However, he became dependent on hemodialysis (132). Fifth case was a 63 year old woman who was taking statin-fibrate combination for the treatment of hypercholesterolemia was diagnosed of acute renal failure secondary to the statin-fibrate-derivative combination induced rhabdomyolysis and auto-immune thyroiditis induced hypothyroidism. Although saline, furosemide and sodium bicarbonate infusions enabled diuresis and have led to a rapid recovery of renal function and normalization of blood pressure in five days (creatinine level decreased from 4.5 mg/dl to 1.2 mg/dl), only thyroid replacement therapy (0,1 mg thyroxine) that begun after the exclusion of adrenal insufficiency resulted in complete resolution of rhabdomyolysis (133). Sixth case was defined as the second reported case with severe rhabdomyolysis caused by cerivastatin-gemfibrozil combination. It is obvious among all these cases that rhabdomyolysis can cause renal failure. Renal failure can be recovered by rehydration or can progress to life-long hemodialysis (134).

When we compare the total costs for scenario 1 and 2, there appears a big difference between these two costs. It should be taken into consideration that the cost of second scenario is calculated with two costs. First one was calculated taking into account only the first continuing hemodialysis. The other calculation was done by taking into account the lifelong hemodialysis cost. But most probably, the patient will need hemodialysis lifelong. In addition, I have done my calculations for one day in scenario 1. Because it is not exact how many days pass during rehydration. It changes case by case. So in order to make a calculation, I assumed that the patient was

rehydrated for one day. If this time increases, the cost of the drugs used in rehydration will also increase.

I've done my calculations by using direct costs. But there are also indirect costs about these 2 scenarios. Cost of a doctor or nurse to the hospital, cost of hospital attendants for the second scenario are normally direct medical costs. But in my assumption these costs are thought as indirect costs. These costs are not included in my calculation because the procedures mentioned in my calculation are not based on the performance of the healthcare personel. So, there won't be extra cost to the payer because of the laboratory tests or the examination of the patient.

Also, there may be extra costs due to complications of acute kidney impairment. In addition, hemodialysis will also bring extra costs such as the cost of insertion catheter, atrioventricular shunt or canules for hemodialysis.

When we compare total cost results of the two scenarios, for one day hemodialysis cost of the second scenario is approximately 1.73 times the cost of first scenario. This value increases to approximately 3140 in case of life long hemodialysis. Life quality also decreases in the second scenario.

Application of routine CK tests to all patients taking statin may not be cost effective as it is also advised by Muscle Experts Panel (90). I agree this approach according to my calculations. But differently from this claim, I conclude that routine measurement of CK levels in patients with risks mentioned in part 3.9.6. Risk factors that may precipitate drug induced myopathy carries a very big importance to decrease all costs caused by statins. According to my opinion, application of routine measurement of CK levels in high risk patients should be added to the SPCs, PILs of statin drugs and "Diagnosis and Treatment Guideline" and "Health Application Announcement" of Turkey.

In addition, in the first scenario, MR screening was added to the calculation. Because in order to detect the right extremity in which muscle damage is suspected, a MR screening is performed. This diagnostic tool brings extra cost in short term. But in order to detect the exact muscle with damage, this tool carries a big importance. So, according to my opinion, use of MR screening in suspected patients should also be added to the "Diagnosis and Treatment Guideline" and "Health Application Announcement" of Turkey.

In addition to the routine measurement of CK levels in high risk patients, in order to minimise all these costs and risk, it is really important to increase both the patients' and doctors' awareness about the muscle related adverse effects of statins. the recommendations summarised below carry a very big importance.

Patients;

Patients should discuss any new muscle discomforts, muscle weakness, or muscle cramps with their physician. Patients should be educated regarding the signs and symptoms that may indicate an adverse effect of their statin medication, including unusual exertion in performing their daily activities and discoloration of their urine (31). Also, a patient started on new medications, should inform his or her physician and pharmacist about the use of the statin, because some medications can increase the risk of muscle injury with statins. Some over-the-counter medications, specifically Chinese red rice fungus, contain statins and should not be taken with the prescription medication. In addition, patients should avoid drinking or eating a lot of grapefruit products, because grapefruit can increase statin blood levels (90).

Healthcare professionals;

Statin therapy should be initiated at low doses, and patients should be made aware of myotoxicity as a potential adverse effect (72). Combination therapy with other classes of hypolipidaemic agents may be opted for when aggressive lipid lowering therapy is required (32).

Statin-induced myopathy should be considered in all patients taking HMG-CoA inhibitors in whom myalgias, muscle weakness, or increased levels of serum CK develop. It is important to consider other potential causes for the development of a myopathy and conduct the relevant history, physical examination, and investigations (72). Hypothyroidism and other predisposing conditions should be excluded in patients who develop myalgias (52).

When the CK level is >10- times normal, testing for renal dysfunction is indicated. When renal dysfunction has developed, the patient must be admitted for monitoring and supportive measures in hospital. Depending on the severity of the myopathy and the lifetime risk-benefit of statin therapy, a clinical decision must be taken: continue witholding statin therapy or switch to a different statin drug (eg, hydrophilic statin) with close clinical and biochemical monitoring.

Furthermore, the clinician should be fully aware of drug interactions, especially in view of the prevalence of polypharmacy in our elderly population. Further research and sound clinical judgment may lead to the identification of high-risk individuals in whom statin drug use should be avoided. Identifying such patients would diminish the incidence of myopathy and prevent the unnecessary discontinuation of medications that have truly revolutionized the care of coronary artery disease (72).

Apart form all these actions taken specific for statins, doctors also be educated about the importance of pharmacovigilance and safety of drugs. Because especially in Turkey, the incidence of spontaneous reports are very low. Post-marketing safety data is very important for the safe use of medicines. Because in clinical trials, the patient population does not exceed approximately 10.000 patients. But in daily life, drugs are used by millions of people and there are also coexisting factors such as co-administered drugs or co-existing illnesses. Spontaneous reports which constitutes an important tool of post marketing experiences are very critical. Because these reports may lead to the withdrawal of the drug from the market as it is seen in the example of cerivastatin. In addition, it must not be forgotten that drug metabolism is influenced by genetic polymorphism. So, it is important to evaluate the spontaneous reports by each country's health authority to define the risks specific to the population live in that country. Ministry of Health of Turkey may organize pharmacovigilance seminars to increase doctors' awareness about pharmacovigilance and drug safety. This can be also performed in coordination with pharmaceutical companies. In addition to these, Ministry of Health may find solutions to encourage doctors' about spontaneous case reporting. Because today, in practical life doctors' behave timidly in spontaneous case reporting. They think that reporting spontaneous reports will bring them problems in the future. So they prefer not reporting spontaneous cases. Ministry of Health should provide the doctors' feel safe in this issue.

In addition to the doctors, pharmacists also have a big role in the management of adverse effects. Pharmacists should also be educated about the importance of pharmacovigilance and they should be aware about the signals of adverse reactions and possible interactions between drugs. Especiially community pharmacies have a great role in this issue.

6. SUGGESTION

In order to calculate the total cost of rhabdomyolysis to Turkey, the incidence of rhabdomyolysis in Turkish population should be known. In order to make a logical calculation, rhabdomyolysis adverse effect reports for a specified period (especially for 6-7 years period, because pharmacovigilance regulation was published in 30.06.2005 in Turkey) should be gathered from TUFAM (Turkish Pharmacovigilance Center). If this is not possible, the incidence of rhabdomyolysis can be estimated by taking key opinion leader specialists' opinions. These specialists may be the prescribers of statins or especially orthopedists or cardiologists.

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CURRICULUM VITAE

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