Thesis

STATINS
A critical assessment of the effects and the effectiveness of one of the most prescribed drugs

submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 03/08/2023 Bianca Bergner m.p.

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List of Abbreviations

- HMG-CoA reductase = 3-hydroxy-3-methylglutaryl-coenzym-A-reductase
- LDL = low density lipoprotein
- agLDL = aggregated low density lipoprotein
- oxLDL = oxidated low density lipoprotein
- HDL = high density lipoprotein
- VLDL = very low density lipoproteins
- IDL = intermediate density lipoproteins
- TF = tissue factor
- T2DM = type 2 diabetes mellitus
- DM = diabetes mellitus
- ASCVD = atherosclerotic cardiovascular disease
- CV = cardiovascular
- CAC score = coronary artery calcium score
- FDA = Food and Drug Administration
- Lp(a) = lipoprotein a
- NO = nitric oxide
- eNOS = endothelial NO synthase
- NPC1L1 = Niemann-Pick C1-like 1
- PCSK9 = proprotein convertase subtilisin/kexin type 9
- MACE = major cardiovascular event
- MI = myocardial infarct
- VSMC = vascular smooth muscle cells
- NF-κB = nuclear factor kappa B
- TNF-α = tumour necrosis factor alpha
- AST = aspartat-aminotransferase
- ALT = alanin-aminotransferase
- hsCRP = high-sensitivity C-reactive protein
- FH = familial hypercholesterinaemia
- HeFH = heterozygous familial hypercholesterinaemia
- HoFH = homozygous familial hypercholesterinaemia
- WHO = world health organization

- EOC = early onset cataract
- COX = cyclooxygenase
- TTB = time to benefit
- GD = gestational diabetes
- PCOS = polycystic ovary syndrome
- TOD = target organ damage
- PI = proteinase inhibitors
- CTA = computed tomo-angiography
- LpPLA2 = lipoprotein phospholipase A
- eGFR = estimated glomerular filtration rate
- MMF = Mycophenolate mofetil
- AZA = Azathioprine
- CKD = chronic kidney disease
- SACM = statin-associated cardiomyopathy
- HCC = hepatocellular carcinoma
- NAFLD = non-alcoholic fatty liver disease
- NASH = non-alcoholic steatohepatitis
- CYP450 = cytochrome-P 450
- SAMS = statin-associated muscle symptoms
- SAMS-CI = statin-related muscle symptom – clinical index
- ULN = upper limit of normal
- CK = creatinine kinase
- SINAM = statin-induced necrotizing autoimmune myopathy
- NODM = new-onset diabetes mellitus
- ATP = adenosine triphosphate
- ER = endoplasmic reticulum
- cAMP = cyclic adenosine monophosphate
- GLUT = glucose transporter
- SARS-CoV-2 = severe acute respiratory syndrome coronavirus type 2
- COVID-19 = coronavirus disease 2019
- ICU = intensive care unit

List of tables

Abstract in german

Statine gehören weltweit zu den am häufigsten verschriebenen Medikamenten. Viele Menschen leiden unter zu hohen Lipidspiegeln, gefolgt von einer atherosklerotischen Herz-Kreislauf-Erkrankung, die zu einem schwerwiegenden kardiovaskulären Ereignis auch mit tödlichem Ausgang führen kann. Statine können den LDL-C-Spiegel senken, indem sie ein Schlüsselenzym bei der Produktion von Cholesterin hemmen. Es wird weniger Cholesterin produziert und dadurch mehr LDL-Cholesterin aus dem Blut in Zellen aufgenommen.

Aber bei der Verordnung von Statinen treten einige Unsicherheiten auf. Die wichtigste Frage ist, welchen Nutzen Statine haben. Wie viele kardiovaskuläre Ereignisse und vor allem wie viele kardiovaskuläre Todesfälle können mit dieser Therapie verhindert werden? Weiterhin stellt sich die Frage, ob sie zur Primär- oder Sekundärprävention verordnet werden sollen und was bei älteren Patientinnen und Patienten zu beachten ist. Primärprävention mit Statinen wird nicht generell für alle empfohlen. Behandelt werden sollen nur Menschen mit sehr hohem Risiko. In den Leitlinien sind klare Zielwerte definiert und werden diese nicht erreicht, sollte das Statin entweder höher dosiert oder die lipidsenkende Therapie erweitert werden. Die europäische Leitlinie empfiehlt wegen des erhöhten Rezidivrisikos den großzügigen Einsatz von Statinen als Sekundärprävention.

Die Geschlechtermedizin hält immer mehr Einzug in die klinische Praxis und der Unterschied zwischen Männern und Frauen muss berücksichtigt werden, wenn es um das kardiovaskuläre Risiko geht. Häufige und wichtige Komorbiditäten, die mit dem Herz-Kreislauf-System zusammenhängen, wie Diabetes, HIV, chronische Nierenerkrankung oder Herzinsuffizienz, müssen berücksichtigt werden, und Statine sollten bei diesen Patientinnen und Patienten angemessen angewendet werden.

Wichtig sind auch mögliche Nebenwirkungen, die bei der Einnahme von Statinen auftreten können, wie sie vermieden werden können und wie das Risiko einen Schaden zu verursachen im Verhältnis zum möglichen Nutzen steht. Muskelsymptome sind die häufigsten Nebenwirkungen. Sie können sehr harmlos sein, aber in seltenen Fällen kann es zu einer Rhabdomyolyse mit Nierenversagen kommen. Neu aufgetretener Diabetes kann durch Statine verursacht werden und auch grauer Star.

Die familiäre Hypercholesterinämie spielt eine wichtige Rolle bei der Verordnung von Statinen. Sie wird oft nicht diagnostiziert und viele Menschen bleiben unbehandelt.

Statine wurden als COVID-19-Medikamente erprobt, die bei diesen Patientinnen und Patienten keinen Nutzen zeigten.

Abstract in english

Statins are one of the most prescribed drugs worldwide. Many people have the condition of too high lipid levels followed by atherosclerotic cardiovascular disease which could end up in a fatal or non-fatal major cardiovascular event. Statins can reduce the level of LDL-C by inhibiting a key enzyme in the production of cholesterol. Less cholesterol is produced more LDL-cholesterol is cleared out of the blood.

Some uncertainties occur with the prescription of statins. The most important question is what benefit there is with statins. How many cardiovascular events and more importantly how many cardiovascular deaths can be prevented with this therapy.

Furthermore, the questions arise as to whether they should be prescribed for primary or secondary prevention and what needs to be considered in older patients.

Primary prevention with statins is not recommended generally. Only people at very high risk are supposed to be treated.

Clear target values are defined in the guidelines and if these goal levels are not achieved, the statin should either be up titrated or the lipid-lowering therapy should be extended.

The European guideline recommends liberal use of statins as secondary prevention because of the increased risk of recurrence.

Gender medicine is finding its way more and more into clinical practice and the difference between men and women must be considered when talking about cardiovascular risk.

Common and important comorbidities that are related to the cardiovascular system, like diabetes, HIV, chronic kidney disease or heart failure must be considered and statins should be used appropriately in these patients.

Possible side effects that can occur when taking statins are very important, how they can be avoided and what about the risk of harm compared to the benefit. Muscle symptoms are the most common adverse events. They can be very harmless, but in rare cases rhabdomyolysis with kidney failure can occur. New onset diabetes can be caused by statins, as well as cataracts.

Familial hypercholesterolemia is often underdiagnosed and many people are untreated.

Statins were tried as COVID-19 medication, which ultimately showed no benefit in these patients.

1 Introduction

Cardiovascular events are one of the most prevalent causes of death in the western world. The high number of cardiovascular events depends on several risk factors. One risk factor is said to be low density lipoprotein – cholesterol (LDL-C). Knowing that plaques in artery walls contain LDL-C, the conclusion from that was that lowering the LDL-C level should be the key factor to stop the development of these plaques.

There is some uncertainty in different questions. For instance, it is not clear who exactly should get a lipid lowering therapy, should it be prescribed for primary, secondary prevention or both, does it prevent mortality, which adverse events could occur, do patients with different comorbidities experience adverse events more frequently or more severely, do the doses need to be adjusted considering different conditions of patients, which harm can be caused and is there a difference between women and men.

Another important question is at which age a statin should be prescribed to stop the progression of the disease early and at which age a prescription tends to be useless or provides a higher risk of adverse events. Age is an important risk factor and an indicator for therapy as well.

The European guideline from 2019 had misleading suggestions of the use of statins because many studies with different outcomes were ignored by many reviews and meta-analyses.

First, the main topic of this paper should have been the individual use of a statin treatment in different patients with comorbidities and what there is to consider in the use of it with different illnesses or in combination with other drugs. But due to different statements about the benefit of statins, first the questions how statins work, which impact they do have, why several studies did show no decrease in mortality, and the situation of elderly patients, their risks and their benefits from this treatment, needed to be answered.

Now two main topics, first the benefits of statins and then the use in patients with different comorbidities are discussed on the following pages as well as adverse events and the use in patients with COVID19.

1.1 How did we get to statins?

Statins are molecules of fungal origin and were discovered 50 years ago. The scientist who discovered statins wanted to stop bacterial growth by inhibiting the key enzyme of the cholesterol synthesis = 3-hydroxy-3-methylglutaryl-coenzym-A-reductase (HMG-CoA). [1]As many discoveries in medicine, it was a coincidence. Dr. Kuroda searched for HMG-

CoA reductase inhibitors produced by microorganisms to fight other microbes. By inhibiting this enzyme, microbes, which require sterols for growth, get stopped which means they get dispatched. [2]

In two years‘ time, 6000 strains of microbes were tested to discover one which was able to block lipid synthesis. The antibiotic citrinin was found, originally from a mold, to inhibit HMG-CoA reductase irreversibly. Subsequently, the isolation of active compounds of a strain of Penicillium citrinum could be released. The isolated compound was called mevastatin.[2]

Mevastatin, the first statin, was born in the early seventies. Lovastatin, discovered years later, is a mevastatin analogue and turned out to be more effective than the parent compound.[2]

In the early eighties, lovastatin was investigated extensively to find out how exactly it works. Theoretically, due to findings in dogs, there are two pathways how HMG-CoA reductase inhibition should reduce LDL-cholesterol: less production and more catabolism of it. Investigations in patients with familial hypercholesterinemia showed that homozygote patients, which means patients who cannot synthetize LDL-receptors, had no reduction of LDL-cholesterol in the blood. These findings support the thesis that HMG-CoA inhibitors do not mainly work by inhibiting the synthesis of lipoproteins, their principal action is to increase the number of LDL receptors on liver cells to transport lipoproteins out of blood.[2]

After mevastatin and lovastatin, which was approved by the FDA in 1987, many derivates have been developed synthetically, like simvastatin or pravastatin.[2]

Today, statins are mainly applied to reduce fatty particles in the blood to subsequently decrease cardiovascular diseases and life-threatening events caused by that.[3]

1.2 Lipoproteins

The first statin mevastatin was tested in 1982 in a population of men and it showed a reduction of LDL while HDL, VLDL, and triglycerides remained unaffected. The tested men were healthy volunteers and had no documented adverse events. Later the answer to that was detected:

Cholesterol synthesis is done in liver cells and human bodies are also supplied with cholesterol by, for instance, eating animal products. Humans need it to produce hormones, vitamin D and bile. In the blood, cholesterol is bound on proteins termed apoproteins for transportation, and this complex is called lipoprotein.[4]

Lipoproteins are complexes with carry cholesterol and triglycerides in their core and apolipoproteins, phospholipids and free cholesterol form the envelope around them. There are different types of apolipoproteins, and every lipoprotein with atherogenic potential carries apoprotein B-100. The plasma lipoproteins are classified by size. The largest ones are chylomicrons and the smallest one is lipoprotein a (Lp(a)). In between there are chylomicron remnants, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). Chylomicron remnants, VLDL, IDL, LDL and Lp(a) are atherogenic while HDL is not, in fact it is said to be anti-atherogenic.

However, studies of drugs that increase HDL have not been successful in terms of cardiovascular benefits. [5]

During the circulation through blood, the chylomicrons are metabolized by different cells, after that chylomicron remnants are left. These remnants are incorporated by the liver and are formatted to VLDLs. These VLDLs then circulate and the triglycerides they carry get metabolized. After getting back to the liver, IDL are shaped and after metabolizing them LDLs are formed and get enriched with cholesterol. LDL particles contain the most cholesterol of any particle in the blood. It is catabolized mainly by the liver (70%). This happens predominantly in a receptor-mediated (75%) as well as a non-receptor-mediated way. The LDL receptor is important for the LDL plasma level, which is shown by the severe hypercholesterinemia in familial homozygous and heterozygous hypercholesterinemia patients. Patients with heterozygous familial hypercholesterinemia express only 50% of LDL-receptors and homozygous carriers express no LDL-receptors.[6]

Not just lipoproteins differ in size, LDL particles show a variation in size too.

A higher proportion of small dense LDL particles is observed in association with obesity, type 2 diabetes mellitus (T2DM), hypertriglyceridemia, low HDL levels, or infectious and inflammatory diseases. These small dense LDL particles are thought to be more atherogenic due to their reduced affinity for LDL receptors and the associated prolonged stay in circulation. In addition to that, they have an increased ability to enter the artery wall. Numerous tissue cells incorporate LDLs via LDL receptors.

HDLs can perform a reverse cholesterol transport back to the liver directly or indirectly by transferring cholesterol to VLDL or LDL. HDLs can do a reverse cholesterol transport back to the liver. This can be done directly or indirectly where cholesterol is transferred to LDL or VLDL.

Due to these two different abilities, LDL is called the “bad” and HDL the “good” cholesterol. In simple words it can be said, LDL should be kept low and HDL high.[7]

1.3 HMG-CoA reductase inhibition

The way how statins work is by inhibiting HMG-CoA reductase. Inhibiting this enzyme is the committed step for the endogenous production of cholesterol. The reaction from HMG-CoA to CoA and mevalonate, catalyzed by HMG-CoA reductase cannot take place. All statins inhibit the enzyme HMG-CoA reductase.[8]

Therefore, cholesterol synthesis is limited, and the hepatic amount of cholesterol is lowered. This leads to a higher expression of LDL receptors in cells to remove more LDL cholesterol particles from the blood to get more of the needed lipids into the cells.

The less LDL is in the blood, the less harm to vessels can occur. [1]

1.4 Anatomy and physiology of artery walls

How a high lipid level is responsible for the damage of the arteries followed by cardiovascular events, needs to be answered to get an understanding of the use of statins. Rudolph Virchow observed the damage of endothelium 160 years ago. Since then, modern techniques helped us to get a better understanding of what happens in the artery wall.

The arteries consist of three laminar structures. Tunica intima is made of endothelial cells and is in contact with the blood, it is the inner layer of arteries. Beside the monolayer of endothelial cells, smooth muscle cells and collagen can be found there.

An elastic lamina separates the intima from the tunica media, the middle layer of the arteries. Smooth muscle cells are the main type of cells there. With the help of elastin, they store kinetic energy to enable the transmission of the pulsatile flow.

A further elastic lamina separates the media from the adventitia. The outer layer, tunica adventitia, has fibroblasts, mast cells and matrix containing collagen and proteoglycans.

In 1856, Rudolph Virchow described the causes of thrombogenesis. He said that either the constituents of the blood or the blood flow are abnormal or there are abnormalities in the vessel wall. Virchow knew it then, and we know it even better now, that the endothelium is very important in regulating the physiological systems of the vessels.

A healthy endothelium keeps the balance between vasodilation and vasoconstriction, thrombogenesis and fibrinolysis and it regulates the amount and migration of smooth muscle cells. [9]

Endothelial cells regulate this homeostasis by releasing substances. Vasodilators are nitric oxide (NO), prostacyclin and bradykinin. The last two also inhibit platelet aggregation. Vasoconstrictors are endothelin and angiotensin II and they also promote the proliferation of smooth muscle cells in the intima.

Nitric oxide inhibits inflammation, cellular proliferation and thrombosis and maintains the vascular wall in a calm state. NO does that by initiating the expression of genes that downregulate the nuclear transcription factor kappa B. [9]

The endothelium is physiologically activated by infection or cardiovascular risk factors. Then less NO is produced and this creates an imbalance between vasodilators and vasoconstrictors. In this case more reactive oxygen species are produced and endothelial cells get activated by that. This activation is reversible, but it could end up in irreversible injury, endothelial cell dysfunction with chronic inflammation and a loss of antithrombotic factors which elevates the risk of a cardiovascular event even without a coronary artery disease.[9]

In the evolution of a coronary artery disease, endothelial activation and dysfunction occur early. Many studies tried to find out the risk factors which lead to this.

The INTERHEART study is a case control study of acute myocardial infarctions in 52 countries and it investigated how smoking, hypertension, diabetes, waist/hip ratio, dietary patterns, physical activity, alcohol, apolipoproteins, and psychosocial factors affect myocardial infarctions. These risk factors are responsible for 90% of the risk getting a myocardial infarction and the median age of myocardial infarctions in men were about nine years lower than in women. 15.152 cases and 14.820 controls were enrolled. All risk factors were significantly related to myocardial infarctions except alcohol. According to subanalyses, the two strongest risk factors were current smoking and abnormal lipids. Together they account for about two thirds of the risk. The more cigarettes were smoked per day, the higher the risk got. Already five cigarettes per day increased the risk. The body mass index was also related with a higher risk, but the relation was weaker with the hip/waist ratio which implements the abdominal obesity. A daily consumption of fruits or vegetables, a moderate or heavy daily work out lowered the risk. These dietary habits as well as exercising and the avoidance of smoking reduces the relative risk of about 80%. The consumption of alcohol for three or more times a week seems to be protective as well. But drinking alcohol should not be encouraged. First for cultural and religious reasons and secondly to avoid addiction and the enhancement of other diseases like stroke, cancer,

cirrhosis or injuries. Adding the family history to the risk factors does not have a big effect. 90% of the risk is covered by the risk factors mentioned above and with the family history it raises up to 91%. This finding suggests the hypothesis that the main effect is mediated to known risk factors like a shared lifestyle in families and genetic factors. It seems that there is no independent pathway.[10]

Treating the risk factors can reduce atherosclerotic progression, but the presence of many risk factors increases the cardiovascular risk exponentially, and there is a reduced capability of repairment.[9]

1.5 Atherosclerotic plaque formation

In the 1970s Russel Ross published the "response of injury" theory and helped a lot in understanding what happens in the artery wall. If there were no injury, there would not be a response to injury. There are many possibilities that could cause the injury like some of the risk factors, smoking, diabetes, genetics or there could also be immunologic or infectious reasons. [9]

If the stimulus of the injury persists, the endothelium response with exposure of collagen, platelet adherence and aggregation as well as medial and intimal smooth muscle cell proliferation does not stop. A consistent altering between endothelial injury and repair ends up in a progressive smooth muscle proliferation.

Although atherosclerosis is a systemic disease, mostly the aortic, coronary, cerebral, femoral and iliac arteries are affected.

Russel Ross described three important events before atherosclerotic lesions occur.

- First the proliferation of smooth muscle cells in the tunica intima.
- These cells lead to the production of large amounts of matrix (for tissue connection), including collagen, elastic fiber proteins and proteoglycans.
- The third event is a deposition of intra- and extracellular lipids which can shape a necrotic core if advanced. [9]

Statins affect the LDL-level and in the following it is described why this is one of the most important steps to reduce atherosclerotic lesions and the risk of cardiovascular events.

LDL decrease the bioavailability of NO. This leads to endothelial dysfunction, which is the preceding step to LDL entry. The amount of LDL that entries depends on the LDL plasma levels.

LDL particles most likely interact with proteoglycans. Proteoglycans catch LDL particles. They build insoluble complexes. Once retained, LDL particles get modified because of

oxidants and enzymes. These changes generate different LDL types like aggregated (agLDL) or oxidated (oxLDL) LDLs. These are the most occurring ones. All of that happens in the extracellular matrix.

To get into the cells of the vascular wall, they take two receptors, LDL receptors and scavenger receptors. In the cells, LDL particles increase the expression and secretion of chemotactic compounds, which attract blood cells, especially leukocytes (monocytes and T-lymphocytes). They also increase the expression of adhesion molecules (integrins, selectins), to trap more cells from the blood.

Not just the endothelium, also modified LDL particles themself help monocytes to entry the vascular wall. It remains still unclear how this process works, CD11, a scavenger receptor and protein kinase C, an enzyme, could be responsible for that.

Due to these functions, monocytes go through spaces between the endothelial cells. There they differentiate into macrophages. As macrophages they express scavenger receptors. With these receptors, they can get contact to modified LDL particles and internalize them, which means they kind of eat them and carry them inside.

A macrophage with LDLs is called a foam cell. These foam cells secrete proinflammatory cytokines, growth factors, tissue factor (TF), interferon delta, metalloproteinases, and reactive oxygen. Most of these compounds are important to keep up the inflammation in the artery wall. An activated tissue factor in contact with blood can be very dangerous because it activates the aggregation of the platelets and ends up in a thrombus.

Tissue factor (TF), which could originate from macrophages or foam cells, is found in the lipid cores of atherosclerotic lesions and is six times more thrombogenic than all the other components.

Reactive oxygen releases the chemotactic stimulus for leucocytes to better adhere on the vascular wall and keep the level of these chemokines, thus continuing this mechanism. They also raise the scavenger receptor expression, regulate smooth muscle accumulation in the intima and increase macrophage replication.

Vascular smooth muscle cells undergo changes due to atherogenic stimuli. They transform from non-proliferative contractile cells into active proliferative cells and migrate from the middle layer to the inner layer of the arteries, the intima, attracted by chemokines.

These smooth muscle cells express a lot of receptors for cholesterol uptake.

In initial lesions the amount of smooth muscle cells is 90–95%, in advanced lesions it drops to 50%, which ends in an instability of these lesions. Plaques can be at different stages. The classification is done by histological composition and structure.

Unstable plaques have a lipid core, some collagen and some smooth muscle cells. It is important to identify, why smooth muscle cells get lost, to maybe keep these lesions stable this way.[11]

Upcoming problems due to that plaque performing process are:

- Stiffness of the artery wall, which increases the peripheral resistance, causing blood pressure to rise.
- The increase of lesions and potential rupture of them which sets free the tissue factor that may cause a thrombus.
- Narrow arteries can reduce the blood supply and cause pain.[9]

2 Methods

This thesis was designed to get an overview about statins, their use, their benefits and their adverse events. Books, journals and guidelines were selected using PubMed and guideline publications. Whenever available the lates literature published was used to provide up-to-date information in this thesis. Literature citations were performed using RefWorks.

3 Results

3.1 Evidence of statins

3.2 European Guideline

There are different guidelines around the globe. In Europe the guideline of the "European Society of Cardiology and the European Atherosclerosis Society"[12] is applied for clinical decisions. A guideline like this is based on many clinical trials. However, every trial is implemented and operated differently, with more or less evidence for recommendations in therapy. A main question of the European guideline is, who should get a statin followed by how much should be given.

3.2.1 Risk factors

Depending on different risk factors, people of a certain age have a higher or lower risk to develop a cardiovascular disease. Different risk factors play a role in getting ASCVD and one very important one seems to be LDL-cholesterol.

However, there are other major vascular risk factors as well. Anyone with one or more of following risk factors is recommended to evaluate the ASCVD risk.

- Family history
- Familial hypercholesterolemia
- Smoking
- Arterial hypertension
- Diabetes mellitus
- Elevated lipid levels
- Obesity
- Comorbidities affecting CVD risk

The screening of risk factors including the lipid status should be done in men over 40 years and in women over 50 years or post-menopausal.[12]

To quantify the risk, an estimated value is taken. Till the guideline of 2019, the risk was evaluated with SCORE. For evaluation, the gender, smoking status, age, blood pressure and total cholesterol are determined.

SCORE was developed from cohorts before 1986 and needed to be refreshed with more recent data. 200 investigators developed the risk score SCORE2 including 45 cohorts with 700,000 participants in 13 countries.

In Europe there are four stages of risk. Because of the overestimated risk in countries with a decreasing CVD mortality and the underestimated risk in countries with increasing CVD mortality, there are different risk charts for different countries. Austria is a country with a moderate risk of getting a CVD with 100–150 per 100,000 per year. The lowest risk exists in the western countries of Europe and it increases by approaching the east of Europe.

Compared to SCORE, in SCORE2 not only the risk of getting a fatal event, also the risk of getting a non-fatal event is included, which is important for the younger population.[13]

The risk of getting a non-fatal event is three times higher than getting a fatal event as estimated in SCORE. This was seen in trials with men, and the non-fatal rate is even higher in women but lower in elderly people.[14]

In the new version of 2021, the use of new modified risk scores is recommended. In apparently healthy people under 70 years old, a risk evaluation with SCORE2 is recommended and in those over 70 years of age the SCORE2-OP should be applied. [12]

In the SCORE2-OP, the systematic coronary risk estimation for "older people" over 70 years, participants aged between 70 and 89 were assessed.

The main difference between SCORE and SCORE2 is the biomarker taken for lipid levels. SCORE used LDL-C while SCORE2 uses non-HDL now. Different trials support the hypothesis that not only LDL-C is a risk factor, other blood lipids with the transporter protein apo-B are also relevant to calculate an appropriate risk. All lipoproteins that are not high density lipoprotein contain proteins of the type apo-B. This value is calculated by total cholesterol minus HDL-C. The relation to CV risk is as strong with this value as it is with LDL-C. It is the same information as measuring the plasma concentration of apo-B.
More HDL-C indicates a reduced CVD risk, but in people with very high HDL-C levels the CVD risk seems increased. There is no evidence that raised plasma HDL-C reduces the CVD risk.[12]
Limitations of the SCORE2 are that there is no cohort group data on medication use, family history, socioeconomic status, physical activity, nutrition, renal function or ethnicity and cannot be used in people with high-risk conditions like diabetes mellitus, familial hypercholesterinemia, genetic lipid or blood pressure disorders, chronic kidney disease or in pregnant women. Maybe the CVD risk evaluated with this risk model is underestimated because also people on CVD prevention therapy like statins or antihypertensive drugs were included.[13]
Besides the estimated 10-year risk of a fatal or non-fatal event, there is another important value, the so-called lifetime risk. Logically the higher the number of risk factors, the higher the lifetime risk. This could be helpful especially in younger people because there is a greater exposure time for them to illustrate the risk. The lifetime risk is not used as a guide to treatment. [14]
Treatment recommendations are depending on the evaluated risk:

- Low to moderate risk of CVD: no risk factor treatment is recommended.
- High risk of CVD: a treatment of risk factors could be considered.
- Very high risk of CVD: a risk factor treatment is generally recommended.

There are different classifications of recommendations because not all statements are proved by RCTs and meta-analyses. The less qualitative evidence there is, the lower the number of the class.
Lifestyle recommendations and a systolic blood pressure below 160 mmHg are recommended in all people at every age. Age is a major risk factor and the benefits of treatments are higher in younger people because of the cumulative effect.

What should be added is, that there is just a Class IIb recommendation for lipid lowering drugs in people over the age of 70, regardless of the risk score.

A number like the risk estimation is not supposed to decide about treatment or non-treatment. It has to be evaluated what the risk factors are. Maybe smoking cessation could lower the risk without an indication of another treatment. The lifetime CVD risk, different comorbidities and, of course, the patients' preferences have to be considered.

In apparently healthy young people under the age of 50, the 10-year CVD risk could be low on average even when high risk factors are present. The lifetime risk of CVD with some risk factors would be very high though and a treatment could be recommended. At the age of below 40 years, it is difficult to predict CVD risk and the benefit of a treatment is often imprecise. Only in people with FH or with blood pressure disorders, a drug treatment is recommended. Introducing a healthy lifestyle to young people is very relevant because even small changes in LDL-C or systolic blood pressure have a large impact over the span of life. For primary prevention in apparently healthy people there is no Class I recommendation of lowering LDL-C to a goal level. In adults at immediate or borderline risk for a 10-year ASCVD, it often remains uncertain if preventive interventions should be set. Research indicates that measuring a coronary artery calcium score could help answering this question.[14]

Adding the coronary artery calcium (CAC) score to the risk estimation, the risk could be lowered or increased. Especially men and women with levels at thresholds could be considered to evaluate the CAC score. Not everyone can get a CAC scan because of availability and cost reasons. The measured values should be compared with the average values of the general population of the same age and sex to determine the final CVD risk. CAC is not able to tell the plaque burden because as with soft, non-calcified plaques the score can be zero. [12]

In apparently healthy people with low or moderate risk and high LDL-C levels, the "Multi-Ethnic Study of Atherosclerosis"[14] showed that approximately 50% of these patients had a CAC score of zero and the number of CVD events were low in the following 10 years.[14]

In conclusion, risk estimation could be helpful in treatment decisions. Although even with that model, several additional factors need to be considered. Beside the 10-year CVD risk, the mentioned lifetime risk is also very important, as are different comorbidities, the patients' preferences, frailty and the relation between harm and benefit of the treatment of each individual.

Treatment recommendations in the guideline of 2021:

Very high risk

- Class I
    - Stepwise treatment in apparently healthy and those with ASCVD and/or diabetes mellitus (DM).
    - Apparently healthy with a SCORE2 over 7.5% at an age under 50 years or with over 10% at an age of 50 to 69 or with a SCORE2-OP of over 15% in those over 70 years of age are recommended for treatment.
    - In patients with type 2 diabetes mellitus, a reduction in baseline LDL-C of more than 50% and a target value of less than 55 mg/dl is recommended.
- Class II
    - LDL-C goal under 55 mg/dl and LDL-C reduction from baseline level of more than 50% (apparently healthy under 70-year-old).
    - Primary prevention: In people without FH but at very high risk who do not reach the LDL-C goal with statin and ezetimibe, a PCSK9 inhibitor should be considered.

High risk

- Class I
    - Stepwise treatment in apparently healthy and those with ASCVD and/or DM.
    - In patients with type two diabetes mellitus and over the age of 40 LDL-C should be reduced by more than 50% and 70 mg/dl should be achieved.
- Class II
    - Apparently healthy with a SCORE2 under 7.5% at an age under 50 years or with 5% to 10% at an age of 50 to 69 or with a SCORE2-OP between 7.5 to 15% in those over 70 years of age are recommended for treatment.
    - LDL-C goal under 70 mg/dl and LDL-C reduction from baseline level of more than 50% (apparently healthy under 70 years old).
    - In people older than 70 years but with high risk or above, a statin treatment could be started for primary prevention.

The steps from the evaluation of the risk to the administration of a drug are as follows:

- Cardiovascular risk evaluation.

- Determine treatment goals.
- The patient should be involved in decision-making and management.
- Assessing the clinical condition of the patient and the current medication is very important to avoid harms.
- Choosing a lipid lowering therapy, as first line therapy statins are recommended. If treatment goals are not met, the statin needs to be up-titrated before adding an additional lipid lowering drug because of individual responses to it.
- Finally, the drug and the dose are set.[14]

3.2.2 Evidence for causal effect

Myocardial infarction and ischemic strokes are one of the main causes of death. Many exposures do increase the risk for a cardiovascular event and the most extensively studied one is LDL.

In clinical practice, LDL is not measured directly, but the cholesterol amount of it, LDL-C. Most of the time, the LDL-C concentration and the LDL particle number are almost the same, so the LDL-C concentration can be equated with the LDL particle number. Many trials are done with statins to investigate how a high LDL-C level is responsible for the development of an atherosclerotic disease.

In a paper with many included studies and study participants from whom data was collected of many person-years, evidence was sought and listed why LDL-C is a major risk factor for ASCVD. Over 150,000 cardiovascular events were observed in this group of people.

Criteria for causality:

- Atherosclerotic changes were detected in all mammalian species after increases of apo-B containing lipoproteins.
- Lifelong LDL elevations have a higher lifetime risk for ASCVD.
- There is an association between the level of LDL and the risk of ASCVD. Many studies including randomized intervention trails demonstrated that.
- A temporal connection exposure to raised LDL and the onset of ASCVD is seen in many trials as well as in people with a monogenic lipid disorder.
- Independent of other risk factors which are mentioned in the INTERHEART study[10], there is evidence of the link between LDL and ASCVD.
- The risk of ASCVD is reduced by therapies which lower the level of LDL-C (statins, ezetimibe, PCSK9 inhibitors) proportionally to the decrease of LDL-C.

Evidence I

- The inherited lipid-disorder FH causes elevated LDL-C levels. If siblings with and without FH get compared, the one with the mutation has an increased risk of ASCVD for a lifetime, compared to the sibling without the mutation. [15]

Evidence II

- Another mutation ends up in higher LDL-C levels, a gain of function mutation in PCSK9 (proprotein convertase subtilisin/kexin type 9). Those people have also an increased risk of getting ASCVD, where compared to those who have the opposite, a loss of function mutation of this gene have lower LDL-C levels, which correlates with a decreased risk of ASCVD for a lifetime.[16]

Evidence III

- In many studies and meta-analyses with many participants there where strong associations between high LDL-C plasma levels or low HDL-C levels and a coronary heart disease and associated mortality.
- Studies demonstrate, “the lower the level of LDL-C, the lower the risk of an ASCVD”. [15]
- ASCVD decreases independently of how LDL is lowered, whether by statins, PCSK9 inhibitors or ezetimibe, Ezetimibe binds on a transporter protein [Niemann-Pick C1-like 1 (NPC1L1)] in the intestine to inhibit the absorption for cholesterol. [15]

Evidence IV

- Results of different trials say that the proportional reduction decreases by 22% to get a major cardiovascular event in five years. This reduction occurs in all patients independent of the baseline level of LDL-C. [15]

- If an LDL-C level of below 70 mg/dl is reached, measurements with intravascular ultrasound demonstrated that atherosclerotic plaques show no further progression. [15]

Evidence V

- Ezetimibe as mentioned above inhibits the absorption of cholesterol but as monotherapy no benefit occurs. By adding a statin to this therapy, only then a greater risk reduction is achieved. [15]

Evidence VI

- A PCSK9 inhibitor achieves together with a statin a 20% relative risk reduction for myocardial infarctions, stroke or cardiovascular death (combined endpoint) within 2.2 years.[15]
- If the treatment of each year is analyzed, the PCSK9 inhibitors evolocumab shows very similar results as statins in risk reduction.[15]

Evidence VII

- There is a greater risk reduction of getting ASCVD if LDL-C is kept low for a longer time, means an extended lipid lowering treatment compared to a shorter treatment. This implies or recommends an earlier administration of the drug before atherosclerosis develops.
- So, LDL seems to be connected to ASCVD in level and duration of exposure.[15]

Evidence VIII

- There are other risk factors for ASCVD beside an elevated LDL-C like smoking or high blood pressure. But with or without other risk factors the risk reduction of statins remains constant.[15]

The authors say that an individual's risk reduction depends on the LDL-C level at the start of therapy, called the baseline LDL-C level, but also on how much LDL-C is lowered and for how long therapy has been used. These suggestions made LDL-C the main target value to be reduced. Beneath the evidence for benefit, the fear of causing possible harm with this treatment needs to be considered as well. Every drug has side effects, and the question is whether the benefit outweighs these possible adverse events in an individuum. In people at a very low risk of a major vascular event, a treatment with a statin is mostly safe, is said in this paper. On the one hand, clinical myopathy occurs with an incidence in 0.5 of 1,000 statin-treated patients in 5 years, a rhabdomyolysis happens in 0.1 of 1,000. To get diabetes during a statin therapy is estimated with 10%. On the other hand, 43 people are prevented

from a major vascular event per 1,000 people treated in a period of 5 years and 11 of the prevented ones had a 5-year risk below 10%.[15]

3.2.3 Statins and mortality

After cancer, "cardiovascular disease is the second leading cause of death" in wealthy nations.[17] If statins are able to prevent people from a heart attack or stroke, the mortality rates have to decrease as well. When there is a reduction in events, there has to be a reduction in mortality as well, was the assumption. Lowering LDL-C does have an effect on cardiovascular events, that was proven from a lot of studies. However, in many trials, mortality remained unaffected. Many questions came up why this paradox occurred.

The following meta-analysis is taken to prove the association between LDL-C and statins and total and cardiovascular mortality from the European guideline.

It included 34 randomized clinical trials with 270,288 participants. Statin monotherapy was applied in 26 trials, statin plus ezetimibe in 3 trials and statins and PCSK9 inhibitors in 5 trials. 10 trials had patients for primary and secondary prevention, 16 for secondary prevention alone and 8 for primary prevention. The mean follow-up was 3.9 years and the patients had baseline levels of LDL-C from 92 mg/dl to 192 mg/dl.

There was no reduction seen in cardiovascular mortality over 5 years with a moderate or high intensity statin therapy or by adding ezetimibe or PCSK9 inhibitors to a statin therapy compared to a less intensive statin therapy. Therefore, this meta-analysis had the aim to determine whether the baseline level or the magnitude of reduction with statins, ezetimibe and PCSK9 inhibitors is associated with the fatal or non-fatal events of an individual.

- All-cause mortality

7.08% died in the more intensive, versus 7.70% who died in the less intensive lipid lowering therapy group during the follow-up. For each 40 mg/dl reduction of LDL-C "there was a significant reduction in all-cause mortality"[18], the authors say. The outcomes are specified as absolute risk difference and they are determined as events per 1,000 person-years. The absolute risk difference was -1.05 incidents per 1,000 person-years. With an average treatment duration of 5 years, 200 people needed to be treated with a more intensive LDL-C lowering therapy to prevent one event per 40 mg/dl lower level. The baseline level of LDL-C is a relevant factor because there was no survival benefit in all-

cause mortality with baseline levels of LDL-C below 100 mg/dl and the most benefit was seen in those with a baseline level of LDL-C of over 160 mg/dl.

- Cardiovascular mortality

Considering cardiovascular mortality, 3.44% died in the more intensive lipid lowering group versus 3.99% in the less intensive therapy group. The lowest rate of cardiovascular death and of total death was in those with a baseline level of 100 to 129 mg/dl.
A significant risk reduction was even seen in patients with LDL-C levels below 100 mg/dl. In patients with a baseline level of LDL-C of more than 160 mg/dl, the risk of dying a cardiovascular death further decreased compared to lower LDL-C levels. The association between a higher baseline level of LDL-C and a greater risk reduction was not significant. 4.3 cases can be prevented in 1,000 person-years with a lipid lowering therapy in these patients, the authors say. That means an average of 4 out of 200 people treated with a lipid lowering therapy for 5 years are prevented from a cardiovascular death.

- MACE (Major cardiovascular event)

11.09% experienced a major cardiovascular event with a more intensive LDL-C lowering therapy where 13.35% experienced a major cardiovascular event with a less intensive LDL-C lowering therapy. Even in the group with LDL-C levels below 100 mg/dl, a significant risk reduction for MACE was detected. In numbers this means 3.66 cases per 1,000 person-years were prevented. 5,51 incidents per 1,000 person-years were prevented in the group of baseline LDL-C levels of 100 to 129 mg/dl.
In contrast to cardiovascular events, no significant difference was detected between a less or more intensive LDL-C lowering therapy for cerebrovascular events. The reduction of strokes with a lipid lowering therapy remains steady at 21% independent of baseline LDL-C levels or with different ranges of LDL-C lowering. Similar findings which lacked an association for ischemic strokes and baseline LDL-C or magnitude of LDL-C lowering, support these results. Maybe a further reduction could elevate the risk reduction of ischemic strokes, but at the same time the incidence of haemorrhagic strokes seems to rise. Further investigations are needed.

Beside the baseline levels of LDL-C, there are the achieved levels of LDL-C and it was seen, that regarding all-cause mortality a reduction of more than 65 mg/dl did not show significant results in lowering the rate.

Similar findings were seen in cardiovascular mortality with greater risk reductions than regarding all-cause mortality but no significant results in reductions of greater than 65 mg/dl.

Divergent results of the included studies are attributed to different baseline LDL-C values. Further a sensitivity analysis was done, were the impact of every trial on the meta-analysis was investigated. No deviation in the results was shown when the individual trials were not included.

The main question of this meta-analysis was whether the baseline level or the magnitude of reduction with statins, ezetimibe and PCSK9 inhibitors is associated with the fatal or non-fatal outcome of an individual.

A greater reduction of LDL-C was not automatically associated with a lower risk in all-cause. The magnitude of the reduction of LDL-C did not change the association between baseline LDL-C and the risk reduction of all-cause or cardiovascular mortality. It depends on the baseline level of LDL-C, the higher the baseline level the greater the risk reduction. No risk reductions were seen in people with a baseline level of below 100 mg/dl regarding all-cause mortality. Considering major cardiovascular events there was a risk reduction even there. First, it was assumed that each reduction of 1 mmol/l, means 39 mg/dl of LDL-C, reduced the risk of suffering a major cardiovascular event by about 22%. But that value depends on the average baseline LDL-C level of 120 mg/dl and is not generalizable to people with a higher or lower LDL-C level. These findings support the individualized estimates for not only the patient risk and current LDL-C levels, but also the risk reduction based on the current LDL-C level and resulting desired outcomes. It has to be noted that several authors received research grants of different pharmaceutical companies.[18]

This meta-analysis reported separate results for trial and post-trial period in mortality. Six RCTs with all in all 47,296 patients with follow-up years between seven and fifteen were included. Evidence was found of post-trial reduction in CVD mortality and for all-cause mortality at 2 years post-trial. There is also evidence of a reduction of the rate for major coronary events after 2 years post-trial and throughout the total post-trial period. It is not declared whether the treatment was for primary or for secondary prevention. These

findings confirm a reduction in mortality and major coronary events with a statin treatment with evidence of randomized controlled trials in the long term.[3]

The recommendation in the guidelines is that those at highest short-term risk of a cardiovascular event should be treated. However, due to findings of efficacy and safety of statins the threshold was lowered. In the United Kingdom people at 20% 10-year risk of CVD got a lipid lowering treatment, it was decreased to 10% and in the United States of America the threshold was reduced from 10% to 7.5% 10-year risk of CVD to start a statin treatment. This short-term risk is mostly determined by age. Young people usually do not have a high risk like that. On the one hand, young people with a high lifetime risk could benefit from a treatment, and on the other hand there is the question, if a long-term treatment started at an early age for primary prevention could reduce the mortality rate in the long term.

A meta-analysis distinguished between the use of statins for primary or secondary prevention to get to know if statins are able to reduce mortality in primary or secondary prevention. Therefore, all-cause and cardiovascular mortality were assessed. Only randomized controlled trials were included. More than 1,000 participants had to be in one trial. These trials assessed mortality within the trial period and reported about the surviving participants afterwards.

The original randomized controlled trials were performed between 1994 and 2003. Simvastatin, pravastatin, fluvastatin and atorvastatin were used in individuals of an age of 50 to 75. Eight trials are included with 55,732 participants and there was a post-trial follow-up of 1.6 to 15.1 years. 13,781 participants died during this time and 6,685 of them died a cardiovascular death. No evidence is shown in a reduction of cardiovascular mortality with statins, but some evidence is there in all-cause mortality.

Six of the eight included trials showed a significant reduction of CVD mortality during the trials, but the post-trial period showed less benefit. Just one of these trials had a reduction in CVD mortality in the post-trial period (WOSCOPS-trial). Four of them demonstrated a significant reduction in all-cause mortality during the trial which was similar to cardiovascular mortality but had no evidence in the post-trial. The other two trials lacked evidence within the trial as well as post-trial and one had no significant reduction in mortality during the trial-period but demonstrated a benefit afterwards.

The subgroup analysis showed that there is a difference between primary and secondary prevention use. The (pooled relative) risk of CVD death was significantly lower post-trial

for primary prevention, but there was no evidence for secondary prevention. The same was seen regarding all-cause mortality. The reduction of mortality was much greater during trials than after the long-term trials. This leads to the suggestion that mortality rates assessed during trial periods do not reflect empirical evidence. In the two trials investigating mortality after primary prevention use, 4% of the participants did not continue the intake which exaggerated the post-trial effect. In contrast to that, there could be some survivors in the statin groups at the beginning of the post-trial period who no longer show a difference post-trial anymore, possibly lowering the legacy effects.

Limitations of this review are that post-trial data is no longer randomised and compared. In addition, no assessment could be done of those treated with a statin like how long they have been treated, at which cardiovascular risk they are and what other confounders play a role. These results indicate a possible benefit from primary statin therapy for all-cause mortality. Other RCTs with a population at lower risks are needed to confirm these suggestions. [19]

The only study that reported a lower CVD death rate and all-cause mortality after the study in primary prevention is called WOSCOPS. It is an acronym for "West of Scotland Coronary Prevention Study". In this large randomized controlled trial, 5,529 healthy men aged 45 to 64 with a mean elevated LDL-C level of 190 mg/dL received pravastatin 40 mg per day or placebo for five years. The participants were separated into above or below LDL-C levels of 190 mg/dl. With pravastatin, LDL-C was reduced and major cardiovascular events too.[20]

The main limitation of this trial is, that the participants did not represent the general population. All women were excluded and men with a prior atherosclerotic disease as well. In addition to that, the population had a median predicted 5-year cardiovascular risk of 9.2% which is a 10-year cardiovascular risk of about 18%. This value does not indicate a low, more an intermediate to high risk profile. More than 40% of the participants were active smokers. After these finding they suggested a broad use of statins in the general population with a LDL-C level above 190 mg/dl. But using a high LDL-C level to start a statin therapy could lead to overprescribing, was argued. To evaluate the individual risk of every patient for a correct prescription of a lipid lowering treatment, is what "Löwe" recommends in his letter.[21]

The follow-up study of the WOSCOPS trial said there is a reduction in cardiovascular and all-cause mortality in this group of men after 20 years.

Five years after the trial ended, 38.7% of the active group and 35.2% of the placebo group took a statin post-trial. Many stopped the treatment with statins for different reasons. From the last 10 years there is no available data and there could be many differences within or between the groups. [22]

Cardiovascular death and all-cause mortality did decrease after the trial, but the results were only significant in the groups of baseline LDL-C levels over 190 mg/dl. During the trial no significant reduction was seen in CV or all-cause mortality.

Beside relative risk reduction, the absolute risk reduction of a coronary heart disease in these patients was 2.34% in death of coronary heart disease, 3.25% in cardiovascular death and 5.39% in all-cause mortality. WOSCOPS supports the suggestion of long-term benefit for primary prevention, but there is to note that the levels of other CVD risk factors were elevated as well. [20]

Another meta-analysis investigated different endpoints, also cardiovascular and all-cause mortality, when taking statins for primary prevention. This meta-analysis included systematic reviews, open-label or double blinded randomized controlled trials. A random-effect pairwise meta-analysis was performed with all statins and a network meta-analysis for specific statins. Different risk profiles were excluded. Trials on primary prevention were done with simva-, lova-, fluva-, atorva-, prava-, and rosuvastatin. A class effect was detected, meaning all statins showed similar results in terms of a significant reduction of cardiovascular disease events and all-cause mortality. Atorvastatin and rosuvastatin showed the greatest reductions in CVD events and atorvastatin seems to be the safest statin. In 25 of 40 trials a moderate-dose, in 10 a low-dose and in 5 a high-dose therapy of a statin was administered. Not all trials had the same primary endpoints, but CVD events or all-cause mortality was a primary the endpoint in all trials. The follow-up time was in median 1 year and the median age was 58.3 years. Non-fatal myocardial infarcts (MI) were significantly prevented with statins in primary prevention, where the results of the prevention of fatal MI were not significant except with atorvastatin. Non-fatal strokes were significantly reduced by atorvastatin and rosuvastatin. In contrast to that considering fatal strokes no significant risk reduction was seen neither with individual statins nor statins as a class. The reduction in all-cause mortality was significant with atorva-, rosuva- and pravastatin and CVD mortality was significantly lowered by rosuva- and pravastatin. The risk of getting a major cardiovascular event was reduced by 26%, which means 14 events are prevented per 1,000 people over 10 years. In major cardiovascular events fatal stroke

and heart failure and all-cause mortality were excluded. A weakness of this meta-analysis is that composite outcomes are analysed, effects for different outcomes were estimated and there was also a short trial duration. Notable is the finding that there is no significant effect in reducing the risk of a fatal MIs except atorvastatin, but that cardiovascular mortality was only significantly lowered by rosuvastatin and pravastatin.[23]

Another important risk factor beneath LDL-C is the age. The risk evaluation with SCORE is also adapted to age with the SCORE2-OP for older people (above 70 years of age).

With increasing age, the individual risk of having a fatal or non-fatal major cardiovascular event rises. Total cholesterol, however, seems to become less of a risk factor for cardiovascular death or all-cause mortality.[24]

19 cohort studies containing 68,094 elderly people reported about cardiovascular and all-cause mortality. In 16 cohorts which contained 92% of the participants, an inverse association of LDL-C and mortality was observed. The higher the level of LDL-C was, the lower was the mortality. Three studies, which included 70% of the participants, showed a significantly inverse association with all-cause mortality. In the other cohort studies, no association between these two factors were found and in two cohorts the cardiovascular mortality was significantly at highest when LDL-C was at lowest. Elderly people (defined in this analysis as over 60 years of age) with a high LDL-C value lived as long or longer as those with a low LDL-C value, is what this review demonstrated. Low LDL-C was associated significantly with all-cause mortality in 80% of the individuals. Therefore, the cholesterol hypothesis needs to be questioned, the authors say. [24]

It is necessary to keep an eye on the risks of confounding factors. Suggestions are that maybe some diseases lower LDL-C soon before death occurs. In 10 of the 19 studies participants at terminal illness were not excluded, but in four of these trials people who died in the first observational year with a terminal illness were excluded. In five studies of the others of the nine, they showed a significant association between the highest mortality rates and the lowest LDL-C levels. Therefore, this hypothesis is apparently not a likely explanation. Another limitation of this review is that not all studies corrected the same risk factors or did not inform about which risk factors were corrected. [24]

Diseases which are caused or aggravated by microorganisms seem to occur more often in people with low levels of LDL-C, observational studies showed. In these 19 cohort studies it was demonstrated that mortality of respiratory or gastrointestinal diseases of mostly infectious origin were significantly inversely associated with total cholesterol. It is likely

that the low total cholesterol occurred before the disease. In the 15-year follow-up it was seen that those with low total cholesterol at the beginning were significantly more often hospitalised due to infectious disease. Due to the fact that many cancer types are caused by viruses and people with lower LDL-C are more likely to get infectious diseases, a higher LDL-C level could be protective against cancer, according to another hypothesis. [24]

The assumption, that low cholesterol does not provide a benefit in mortality especially not in elderly people is supported by the reevaluation of the diet heart hypothesis. The double blind randomized controlled trail investigated which effect there is if saturated fat is replaced with vegetable oil rich in linoleic acid. Lower saturated fat should reduce coronary heart disease and death. 9,423 men and women between 20 and 97 years of age were included. The group which underwent the diet had significant reductions in serum cholesterol but no benefit in all-cause mortality. In addition to that, patients older than 65 years at baseline had a higher risk of death when serum cholesterol was decreased of about 30 mg/dl. These findings do not support a broad use of statins, especially not in elderly patients.[25]

3.2.3.1 LDL-C lowering

Treatment goals should be defined, is what the European guideline recommends. This can also be helpful for the communication between patient and clinician and it could also raise adherence, the guideline says. Lowering beyond the goals is associated with fewer ASCVD events. Reducing LDL-C as low as possible is recommended, at least in very high-risk patients. Mortality rates, as mentioned above are not discussed and included sufficiently in the guideline.[12]

Good evidence:

- Patients at very high risk should achieve greater than 50% LDL-C reduction from baseline and LDL-C target less than 55 mg/dL for primary and secondary prevention.
- High risk patients have an LDL-C goal below 70 mg/dl, and a 50% reduction from baseline is recommended as well.

Poor evidence:

- For primary prevention in patients with FH the same targets as mentioned above should be reached.

- Patients with ASCVD who got a second vascular event within two years are recommended to achieve an LDL-C goal of below 40 mg/dl while taking the maximally tolerated statin therapy.
- Patients at moderate risk should achieve a target value of LDL-C of <100 mg/dl and patients at low risk should get to <116 mg/dl.

How much of LDL-C is reduced depends on the baseline level of LDL-C, the type of statin and its dose. A high intensity therapy is defined as being able to reduce LDL-C by more than 50%, a moderate intensity therapy achieves a reduction of 30–50%. In patients who cannot achieve the therapy goal or cannot tolerate the recommended dose of a statin, other lipid-lowering drugs are recommended up to the maximum tolerated statin dose. There it needs to be kept in mind that poor responses could be due to compliance or because of genetic backgrounds. Therefore, a monitoring of the responses when initiating the therapy should be done.[14]

If the maximum of a statin dose is not enough to decrease the LDL-C value to a certain level, other drugs with different pathways can be used. Ezetimibe is a lipid lowering drug which works by inhibiting the cholesterol absorption in the small intestine. Another lipid lowering drugs are PCSK9 inhibitors ("proprotein convertase subtilisin/kexin type 9"). They work by neutralizing the effects of this protein with monoclonal antibodies or by inhibiting the synthesis of this protein in the liver. In the American and European guidelines statins are recommended as first line treatment for people at elevated cardiovascular risk. If a certain aim of LDL-levels is not achieved with the highest dose of a statin or if people do not tolerate it, ezetimibe as second line treatment is recommended. After that, if LDL levels remain high, PCSK9 inhibitors should be prescribed.

In the IMPROVE-IT trial, simvastatin and added ezetimibe achieved more reduction of LDL-C than simvastatin alone at higher doses. PCSK9 inhibitors proved their potential in FOURIER and ODYSSEY OUTCOMES trials added with a statin by strongly reducing LDL-C.

PCSK9 inhibitors are able to lower LDL-cholesterol to more than 50 percent. The guideline recommends adding a PCSK9 inhibitor or ezetimibe to a statin to achieve a lower LDL-C level. People with CVD and those at a high or very high risk of it should receive it. The following meta-analysis supports these recommendations due to their findings. It should be added that there was no benefit in terms of mortality, but the duration of the trials was also limited.[12]

The meta-analysis examined ezetimibe or PCSK9 inhibitors given to people who were on the maximum tolerated dose of a statin or who were receiving one of these lipid-lowering drugs while being statin-intolerant.

For assessing the impact of the lipid lowering mechanism in the long term, four outcomes were assessed. These outcomes were defined as non-fatal MI or stroke, all-cause mortality and cardiovascular mortality.

In addition, potential harms by these two treatments were assessed. For PCSK9 inhibitors it was new-onset diabetes, neurocognitive effects, cataract, gastrointestinal hemorrhage and reasons to discontinue the treatment like reactions to the injection spot, flu-like symptoms, myalgia or muscle pain. For ezetimibe, the safety outcomes were defined very similarly.

The included trials needed to be RCTs containing patients with LDL-C levels of above 70 mg/dl at different cardiovascular risks. Groups of a minimum of 500 people had to be formed receiving PCSK9 inhibitors or ezetimibe and were compared with a control group, and PCSK9 inhibitors were compared to ezetimibe for more than six months. The 14 trials contained 83,660 individuals. In average, the participants were 61 years old, had a median LDL-C level of 105 mg/dl and were followed two years.

The results of the lipid lowering therapy with statins and PCSK9 inhibitors are as follows:

- No significant effect on cardiovascular or all-cause mortality in all cardiovascular risk groups compared to control group
- Significant and greater risk reduction than ezetimibe of non-fatal stroke or myocardial infarction
- In people at very high cardiovascular risk
    - PCSK9 inhibitors + statins: Stroke 21 per 1,000, MIs 16 per 1,000
    - PCSK9 inhibitor + ezetimibe: Stroke 11 per 1,000
- High cardiovascular risk
    - PCSK9 inhibitor + statin: Stroke 16 per 1,000, MIs 12 per 1,000

Ezetimibe:

- No significant effect on cardiovascular or all-cause mortality in all cardiovascular risk groups compared to control group.
- The risk reduction of non-fatal stroke or myocardial infarction was significant.
- In people at very high cardiovascular risk with different combined therapies of lipid lowering drugs showed following prevented events in five years:

    - Ezetimibe + statin: Stroke 14 per 1,000
    - Ezetimibe + statin + PCSK9 inhibitor: Stroke 17 per 1,000, MI 14 per 1,000 (these results are of low certainty)
    - With ezetimibe + statin or ezetimibe + PCSK9 inhibitor the results for prevented myocardial infarctions did not reach the MID (minimal important difference)
- High cardiovascular risk
    - Ezetimibe + statin: Stroke 11 per 1,000
    - Ezetimibe + PCSK9 inhibitor or ezetimibe + statin + PCSK9 inhibitor had results with low certainty

More events are prevented in the very-high risk group than the high risk group and patients with moderate or low cardiovascular risk did not benefit from any of these two therapies. Adding PCSK9 to ezetimibe prevented less non-fatal MIs or stroke than PCSK9 alone, but that observation is not significant. The weaknesses of this review were that ezetimibe and PCSK9 were just compared indirectly. A similar lack of evidence concerns the addition of these two to one another. In addition to that, there is also low evidence in the moderate and low risk groups. No trial investigated a cardiovascular end point in statin-intolerant patients, estimates are done based on patients taking statins. The conclusion is that in people with the maximal tolerated statin therapy or who are statin-intolerant and do not achieve an appropriate LDL-C level, ezetimibe and PCSK9 inhibitors are recommended. They show a greater reduction of non-fatal MI and stroke but not cardiovascular or all-cause mortality. There seems to be just a benefit in very high or high cardiovascular risk groups. Investigating all-cause or cardiovascular mortality, neither ezetimibe nor PCSK9 inhibitors or both together showed a benefit, although an intensive lowering of LDL-C levels. There is to consider that the length of the follow-up is limited. [26]

In three trials with PCSK9-inhibitors with all in all 73,926 participants, half of them were treated with an PCSK9-inhibitor and only 37 more died in the control group. That means 1,000 patients had to be treated for about 2 years to prevent the death of one patient. [27]

In six trials using non-statin cholesterol lowering drugs including 132,029 patients with CVD, the mortality was not decreased, which leads to the assumption LDL-C lowering may not be the key to success considering a better survival rate.[27]

Because of the risk reduction of getting a major cardiovascular event which seems to be proportional to the reduction of LDL-C, the lower it gets, the better it is, many authors say.

But can we get too low? Studies with intensive lipid lowering showed no increased adverse events. In these trials, LDL-C was reduced to levels down to 40–50 mg/dl. PCSK9 inhibitors as high-intensive therapy are able to reach those values. In trials with evolocumab, no raised rates in adverse events were detected, but there were few concerning findings in the long-term odyssey trial with alirocumab. There, a higher rate of neurocognitive disorders was found. In the OSLER trials with evolocumab, the rate was low in the drug and control group regarding neurocognitive events. What should be added is, that the occurrence of neurocognitive disorders was independent of the levels of LDL-C. On the other hand, a meta-analysis of 17 randomized trials and 13,083 participants showed a significantly higher rate in neurocognitive events with PCSK9 inhibitors. In conclusion, more studies are needed to assess the association between neurocognitive disorders and LDL-C over the long term, as most of the data comes from short-term studies.

No increased haemorrhagic stroke risk was seen in major LDL-C lowering trials neither with statins nor with PCSK9 inhibitors. Another adverse event is discussed in safety trials of LDL-C lowering therapies: the risk of getting cancer. In one million women, there was no significant association seen between LDL-C levels and breast cancer, and large meta-analysis did not show an elevated risk of cancer in people taking statins. In addition to that, studies with a follow-up of more than 10 years also show no increased risk of cancer with statins. Authors of this review declare LDL-C levels of below 50 mg/dl as safe and there are greater CV benefits than harms, they say. [28]

Another meta-analysis investigated the safety and efficacy of a massive LDL-C lowering which means lowering LDL-C more at already low levels. Patients with a median LDL-C of 63 mg/dl were reduced to a median of 21 mg/dl. It was found that there is clinical benefit from further lowering LDL-C because the relative risk reduction stays the same at every LDL-C level, they say, and it is 21% per 1 mmol/L = 38.7 mg/dl. No evidence of increased adverse events was detectable. Limitations of this analysis are the small number of randomized clinical trials. There were different entry criteria and follow-up durations. Long-term safety data is required for very low LDL-C in a large number of individuals. Support grants were received from many pharmaceutical companies. [29]

Reduced LDL-C for a prolonged time is associated with lower ASCVD risk, randomized controlled trials demonstrated that. The relative reduction in CVD risk is proportional to the change in LDL-C, regardless of the drug, as the 2021 European guideline points out. In

addition to the proportional relationship between LDL-C lowering and reduced risk of ASCVD, randomized studies have shown that longer exposure to lower LDL-C levels reduces the risk of having a cardiovascular event compared to shorter exposure. These findings support a cumulative effect. [12]

What is important when talking about risks is the difference between relative risk and absolute risk. A recent meta-analysis investigated the outcome for primary and secondary prevention regarding all-cause mortality and cardiovascular event which means a stroke or a myocardial infarction. The statin treatment group was compared to a control group. The reduction of the absolute risk for all-cause mortality was 0,8%, for a MI it was 1,3% and 0,4% for stroke, where relative risk reductions were much greater. The relative risk reduction for all-cause mortality was at 9%, for MIs at 29% and for strokes at 14%. A meta-regression was done and there was no clear association between statin-induced LDL-C lowering and lower all-cause mortality, myocardial infarction rate or strokes.[30]

3.2.3.2 Limitations of the European Guideline of 2019

The guideline is aware of several limitations and has arguments why trials and reviews with limitations were considered.

Just limiting the current data to results of RCTs may reduce the potential available to prevent ASCVD, the guideline points out. For some of the research questions there were no RCTs available and they wanted to consider the totality of evidence. [14]

19 studies including 68,000 elderly people followed several years showed that those with the highest LDL cholesterol lived the longest with or without statin therapy, as mentioned above. Many previous studies showed that high LDL-cholesterol is just a CVD risk factor in young and middle aged. An explanation could be that mental stress is more common in the younger group of age than the seniors. Mental stress can raise the cholesterol level but has several other effects too. It does not have to be the cholesterol elevation causing the heart disease, the authors say. The Mendelian randomization showed that people at a lower LDL-C level that is determined genetically are at a lower risk of all-cause mortality. However, the Mendelian randomization had potential flaws, as pointed out by Burgess. It took some time in the medical field to administer lipid lowering therapies due to a risk factor profile and not because of an elevated LDL-C value. Doctors should not treat a laboratory value, is said. As an example, the review with the elderly people shows, LDL-C alone does not indicate the degree of an atherosclerotic disease. One way to evaluate plaques and calcifications in the artery wall could be done with imaging. The guideline

says, dyslipidaemias and the degree of coronary artery calcification (CAC) could be used to classify the risk of CVD. Comparing CAC with LDL cholesterol, data from the Multi-Ethnic Study of Atherosclerosis showed that on average half of the patients who should get a statin, had a CAC score of zero, as is also pointed out in the guideline. Comparing CAC to LDL-cholesterol, data showed that, on average, half of the patients who were scheduled to receive a statin had a CAC score of zero, as the guideline pointed out as well. In addition, in a study with 304 women, the correlation between LDL-cholesterol and coronary calcification has even been inverse. [27]

Different authors from all over the world published a paper called "LDL-C does not cause cardiovascular disease". Total cholesterol or LDL-C is considered to be the major cause of atherosclerosis and cardiovascular disease, but there are falsifications of the cholesterol hypothesis, they argue. The Bradford Hill criteria are not fulfilled for causality, statistics are misleading, unsuccessful trials are excluded and contradictory observations are ignored. It has to be considered, that people with low total cholesterol do get atherosclerosis as well, but it is a fact that some studies reported an association between total cholesterol and the degree of atherosclerosis. In sixteen cholesterol lowering trials which were controlled with angiography, there was a correlation in just one of them and there, the only treatment was exercise. The Framingham Heart Study suggested in the 1960s that high total cholesterol should cause CVD. In the follow-up study of 30 years which was published in 1987, they said that for every 1 mg/dl reduction of total cholesterol the risk of coronary or total mortality increased by 11%. Total cholesterol does not seem to be related to future CVD and there is strong evidence in the elderly people for no association, the authors say. An Austrian study investigated mortality of coronary heart disease in 67,000 men and 82,237 women in 2004. Total cholesterol was weakly associated with coronary heart disease mortality in men under an age of 50 and over 64 years. In women there was a weak association in those below 50, but above 50 there was no association detectable. There was also no association found between total cholesterol and mortality of other cardiovascular diseases. In addition to that, total cholesterol was even inversely associated with cardiovascular mortality in women over 60 years of age.[31]

In contrast to that, a meta-analysis with 61 prospective observational studies including almost 900,000 participants showed that total cholesterol is associated with CHD mortality in all ages and at both sexes. The original data is not obtainable and other studies which detected the opposite were ignored. Over time, the main focus went from total cholesterol

to LDL-C. In a study of 1,779 healthy participants who did not have conventional risk factors for CVD, LDL-C was found to be significantly higher among people with subclinical atherosclerosis. There could be different reasons why people with atherosclerosis have higher LDL-C values. Potentially it is just a side effect of the real causation. Considering mental stress, already mentioned, which is very common nowadays, LDL-C could be raised by up to 50% by that within half an hour. Maybe mental stress causes atherosclerosis by other ways than increased LDL-C. Hypertension and increased platelet aggregation are considered for that.[32]

If LDL-C causes cardiovascular diseases, its level must be higher than normal in those with illness. A trial showed, patients with acute myocardial infarction had lower than normal or normal LDL-C levels on hospital admission. The conclusion of that was, LDL-C needs to be lowered more. However, three years later the follow-up showed that total mortality increased with LDL-C levels below 105 mg/dl, hence, it was twice as high (14.8% vs 7.1%). Confounding variables were also adjusted.[33]

One explanation therefore is that cancer and infections lower LDL-C. The mortality could be increased in people with low LDL-C because of these conditions. Another explanation is that infections could cause cardiovascular diseases and that LDL inactivates microorganisms and toxic products. The observation that healthy people with low LDL-C are more likely to get infectious diseases and cancer supports this hypothesis. 20% of all cancer types are associated with microorganisms. Different trials showed a dose response to LDL-C lowering and the degree of benefit. True exposure response is determined by assessing each patient's risk with the degree of cholesterol reduction. Three trials calculated such exposure-response, and this response was absent in all three of them which means no proof of causality. As mentioned above, the baseline level of LDL-C seems more important than the magnitude of LDL-C lowering. In addition to that, benefit seems to decrease with lower LDL-C baseline. This could be the explanation of the failed causality evidence. [32]

In meta-analyses, major vascular events are often determined differently and should not be taken to measure a benefit. Relative risk reduction should be replaced by absolute risk reduction as reported value for benefit, the authors say. More than 30 randomized trials demonstrated a reduction in CVD events proportional to the reduction of LDL-C. Data of only 12 of these 30 trials were included to illustrate an association, but with the data of all

30 trials no association between coronary events and LDL lowering is detectable, the authors of this paper say.[32]

The meta-analysis by Silverman included 26 statin trials and showed a weak positive association of statin treatment and total mortality, where ignored trials detected the opposite.

In this meta-analysis, 26 randomized trials with many participants wanted to compare a more or less intensive lipid lowering therapy and assess the efficacy and safety of the more intensive therapy. A significant reduction of 15% in major vascular events, of 13% in coronary death or non-fatal myocardial infarction, of 19% in coronary revascularization, of 16% in ischemic stroke and 10% in all-cause mortality was detected. Mostly death due to coronary heart disease was prevented, no significant reductions were seen in fatal strokes or other vascular causes of death. In the first year, the benefits were half as large as in the following years. No increased risk for non-cardiovascular causes of death was detected including cancer. People taking statins for primary prevention are usually at lower risk, the absolute benefit in those group is therefore lowered, but the relative risk reduction per mmol/l was the same. For primary prevention, statins reduced risk for all-cause mortality by 9% per mmol/l reduction of LDL-C. The absolute risk reduction depends on the baseline risk of each individual. Most trials were supported by the pharmaceutical industry. [34]

In summary, relative risk reduction for non-fatal cardiovascular events and stroke seems to be constant regardless of baseline LDL-C level. Considering mortality though, baseline level of LDL-C is relevant. The higher the baseline level, the more benefit in mortality occurs. No benefit or maybe even a higher mortality rate can occur in people at LDL-C levels below 100 mg/dl. This needs to be kept in mind especially when treating the elderly, where a low LDL-C value could be a disadvantage regarding mortality.

3.3 Pleiotropic effects of statins

Systemically administered drugs affect the whole body and could cause different effects as well as side effects. It can be very difficult to identify the different modes of action of a single drug. Beside lowering the level of LDL-C in blood, statins could have an effect directly at the artery wall. They should have an effect on the vascular smooth muscle cells (VSMC). The hypothesis is that statins could modulate the activation of the nuclear factor kappa B (NF-κB) in VSMC which is stimulated by agents of atherosclerotic plaques like tumour necrosis factor a (TNF-α) or angiotensin II. Cytokines that are expressed after NF-

κB activation like MCP-1 (monocyte chemoattractant protein 1) or IP-10 (interferon-inducible protein 10) are also investigated. NF-κB is activated by many factors. This activation leads to an expression of different genes which encode proteins for the inflammatory response.

- MCP-1 = monocyte chemoattractant protein 1 is responsible for a migration of VSMC
- IP-10 = interferon-inducible protein 10 attracts monocytes and activates T-lymphocytes.

In cultured VSMC and monocytes the stimulation with TNF-α and angiotensin II leads to an activation of NF-κB. These stimulating agents are found in atherogenic plaques. These findings involve certainly lipophilic statins like atorvastatin or lovastatin, other ones were not tested in this work. HMG-CoA-reductase inhibitors diminish the activation of NF-κB, so the mRNA expression of chemokines like MCP-1 or IP-10 is reduced. This activation is a key event in the development of atherosclerosis. NF-κB is activated by many agents as oxidized LDL or oxidative stress.[35]

Several clinical trials demonstrated an event-reducing effect of statins even without lowering LDL-C. Pleiotropic effects seem to be responsible for that, as well as antithrombotic effects. Statins seem to decrease platelet aggregation, inhibit tissue factor and the expression of plasminogen activation inhibitor-1. In addition to that, thrombomodulin should be increased by elevating the NO synthase of the endothelium by statins. Thrombomodulin reduces the thrombogenicity by binding thrombin. [36]

Inflammatory and immunological mechanisms are associated with statins, is what many studies suggest. These two mechanisms are well known contributors to the development of atherosclerosis. The risk reduction rather depends on the modulation of a plaque than the degree of a stenosis, because the rupture of an atheroma leads to thromboembolic complications. Persistent inflammation causes elevated protein levels of C-reactive protein, interleukin-6 and others. Statins diminish the levels of these inflammatory markers and they do it apparently by a different pathway than by lowering LDL-C. Cells that are important in atherosclerosis are cultured like endothelial cells, smooth muscle cells, monocytes/macrophages and T-lymphocytes. An accumulation of inflammatory cells is seen early in atherosclerosis. The inhibition of HMG-CoA-reductase can diminish the expression of proinflammatory proteins and also inhibit the adhesion of leucocytes to endothelial cells. Interactions with leucocyte-function antigen-1 seems to be responsible

for the lack of adhesion. In mice suffering from peritonitis, the inflammatory response due to the block of adhesion of leucocytes by statins was sufficiently suppressed.

What is diminished:

- Adhesion of macrophages
- Migration of endothelial cells, smooth muscle cells, macrophages and T-cells

  Migration depends on adhesion molecules, chemokines and on the activity of enzymes in the matrix. Proteases of the matrix may also weaken the fibrous cap which makes rupture more likely. Proinflammatory cytokines regulate the expression of that proteases. With statins, there seems to be less migration of cells and less rupture of plaques due to a diminishment of cytokines that leads to an expression of matrix metalloproteinases.
- Proliferation of smooth muscle cells and endothelial cells
- Oxidation of LDL and endothelin-1 in endothelial cells
- Thrombosis by diminished tissue factor, factor VII-a, platelet aggregation and more
- Inflammatory mediators in endothelial cells, macrophages and the peripheral blood.

What is enhanced:

- eNOS (endothelial NO synthase) in the endothelium
- Apoptosis of endothelial cells, smooth muscle cells and macrophages; This probably affects the formation of the lipid core and the fibrous cap. The induction of apoptosis appears to be just with lipophilic statins.

Several anti-inflammatory attributes occur in response to lipid-lowering alone in absence of statins in animals.

If anti-inflammatory drugs could provide a cardiovascular benefit, needs further investigations. Administration of COX-2 inhibitors does not show CV benefits.[37]

Pleiotropic effects of statins were suggested to be responsible for stroke prevention. But randomized trials of treatments for lowering cholesterol showed stroke reductions in both statin or non-statin cholesterol lowering groups. Different trials with different PCSK9 inhibitors showed that the reduction of cholesterol is proportional to the reduction of strokes which outweighs the suggestions about pleiotropic effects.[38]

3.4 The statin and the different patient

3.5 Primary Prevention

People with hypercholesterolemia or more specifically increased LDL-C levels appear healthy. Whether these apparently healthy people benefit from a statin therapy before a cardiovascular event occurs or if the possible side effects justify the early use, is a huge and long discussed question.

Currently statins are prescribed after a risk score as mentioned above. In the European guideline there is no Class I evidence for apparently healthy people to lower LDL-C in any group of age. First, lifestyle recommendations, smoking cessation and lowering systolic blood pressure under 160mmHg are suggested. LDL-C reduction to a goal level of below 100 mg/dl is suggested in apparently healthy people at an age of 50 to 69 years with a 10-year CVD risk of 5 to 10% with consideration of the lifetime risk and treatment benefit as well as the preferences of the patient or in those with a CVD risk of more than 10%. For those over 70 years of age who appear to be healthy and have a CVD risk of 7.5% to over 15%, there is a Class IIb recommendation of lowering LDL-C under the level of 100 mg/dl.[12]

In a meta-analysis, studies from 1946 until 2020 are looked through which were randomized and controlled with a mean follow-up of at least a year. Cardiovascular event rates and mortality were assessed in people with no underlying health condition other than dyslipidemia or hypercholesterolemia compared to a control group. They distinguish between all-cause mortality, all coronary heart disease events, and all coronary and cardiovascular events combined. This meta-analysis showed no difference with statins in all-cause mortality, but there was a 12% relative risk difference discovered in coronary and cardiovascular events which means that apparently healthy participants had 12% less cardiovascular events with statins than those without. Lowering LDL-C does reduce CHD or CVD events, but does not lower mortality. [39]

Apart from the benefits it is also important to evaluate the rate of possible adverse events to prevent patients from any harm. Randomised controlled trials in adults with different types of statins and dosage without a history of a cardiovascular disease were investigated to assess adverse events of a statin use for primary prevention. It is needed to consider the safety profile of a statin not just the efficacy alone, especially when prescribed without an occurred event. In addition to that, the dosage for the optimal therapeutic range is important as well to avoid adverse effects caused by too high dosages.

For adverse reactions, it must be distinguished between self-reported muscle symptoms without creatine kinase elevations or the muscle disorder which is clinically confirmed when there is an massive elevation of CK. Other manifestations of adverse events could be myopathy or rhabdomyolysis in rare cases with their criteria.
A rise of AST (aspartat-aminotransferase) or ALT (alanin-aminotransferase) markers that are indicating a problem of the liver to more than three times was defined as liver dysfunction and other diagnosed liver disorders were considered. Any reduction of renal function or the presence of proteinuria was defined as renal insufficiency. Other renal disorders are included as well.
The adverse events of getting type 2 diabetes or having an eye condition were investigated too. To put possible harms into relation of the benefits it must be calculated as well. It was defined by the appearance of MIs, strokes or cardiovascular death. More than 120,000 participants followed in average for 3.9 years, with a mean age of 61 and a 40% share of women were included in observational studies. Most participants had hyper- or dyslipidaemia and the most common comorbidities were diabetes, hypertension and asymptomatic atherosclerosis. Twenty studies included participants who already had a cardiovascular event (7,673 people, which is 6% of 120,456). This distorts the results just for primary prevention because the treatment of them is defined as secondary prevention.
All seven types of statins were evaluated. Most studies investigated atorvastatin and rosuvastatin and only two studies were done with fluvastatin.
The most occurring adverse event were clinically confirmed muscle disorders, self-reported muscle symptoms and liver dysfunction. Renal insufficiency, diabetes or eye conditions were not that common.
There is a minimally increased risk of muscle symptoms which are assessed as self-report of the patients and statins significantly but with muscle disorders which are confirmed by increased CK levels no significant association was found with statins. These adverse events appeared with all types of statins. With the adverse event of liver dysfunction, atorvastatin and lovastatin show a significantly higher risk. This might be because of their metabolism in the liver. This risk gets higher the higher the dosage of atorvastatin is. Fluvastatin had the lowest risk for the adverse event liver dysfunction followed by the other types of statins in which this risk seems not to be elevated. Routine monitoring of the function of the liver during the treatment is recommended.
In renal insufficiency no significant association to any statin is found.

No association between any statin and diabetes is found in primary prevention, but, however, there is an increased risk in populations taking statins for secondary prevention, a meta-analysis discovered. These findings could be explained by larger populations, older participants and higher statin doses. Estimates from observational studies prefer the treatment for primary prevention and the benefits outweigh the potential harms, is said. The adverse events are mostly self-reported, mild and do not lead to morbidity or mortality. In this review, in some trials the sample size was small, vulnerable individuals maybe developing an adverse event more likely were excluded, and the median follow-up period was very short in half of the trials (below six month). Due to that the appearance of adverse events may be underestimated in primary prevention. No statin type is preferred for primary prevention because of a lack of data.[40]

There are other markers which are risk factors for a potential heart disease and get more attention now. Inflammation seems to play a very important role and so do apolipoprotein B, lipoprotein(a), the number and size of LDL particles, the ratio of lipoproteins and the ratio between HDL and triglycerides. [39]

The JUPITER trial is kind of famous in the history of investigating statins. It is a multinational, double-blind and placebo controlled clinical trial. Patients at low LDL-C levels but elevated levels of hs-CRP (high-sensitivity C-reactive protein) who had no cardiovascular event were included. It investigated statins for primary prevention in patients with low LDL levels but elevated hs-CRP (high-sensitivity C-reactive protein) levels. CRP is a marker for inflammation. The risk reduction based on lowering LDL alone seemed to be too small. Anti-inflammatory effects of statins should contribute to that risk reduction as pleiotropic effects, according to the assumption with which this trial started. Multiple studies found out that hs-CRP is an indicator of cardiovascular events independent from traditional cardiovascular risk factors . Some trials demonstrated that a higher risk reduction with statins is achieved in patients with elevated hs-CRP levels. In addition to that, statins should be responsible for decreasing hs-CRP levels independent of LDL lowering. In healthy individuals with elevated hs-CRP level it was seen that they have a higher risk of MIs and stroke. The statin mediated reduction of hs-CRP is about 20–30%. Individuals who had high LDL and low hs-CRP levels had a lower risk compared to the opposite case with low LDL but high hs-CRP levels. That implicates that the level of CRP may be more relevant than LDL cholesterol in cardiovascular events.[41]

Prescribing statins for primary prevention is one part, the other part is on the side of the patient taking it regularly, which is an issue especially when prescribed for primary prevention. Fear of several adverse events is a major factor, accompanied by many other reasons, why to stop a statin therapy. In 19 studies from 1984 to 2017, where nine are at high quality, the proportion of how adherent people are, was established. The results ranged from 17.8% to 79.2%. Different factors influence the statin adherence ,e.g. older people or patients with more traditional risk factors are more willing to take a statin than younger ones, which affects primary prevention.

Reasons for primary non-adherence are as follows:

- Concern about the medication (63%)
- Decision to change the lifestyle instead of taking the drug (63%)
- Being afraid of side effects (53%)
- The opinion that statins are unnecessary (39%)
- Experiencing a low severity of the illness (35%)
- Being afraid of interactions with other drugs (16%)
- Being concerned of an overuse of medications (16%)
- Financial reasons (12%)
- Do not understand the reason of the medication (11%)
- Do not think a statin is effective (7%). [42]

3.5.1 Statin safety in adults above 65 years (primary prevention)

In people over 65 years of age, the likelihood of adverse events was compared to placebo and showed no increase in these patients. Adverse events, especially muscle symptoms, can occur in people of every age, but they are usually mild and rarely dangerous. In the elderly the leading fact of prescribing a statin should primarily be the cardiovascular risk. In very old and frail patients, statins should be avoided because they have no long-term benefit with limited life expectancy.

By prescribing statins in elderly the different metabolism compared to young adults has to be considered. Also, the difference between statins and how the body catabolizes them is important.

Most statins are metabolized by CYP3A4 in the liver, except pravastatin which is independent of the CYP-P450 system. Because many other drugs are metabolized by CYP3A4 was well, prescribing pravastatin in elderly lowers the risk for drug-drug

interactions. Fluvastatin is metabolized by CYP2D9, which also reduces the risk of drug-drug interactions. [43]

There are several guidelines that provide several suggestions for people at different ages who uses statins for primary prevention.

What most guidelines have in common is the recommendation for a statin therapy at highest risk for ASCVD. The risk is defined either as high-risk condition like diabetes, FH, high LDL-cholesterol, CKD or is evaluated with a risk score. Each guideline uses a different risk score.

Three age groups can be distinguished were the borders of age are following: (The European guideline has different borders of age[12].)

- Middle-aged (40-65 years)

For apparently healthy people at highest risk of ASCVD all guidelines recommend a statin therapy in those. This group of age is mostly well represented in trials.

- Elderly (66-75 years)

Four of these guidelines say statins should be administered in high-risk people in this population. Only the Europeans in the guideline of 2019 have no clear recommendation because the risk score is not attributable for people over 65 years. The guideline says that there is no uncritical use in people over 60 years even when the risk for a cardiovascular event is very high.[44]

The current European guideline (2021) has the following recommendations for the treatment of apparently healthy people at different CVD risks. In people at low or moderate CVD risk a treatment of risk factors is generally not recommended.

For people at high risk of CVD a treatment of risk factors should be considered, for instance LDL-C lowering. According to age, there are different thresholds for people below 50 to over 70 years. In very high-risk patients, the treatment of risk factors is generally recommended. This affects people below 50 years with a SCORE2 value of over 7.5%, people at an age of 50 to 69 with over 10% and people over 70 years with an estimated risk level of over 15% elevated with SCORE2-OP. It has to be added that in apparently healthy people over the age of 70 years, the recommendation for a treatment with lipid lowering drugs may just be considered because it is categorized as Class IIb. What is recommended for all over 70 years old are lifestyle modifications like smoking cessation and achieving a goal level of systolic blood pressure of below 160 mmHg.[12]

Other guidelines recommend a statin therapy in up to 84 year old for primary prevention because of the reduction in relative risk, many trials showed.

- Very elderly (75 years and more)

In the very elderly only one guideline recommended a risk-based prescription of statins in this group of age for primary prevention. It must be noted that everyone over the age of 75 has an estimated risk of a CV event of 10% in 10 years and one guideline suggests therefore a generous use of this drug in people that age. The very elderly are defined as 75 to 84 years of age in this paper and NICE also recommend atorvastatin 20 mg in individuals older than that.

It is a fact that the very elderly are at high risk, but there is rarely an evidence of the efficacy for primary prevention in this age group. But it is not just about efficacy, safety is more important than that.[44]

The term TTB, short for time to benefit, indicates the time from the start of a treatment to a prevented event. This time is of importance because in patients with limited life expectancy, which means estimated time to life beneath the time to benefit, a therapy would be just a risk of adverse events with little chance of experiencing the benefit of it. The time till a benefit with a statin intake for primary prevention occurs is unknown.

One major cardiovascular event is prevented, treating 300 persons for one year. In three years 4 and in five years 7.5 major CV events are prevented in 300 persons treated with a statin. The longer a statin is taken, the higher the number of prevented major CV events gets. Due to those numbers, you can say that 2.5 years of treatment with statins are needed to prevent one major CV event in 100 persons at an age of 50 to 75 years. This is an average value and it varies between studies. When the life expectancy is limited to less than 2.5 years patients do not benefit enough (within years) to outweigh harms that could occur within weeks.

It should be added, that these data are from a healthier group, people with a life expectancy below 2.5 years can't be compared with them. It leads to underestimating the harm of statin adverse events in comorbid patients.[45]

A randomized clinical trial showed, that in patients with a life expectancy of under one year who continued to take a statin, the self-reported quality of life was worse than in those who were withdrawn from the therapy. [46]

3.6 Secondary Prevention

For secondary prevention, the efficacy in the elderly is well documented.

The Prosper trial assessed a benefit in this group of age with known vascular diseases. In comparison to other trials, men and women at a higher age were included. Treating elderly for a period of three years with pravastatin of 40 mg per day results in a relative risk reduction of 15% and the absolute risk reduces by 2.1% to experience coronary death, myocardial infarction (non-fatal) and stroke (fatal or non-fatal).

A combined end point can lead to falsifications, by analyzing the three endpoints it gets obvious that less coronary events occurred compared to placebo, but the rates of strokes remained the same. Pravastatin was well tolerated in this group while many patients took even many other drugs. No adverse effects according to liver function or elevated muscle enzymes are reported.[47]

However, several randomized controlled trials detected an increased incidence of diabetes when statins are used for secondary prevention. [48]

The European guideline advocates the use of statins in people who experienced a cardiovascular event, since on average every patient who has experienced a cardiovascular event has a very high risk of recurrence. [12]

In a meta-analysis of randomized controlled trials, however, an elevated incidence for diabetes for secondary prevention use was detected with statins.

The current recommendation of the European guideline is a generous use of statins for secondary prevention because on average, every patient who experienced a cardiovascular event is at very high risk of a recurrent one.

If someone experiences a stroke, the therapy after this event is in first line a statin for secondary prevention. Some trials showed a higher rate of haemorrhagic strokes in people taking statins compared to those who did not.

A meta-analysis of 11 randomized clinical trials evaluated the primary outcome of a recurrent stroke in patients after a stroke with a more or less intensive LDL-C lowering therapy. Secondary outcomes were major cardiovascular events and haemorrhagic stroke. There were over 20,000 patients with 67% of men, the average age was 65 years and they experienced an ischemic stroke. The results showed, more lowering of LDL-C was associated with a reduced rate of recurrent strokes.

The absolute risk was 9.3% in the group with less intensive therapy and 8.1% in the more intensive therapy group. The results were just significant in the group with a more

intensive therapy of statin plus ezetimibe compared to less intensive statin plus ezetimibe. With statins alone or PCSK9 inhibitors, no significant outcome was detectable.

It has to be added that just those with the evidence of atherosclerosis had a reduced risk of a recurrent stroke. Those with no atherosclerosis had no benefit compared to a less intensive therapy. These findings support the results mentioned above where statins showed no benefit for primary prevention according to strokes.

A more intensive LDL-C lowering ends up in a reduced rate of cardiovascular events, but the risk of getting a haemorrhagic stroke increased. However, the authors of this study support the more intensive therapy due to the greater risk reduction of recurrent ischemic strokes. [49]

The European guideline of 2021 says that in patients with LDL-C levels of 100 to 190 mg/dl and an ischemic or haemorrhagic stroke or a transient ischemic attack, the incidence of strokes and cardiovascular events decreased after the start of atorvastatin 80 mg/day.[12]

An intensive lipid lowering therapy is recommended with goals of more than 50% of baseline level and LDL-C of 70 mg/dl as first step. In step 2 the LDL-C goal is 55 mg/dl.

In people who already had a cardiovascular event, it is evident that the risk of a recurrent CVD event is very high. SMART (Secondary manifestations of arterial disease) is a tool to estimate the 10-year CVD risk for secondary prevention and there is another risk model called European Action on Secondary and Primary Prevention by Intervention to Reduce Events, were the 2-year risk of recurrent CVD events is estimated.

After a discussion between the clinician and the patient about a certain risk, a pharmacological therapy could be started along with a lifestyle modification including a change of dietary habits and more exercise. Besides antihypertensive therapy and aspirin, a statin could be a useful medication to reduce the cardiovascular risk, is said. If the CVD risk remains high with the maximum of tolerated treatment, other drugs may be considered like dual antithrombotic treatment or anti-inflammatory therapy.[12]

3.7 Men and women

European guideline 2021:

- There are considerations for screening of women with different conditions that could lead to an increased CV risk, like pregnancy induced or regular hypertension, any type of diabetes mellitus or gestational diabetes mellitus or history of

preeclampsia or polycystic ovary syndrome. Both screenings can also be considered in women with a history of premature or stillbirth.

- Untreated mental disorders are considered as influencing and migraine with aura is also relevant in the assessment of CVD risk. Hormonal contraceptives may be avoided in women with migraine with aura.
- CVD risk should be assessed in men with erectile dysfunction.[12]

Due to the fact that most studies include exclusively male patients, it is important to investigate if women and men should be treated the same way or if there is a difference.

A meta-analysis examined the absolute difference in men and women in lipid concentrations. A moderate or more intensive therapy with statins was compared to a less intensive therapy regimen or to placebo for one year.

174,149 people were included in all studies, 46,675 were women, that's 27%.

In one year, LDL-cholesterol decreased about 1.1 mmol/l in statin versus placebo trials and about 0.5 mmol/l in more versus less statin therapy, in men and women equally.

Women had a lower cardiovascular risk in these studies in general, but the effects to prevent a major vascular event and mortality were similar in women and men with a similar risk of major vascular events. Not only high-risk populations showed that there is no significant difference between men and women, also low-risk populations delivered nearly the same data.

However, a small difference was noted, in people at a 5-year risk estimated less than 10%, the risk reduction of a CV event for men was lower than for women. Men had a 35% lower risk which means a reduction of more than a third where the risk reduction for women was 26%, which is just a quarter.[50]

The guideline of the "American College of Cardiology/American Heart Association" for CVD prevention were first published in 2004 in a gender-specific manner. There risk factors for women which occur early or conditions during pregnancy which increase the CV risk as well as an increased postmenopausal CVD risk were considered.

What is observed in the USA is that the rate of coronary heart disease and mortality in younger women (35-54 years) rises. Maybe the epidemic of obesity in western countries are responsible for developing certain diseases.

Women who smoke and women with diabetes have a greater relative risk of CVD compared to men but there are other risk factors for women that need to get attention: Pre-

eclampsia, gestational diabetes, polycystic ovary syndrome, early menopause and autoimmune disease.

Women get CVDs 7 to 10 years later than men do. The reason for this is possibly the protective effect of estrogen during reproductive years, but some conditions in women lead to increased CVD risk and sometimes to an early onset of it. Estrogen protects by increasing angiogenesis and vasodilatation, decreasing the proliferation of fibroblasts and it has apoptotic properties.

Using the Framingham risk stratification, the risk in woman is often underestimated. Considering just traditional risk factors alone can be misleading in women because 20% of coronary events appear in absence of these risk factors.

- Pre-eclampsia: 3–5% of all pregnancies develop that condition. It is defined by a new-onset hypertension with proteinuria or hypertension with end-organ dysfunctions (regardless of proteinuria) after 20 weeks of pregnancy. Why exactly pre-eclampsia increases CVD risk, remains unclear. The vascular remodeling seems to be impaired in these patients which accelerates the atherosclerotic process. A meta-analysis in 2008 with 116,175 participants suffering from pre-eclampsia or eclampsia was compared to healthy pregnant women. The risk of CVD and CV mortality was twice as high in the pre-eclampsia group. The higher the pressure of blood the more sever is the condition of pre-eclampsia and the risk of CVD rises more. Another meta-analysis confirmed the association between pre-eclampsia and future risk of CVD and mortality therefrom even when adjusting several other risk factors.
- Early menopause: 10% in average experience an early menopause. It is defined by the ending of reproductive times by 45 years of age. An early loss of estrogen results in an activation of the RAAS system, endothelial dysfunction and inflammation. The hypothesis was: hormonal therapy should help to reduce the risk of CVD in postmenopausal women.

A trial had to be ended because of the harm, the hormone therapy caused. It increased the CVD risk and the risk of invasive breast cancer. There is no recommendation for hormone therapy in the prevention of CVD.

- Autoimmune disease: Women develop autoimmune diseases more often than men. The chronic inflammation accelerates the atherosclerotic process and the endothelial dysfunction. Patients with an autoimmune disease are often treated with steroids for a long time, which leads to hyperglycemia and hypercholesterolemia. People with systemic

connective tissue disorder or rheumatoid arthritis are having the highest risk among autoimmune diseases of CVD and all-cause mortality.

- Gestational diabetes: It is no surprise that GD is a risk factor because diabetes is a very well-known risk factor of CVD. A prospective cohort analysis of nearly 90,000 women confirmed the elevated risk of women with GD compared to women without a history of GD. The median follow-up years were more than 25 and it showed an increased risk of 43%. The highest incidence of these women was 8–15 years after giving birth. Due to these findings a primary prevention for CVD should be started early post-partum.
- Polycystic ovary syndrome: 4% to 8% of women suffer from this condition in reproductive age. Polycystic ovaries combined with oligomenorrhoea and hyperandrogenism are the main symptoms. Insulin resistance is not a part of the criteria for diagnostic but in 50–70% of the patients it occurs. The chronic hyperglycemia increases the CVD risk. In patients with PCO syndrome there is a 1.3-fold higher risk of CVD a meta-analysis pointed out. In a subgroup it was seen that woman with PCOS who developed CVD had other risk factors too. It is suggested that the increased risk is related to a metabolic syndrome, but further investigations are needed.

An early identifying of the risk factors and modification with diet, exercise and/or drug treatment lowers the life-time risk for CVD. Primary care providers have to be aware of the additional risk factors for CVD in women with certain conditions and they have to be treated properly.[51]

As mentioned above at the cardiovascular risk, the guidelines of ACC/AHA say that adults at borderline or mediate risk should be investigated for possible more risk factors.

The family history is adjusted to women, knowing they develop ASCVD 10 years later than men in average. Low HDL, premature menopause and a history of pregnancy-associated conditions which increase ASCVD risk are especially considered in women.[52]

The risk associated with the risk factors hypertension and diabetes seems to be greater in women, as does the protective effect of alcohol and exercise. The reason why hypertension contributes to a higher risk in women is partly because of a higher prevalence in women who are a decade older.[10]

What the current European guideline says:

Pre-eclampsia is a condition during pregnancy with hypertension and proteinuria. 1–2% of all pregnancies are affected. It leads to an increased CVD risk of the factor 1.5 to 2.7 in comparison to other women. It is not investigated if the increased risk with pre-eclampsia

is independent of other CV risk factors. These patients should be screened for hypertension and diabetes mellitus. Hypertension occurs in pregnancies with 10% to 15%. The risk of developing a CVD later is lower in them as it is in women with pre-eclampsia, but it is still increased.

Women with a gestational diabetes mellitus have a 50% increased risk of developing DM in the time of 5 years after the pregnancy. In addition to that, the CVD risk is also doubled. Women with PCO syndrome have an increased CVD and there is also a higher rate of DM. Premature (< 40 years, 1% of women) and early menopause (< 45 years, 10% of women) and an increased CHD risk is associated as well. With every year of premature menopause the risk of a CHD increases by 2%. [12]

3.8 Comorbidities

3.8.1 Diabetes mellitus

The European guideline of 2019 recommends a primary treatment in high-risk diabetic patients to prevent CVD. Two trials are noted to confirm the recommendation of statins but none of them lowered the risk of CVD in diabetics. A high-quality systematic review showed that in type 2 diabetics the mortality and cardiovascular complications are not reduced with statins. It may even worsen their condition because new-onset diabetes is an adverse effect of statins as they interfere with glucose metabolism. High cholesterol is seen as a risk factor for diabetes, but different studies do not see a causality there. Data of half of a million people demonstrated that the level of LDL-C was associated negatively with the prevalence of type 2 diabetes. This was seen in people who received statins as in people who did not. [27]

On the one hand there are people at risk for developing diabetes, and on the other hand there are a lot of patients already suffering from it. Atorvastatin worsens the levels of HbA1c. No difference was seen in rosuva-, lova-, prava- and Fluvastatin. With one statin called pitavastatin HbA1c was moderately reduced as well as the fasting blood glucose level. Therefore, pitavastatin just considering T2DM is a better choice compared to other statins, but, as already mentioned, the greater the cardiovascular risk, the higher and more intensive the statin therapy has to be.

Type 2 diabetes in children and adolescents increases the risk of early cardiovascular disease in a similar way to congenital familial hypercholesterolaemia. This is the conclusion of the American Heart Association in a recent statement. But the early

development of type 2 diabetes is considered even more threatening. According to the expert group, this can even increase cardiovascular mortality far more than type 1 diabetes in this age group. This could be due, among other things, to the more rapid development of nephropathy. While nephropathy often only becomes apparent after a decade in adolescents with T1DM type 1 diabetes, when diagnosing T2DM there is already a manifestation of nephropathy in these patients. In addition to that, adolescents with type 2 diabetes have an increased intima thickness and increased vascular stiffness. The rate of children with the condition of T2DM is rising an now there are almost as much children with T2DM as there are with T1DM in the western world. After diagnosis, screenings for cardiovascular risk factors should be done regularly, the authors say. In an earlier statement, type 2 diabetes was still classified in the moderate risk category compared to type 1, but both forms of diabetes are now considered high risk factors in children and adolescents.[53]

The guideline says in people with well-controlled type 2 diabetes mellitus for a period of under 10 years (short-standing DM) with no organ damage or other risk factors of ASCVD, quitting smoking and lifestyle optimization are recommended.

T2DM with risk factors but without established ASCVD or TOD (target organ damage):

> Step 1: LDL-C < 100 mg/dl and a lower goal is set in Step 2 (70 mg/dl and 50% reduction)

T2DM with established ASCVD and/or severe TOD:

> Step 1: LDL-C < 70 mg/dl and a lower goal is set in Step 2 (55 mg/dl and 50% reduction)[14]

A recent retrospective matched-cohort study assessed the association between statins and diabetes. They defined a progression of diabetes with a new initiation of insulin, an increase of glucose-lowering medication, five or more blood glucose levels of 200 mg/dl or more or the occurrence of ketoacidosis or uncontrolled diabetes. Most of the 83,022 individuals of this study were men with a mean age of 60 from different nations. A progress of the diabetes occurred significantly in nearly 56% in the statin group compared to 48% of active comparators. A sub-analysis showed that there is a faster development of diabetes with a more intensive lipid lowering therapy.[54]

3.8.2 HIV

People who suffer from HIV have an increased risk of myocardial infarction not considering typical cardiovascular risk factors. 80% of those with this condition have dyslipidemia. The risk factors in HIV patients are the prolonged immunosuppression, antiretroviral therapy, chronic inflammation and dyslipidemia. Antiretroviral drugs are metabolized the same pathway as most statins are, via CYP3A4. This could result in a greater risk for adverse events due to drug interactions, like myopathy and rhabdomyolysis. In treatment with PI (proteinase inhibitors), simvastatin and lovastatin should be avoided and the dose of atorvastatin, rosuvastatin, fluvastatin and pravastatin should be adjusted. Non-nucleoside reverse transcriptase inhibitors can increase the metabolism of atorvastatin and higher doses for proper treatment are necessary. When choosing pitavastatin in HIV patients, no significant drug interactions are expected and no dose adjustment is needed.
Other antiretroviral drugs like nucleoside reverse transcriptase inhibitors and CCR5 receptor inhibitors need no dose modifications.
FDA classified lovastatin and simvastatin as contraindicated and is cautious about atorvastatin and rosuvastatin (dose limitations are suggested). They gave no dose limitations for pravastatin and pitastatin, and fluvastatin seems to be safe as well. [55]
Despite an effective antiretroviral therapy, there are residuals of immune activation and inflammation. In epidemiological studies these two occurring factors are associated to CVD. Pleiotropic effects of statins should be responsible for having an impact on the inflammation. In people with HIV, statins are therefore suggested for primary prevention to lower major cardiovascular events.
This study showed the following results: The sub-study investigated plaques with CTA (computed tomo-angiography), inflammatory pathways and pathways of immune activation by assessing circulating biomarkers. 755 individuals aged 40 to 75 without known CVD and with low to moderate cardiovascular risk factors participated, receiving antiretroviral therapy but not a statin treatment. 16% of them were women which is 124 women in total. 54% of all individuals were white, 35% were black, 1% were Asian, 10% were another race. The average LDL-C level was 108 mg/dl and only three participants had diabetes. Nearly 60% got antiretroviral therapy for more than 10 years with good control. Half of them showed a plaque on the coronary CTA and 35% had a CAC of greater than 0. Only 13 people had advanced CAD with a CAC of over 400. 23% had vulnerable plaques and 40% had noncalcified plaques.

What is important to mention is, that coronary plaques were found in 52 of 175 participants of very low ASCVD risk (<2.5%) which is 30% in this subgroup. 13% of them had vulnerable plaque features. Also, in the group of ASCVD risk below 7.5%, 272 of 605 (45%) had plaques and nearly half of them had vulnerable plaques. Those with coronary plaques had higher levels of different biomarkers like the immune marker interleukin-6 and a marker for arterial inflammation LpPLA2 (lipoprotein phospholipase 2) than those without. No difference was seen in hsCRP levels in participants with or without plaques, but considering vulnerable plaques hsCRP values were higher in them.

There are also differences in the treatment of HIV. With prior exposure and during the administration of abacavir, more plaques were detected. In some studies, there was an increased infarction rate with this therapy.

This study wanted to show the connection between arterial inflammation and immune activation to coronary artery disease in people with HIV, even with good virologic control and low traditional risk factors.

Because CAD occurs much earlier in people with HIV, a treatment in people at younger age is recommended. Further studies are needed to determine how the plaque phenotypes relate to major cardiovascular events. Which role a statin therapy plays in these patients, how or if they are able to reduce plaques, needs also further investigations.[56]

3.8.3 Chronic kidney disease

What the guideline of 2021 recommends is a screening of ASCVD in patients with CKD, and the progression of the disease by monitoring changes in albuminuria. In patients at estimated high risk and the condition of CKD, a statin should be combined with ezetimibe.[12]

EGFR (estimated glomerular filtration rate) and albumin excreted though urine are markers of cardiovascular mortality. All-cause mortality and cardiovascular mortality is not increased if eGFR and albumin-to-creatinine ratio show levels in a normal range. [57]

A recent study with PCSK9 inhibitors suggests that there is a greater benefit in those at an earlier stage of CKD (eGFR 30-90 mL/min/1.73 m^2) and people with a kidney replacement treatment should not get a statin therapy.[12]

Most organ transplanted patients die because of a cardiovascular death, due to many cardiovascular risk factors like hypertension, dyslipidemia, or diabetes. In addition to that there can be drug-drug interactions between statins and immunosuppressant drugs and a prescription needs to be well thought and adjusted. Cyclosporine is as many statins are an

inhibitor if CYP3A4. Pravastatin seems to be safe in these patients because the major metabolic pathway is not CYP-enzyme dependent, but a maximum of a dose should not be exceeded.

Steroids, MMF and AZA seem to be safe with every type of a statin. Lovastatin, pitavastatin and simvastatin are not recommended with cyclosporin, tacrolimus, sirolimus or everolimus. With atorvastatin the maximum dose with calcineurin inhibitors is 10 mg and there is no recommendation with cyclosporin. Pravastatin should only be administered at a maximum dose of 40 mg, Rosuvastatin with a maximum of 5 mg and Fluvastatin with a maximum of 40 mg with cyclosporin and calcineurin inhibitors.[57]

In CKD patients, dyslipidemia seems to be a major CV risk factor, but it is not fully clear which role statins play in these patients. There are some trials which tried to find out, but they are not performed that well.

There is a benefit in risk reduction of getting a CV event in patients with CKD with lowering LDL-C, but this benefit decreases with reduced eGFR, especially in patients with an eGFR below 30 ml/min and patients in need of dialysis.

The “Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease” Study (PLANET I) investigated if there is a benefit with atorva- or rosuvastatin on proteinuria or eGFR in diabetic patients. 80 mg of atorvastatin were used and 10 to 40 mg of rosuvastatin. Atorvastatin decreased proteinuria by 18% and eGFR remained stable. In the rosuvastatin group proteinuria did not decrease and eGFR was reduced significantly. The differences in dose between these two groups have to be considered and maybe there are similar outcomes with adjusted doses. A meta-analysis demonstrated that pitavastatin and pravastatin are able to reduce albuminuria too, as atorvastatin does. So, these three substances are currently considered as the medication of choice in CKD patients with proteinuria.

What has to be kept in mind is how statins are excreted. The one that is mainly renally eliminated is pravastatin. Pravastatin is the one that is mostly recommended in elderly patients due to safety reasons, but in patients with CKD the dose has to be adjusted, especially in those with an eGFR below 30. Otherwise, the risk of accumulation rises and could lead to adverse events. Special attention has to be paid to people with renal failure for increased systemic exposure.

No dose adjustment is necessary with atorvastatin and fluvastatin. At eGFR 30–50 ml/min/1.73m^2 there is a dose restriction for pitavastatin of max. 2 mg, pravastatin of max.

10 mg and simvastatin with ezetimibe to the maximum of 20/10 mg. At eGFR lower than 30 ml/min/1.73m^2 but over 15 ml/min/1.73m^2 the following maximum doses are:

- Lovastatin 20 mg
- Pitavastatin 2 mg
- Pravastatin, rosuvastatin and simvastatin 10 mg
- Simvastatin/Ezetimibe 20/10 mg

3.8.4 Heart failure

There are two different types of heart failure patients. The ones with a "preserved ejection fraction" (HFpEF) and the other ones with "reduced ejection fraction." HFpEF patients have a still a normal output of the left ventricle where HFrEF patients have a reduced output. In patients with HFpEF an inflammatory process seems to be the pathophysiological mechanism which impairs the elasticity of the ventricular muscle. Due to anti-inflammatory properties of statins, they may be favorable in these patients.
In patients with reduced EF, a loss of cardiomyocytes and stretching seems to be the pathophysiological mechanism, in which statins are not helpful to improve this condition. To prevent coronary artery disease, statins should be considered in these patients as well.

- HFrEF

These patients are classified according to their symptoms, it ranges from NYHA ("New York Heart Association") I to NYHA IV. 10mg per day of rosuvastatin did not prevent non-fatal acute myocardial infarction, stroke or reduce cardiovascular mortality within 32.8 month. Another study which included almost 5,000 heart failure patients showed similar results over 46.8 month with rosuvastatin. The dosage per day was also 10 mg. Beneath death, even the frequency of hospital admission was counted and no benefit was seen with rosuvastatin.
However, it is suggested that statins could stop a process of remodeling of the heart in these patients. A meta-analysis showed reduced hospitalizations for worsening heart failure with statins but no reduction in sudden cardiac death.[57]

- HFpEF

Observational data with patients with HFpEF were assessed, and those who got a statin had a better outcome. The survival rate of one year was higher regarding cardiovascular death and all-cause mortality and also the cardiovascular hospitalization rate was lower but these findings need to be confirmed by randomized controlled trials.

Big trials were run to evaluate the safety of statins in heart failure patients. Statins have a good safety profile in these patients even at a more severe condition, but there has to be special attention to drug-to-drug interactions because of polypharmacy in heart failure patients. Because of the many people who are treated with statins, statin use is in consideration to may be one of the causes why there are so many heart failure patients nowadays.[57]

There is a raising incidence of heart failure patients, and it occurred in many patients receiving a long-term statin therapy. The relaxation in the diastole depends mainly on adenosine triphosphate. Low levels of Coenzyme Q10 in myocardial cells could lead to impairment in mitochondrial energy production causing diastolic dysfunction. In a small clinical trial, a reverse of diastolic dysfunction was seen with 300 mg CoQ10 per day in statin treated patients with developed heart failure. A new term came up with the new adverse event: SACM = statin-associated cardiomyopathy.

142 patients on a statin therapy who developed heart failure due to no identifiable cause were identified, the statin treatment was stopped and CoQ10 was supplemented with a dose of 300 mg/dl. Mainly these patients had HFpEF and they were followed 2,8 years. 54% of them were women and the average age was 65 years. 28% had coronary heart disease but with a normal ventricular ejection fraction and those with hypertension (49%) had a normal left ventricular thickness of the wall. Patients had a statin therapy in average of 6.8 years and the potency of different statins was acknowledged and adjusted to atorvastatin. The severity of the heart failure was determined by the New York Heart Association classification based on examination and patient history. The echocardiographic investigation was done by one sonographer in the same clinic. A score was used to categorize the diastolic function and the ejection fraction was estimated visually. The HFpEF condition was determined by ejection fractions of greater than 50%. 42 (34%) of the 122 patients experienced a complete normalization and 31 (25%) an improvement without normalization of the diastolic function measured from baseline to the final follow-up. In 42 (34%) patients there was no change in diastolic function and 7 (6%) had a worsening. In the 9 patients with reduced ejection fraction, the ejection fraction improved slightly. 29 patients relapsed to the baseline diastolic dysfunction. 20 of them either stopped, reduced or changed CoQ10 formulation. But the other 9 patients relapsed without a reintroduction of a statin and no change in CoQ10 supplement. In the whole group NYHA classes improved except those who were at NYHA class 4. At baseline ,8% had

NYHA class 1, in the final follow-up 79% had NYHA class 1. Despite the significantly increasing total cholesterol levels, there were little coronary events and 4 deaths, where one died a sudden cardiac death. The authors of this paper say that SACM = statin-associated cardiomyopathy is a cause of iatrogenic heart failure and it is underdiagnosed.[58]

HFpEF is mainly caused by hypertension and occurs more often in the elderely, obese patients and in women. Those who suffer from HFrEF are younger, more often men and do have coronary artery disease more likely compared to HFpEF patients. In addition to an elevated plasma cholesterol as CV risk factor, heart failure patients have a poor prognosis with this risk factor. Heart failure does also cause intestinal congestion and the cholesterol absorption could be lowered as an explanation for the poor prognosis, but cholesterol depends just on a small part of the nutritional status. The main pathway which is responsible for our cholesterol levels is the biosynthesis of cholesterol in the liver. This pathway could also be impaired due to heart failure.

In a trial with 3,957 patients who were hospitalized with a left ventricular ejection fraction of less than 40%, there was a significant inverse relationship between the plasma cholesterol and the outcome of these patients. In a follow-up of a little more than 300 heart failure patients over the age of 20, a low LDL-C level due to a statin therapy was associated with a worse outcome. Because of the fact that heart failure patients are mostly excluded from large trails, there are not much data from major trials. Statins reduce coronary vascular events which means, heart failure that is caused by cardiac damage could be decreased. One meta-analysis including six RCTs showed a lower hospitalization rate with an intensive statin therapy, but in a larger meta-analysis it was seen that statins do just reduce the rate of non-fatal hospitalizations for heart failure but not the rate of heart failure deaths. No difference in people with or without a myocardial infarction were demonstrated, so this hypothesis needs to be questioned. [59]

The European guideline of 2021 first points out heart failure of ischaemic origin and the increased risk of CVD events in them. In people with asymptomatic left ventricle dysfunction or symptomatic heart failure (with reduced or preserved ejection fraction) the risk of hospitalizations and cardiovascular and all-cause death is increased. These findings generally occur in these patients, whether they are asymptomatic or have an acute myocardial infarction. In ischaemic heart failure, statins are recommended in secondary prevention and there is no recommendation in patients HFpEF or HFrEF.[12]

As mentioned, statins are not recommended in HF patients, but maybe there is a benefit in the prevention of HF. A treatment with statins reduced the rate of hospitalization and used for primary prevention, reduced the incidents of heart failure patients. In the WOSCOPS trial, after 5 years of a statin treatment there was a risk reduction of 35% over 20 years to get hospitalized with heart failure. With pravastatin the hospitalization rate of MIs and cardiac damage was reduced. This supports the hypothesis that there are maybe additional factors of statins in HF patients than just a myocardial damage prevention. In the European guideline of 2016, there was no recommendation of statins in most heart failure patients, but if statins are already taken, they can be continued for the prevention of CAD, is said. These recommendations are due to two large placebo-controlled trials. One included just people over 60 years of age and the other included people over 18 years. Rosuvastatin with 10 mg was used in both trials. There were two combined endpoints on the one hand CV death and non-fatal CV events and on the other hand the CV hospitalization rate and time to death. No endpoint was significantly decreased in the trials. In a post-hoc analysis though, one trial showed a reduced hospitalization rate of heart failure patients. CAD events seems to be uncommon in heart failure patients even in ischaemic heart failure patients which means a statin therapy in these patients just have a little impact. Which effect statins have on the size and function of the left ventricular, was investigated in 11 RCTs. It was demonstrated that the left ventricular ejection fraction was increased with statins by 3%, but the results are uncertain because of modest quality of some of these trials. As a conclusion it can be said, data with good evidence suggest that people with heart failure do not benefit from a statin therapy.[59]

3.8.5 Liver diseases

Recent findings support the hypothesis, statins are safe and even beneficial in patients with a chronic liver disease. An increased survival is detected in these patients as well as a lower rate of hepatocellular carcinoma, infections and decompensating events. A lower rate of infections does not support the hypothesis about low LDL-C as a risk factor of infections, to refer to the mentioned topic of statins and mortality. In patients with compensated cirrhosis, statins are also safe, and there is promising evidence that they contribute to a reduction of the fibrosis even when the condition is advanced.

The pathways of the progression of a hepatic disease is poorly understood. Statins may influence key points of fibrogenesis. In addition to that, statins are also said to decrease

inflammation and oxidative stress. What all liver diseases have in common is the increase of the resistance of the liver tissue. This happens due to a dysfunction of the endothelial nitric oxide synthase. Statins activate this synthase and the NO production resulting from that. This could be a rescue of hepatic endothelial cells which are typical of liver injury and cirrhosis.

Current evidence says that a regression of liver fibrosis is possible. There are several studies in primary antifibrotic treatment going on at the time. A meta-analysis showed a risk reduction of developing cirrhosis or the progression of a fibrosis with statins of more than a half. be It has to added that this finding was not significant. But another meta-analysis had a hazard ratio of 0.49 in fibrosis progression, significantly. Limitations of this analysis were that it was a retrospective study, and the group of patients was heterogenous.

Fibrotic progression results in portal hypertension. Four randomized controlled trials showed a small or moderate benefit with statins in these patients, compared to placebo.

An important question is what the causes of death in these patients are and whether a statin can provide a survival benefit.

In a randomized controlled trial of cirrhotic patients with variceal bleeding within 10 days they were randomized to simvastatin + beta-blocker or placebo + beta-blocker. The statin group had a significant better survival rate, but this study did not demonstrate a lowered rebleeding rate compared to placebo. Further studies are necessary to find out why survival was not dependent on the rebleeding rate.

In a study of patients suffering from portal hypertension and who did not show an improvement with beta-blockers, simvastatin was added as treatment and it resulted in a decrease in portal hypertension in almost half of these patients.

Similar findings showed that with a combination of statin and beta-blocker a greater reduction of the portal pressure was achieved, compared to beta-blocker treatment alone. Important evidence came from investigations with Doppler ultrasound showing a significant reduction of the hepatic artery resistance index in the statin group within thirty days. [60]

In a trial with rats who suffered from a cirrhotic liver disease, simvastatin reduced the portal hypertension and the endothelial dysfunction compared to placebo. Besides other causes of death, patients with a cirrhotic liver disease can die due to a bleeding of esophageal varices. In the prevention of re-bleeding and death, simvastatin reduced the risk

of death. There was a survival benefit in 24 months with statin therapy, but the re-bleeding rates were nearly the same in both groups.

Because of different stages of liver diseases, there can be a point where a statin therapy causes more harm than benefit. More adverse events occurred in patients with decompensated liver cirrhosis at a higher dose of simvastatin compared to a lower dose.

Therefore, in patients with decompensated liver cirrhosis or an acute liver failure, statins should be strictly avoided.[57]

A leading cause of death patients with liver cirrhosis is HCC (hepatocellular carcinoma). A huge meta-analysis found an inverse association of the incidence of HCC with statins. There was a risk reduction of 37% with statins developing HCC (confounding factors were adjusted). Statins are thought to inhibit products which are involved in the proliferation of a cell. Non-alcoholic steatohepatitis is an advanced form of non-alcoholic-fatty-liver-disease. It is a very frequent cause of liver diseases nowadays and there is no effective treatment for that except weight loss. 80 mg/day of atorvastatin should have a beneficial effect in patients with NAFLD, as three major prospective RCTs showed. A decrease of CV mortality and morbidity was seen as well as a reduction of the liver enzyme aminotransferase. In addition to that, statins may be also responsible for an improvement of the hepatic tissue. [60]

NAFLD is a very common liver disease. It is characterized by fat accumulations in liver cells over 5% in absence of a chronic viral hepatitis, excessive alcohol intake or other liver diseases. NAFLD is histologically diagnosed by biopsy. The manifestation can be steatosis, steatohepatitis, fibrosis, cirrhosis and could end up in a hepatocellular carcinoma. There seems to be an increased cardiovascular risk in patients with NAFLD. “NAFLD is the hepatic manifestation of the metabolic syndrome”, is said in this paper.

In a trial all participants had a metabolic syndrome with dyslipidemia. They received lifestyle advice like regular exercise and a hypocaloric and hypolipidemic diet. For safety reasons many parameters were checked at every visit, like liver enzymes, cholestasis parameters, lipid levels, fasting plasma glucose, kidney values, etc. Half of the patients got rosuvastatin as monotherapy and the other half got a combination of rosuvastatin and fenofibrate. The results of serum enzymes, ultrasonography and liver biopsy were the same except in the group with the combination treatment: triglycerides were lower but in both groups in a normal range. Today statin-fibrate combinations are given no longer because of liver and muscle side effects. The first biopsy of 20 patients with NASH showed steatosis.

After the treatment with rosuvastatin 10 mg a repeated biopsy 12 month later resulted in a resolution of NASH in 19 of these patients. It can be said, rosuvastatin can have a beneficial effect on NASH resolution. Atorvastatin did not only improve liver tests and liver ultrasounds, also the risk of CV events decreased in NAFLD patients. Liver enzymes where normalized within 6 months and stayed in a normal range and the lipid profile normalized after three months of treatment. The metabolic syndrome disappeared in these patients and did not come back after nine months of the started therapy while waist circumference and BMI did not change.

Patients with NASH should be treated with 10 mg of rosuvastatin, is the recommendation due to those findings, starting at 5mg and when there are no occurring adverse effects, the dose could be elevated. It has to be added that this trial has its limitations. It is not clear which part is responsible for the better outcome of the metabolic syndrome and the liver. To what extent has the situation improved because of the statin and to what extent with modified lifestyle like diet and exercise? In opposition to that, a trial with pitavastatin did not show beneficial results, and using simvastatin or pravastatin in patients suffering from NASH a higher risk of myopathies was seen.[61]

In the European guideline it is said, non-alcoholic fatty liver disease is associated with higher rates of myocardial infarctions and stroke. Patients with NAFLD are often overweight or obese which is often accompanied by higher blood pressure, abnormal glucose and lipid levels. Referring to a trial which investigated the impact of the disease without established risk factors, there was no persistent association. A calculation of the CVD risk of these patients is always recommended as is the screening for diabetes mellitus.[12]

3.9 Pharmacokinetics

Pharmacokinetics describe what the body does with the drug.

Statins need to enter the cells to work. Some are lipophile (simvastatin, fluvastatin, atorvastatin), they go through the membrane and the hydrophile ones (pravastatin) take a carrier. Rosuvastatin is amphiphile. The intestinal absorption rate varies from 30% – 85% and most of the statins undergo a first pass effect of the liver, so bioavailability decreases to 5% – 30%. Pravastatin and partly Rosuvastatin (the hydrophile and amphiphile one) are exceptions which are not eliminated beforehand because of the liver metabolism.

The metabolization of the other five statins happens through CYP enzymes of the liver. They underlie just minimal metabolic handling. There are several CYP gene variants that

can affect the metabolism of statins and their blood levels, as well as drugs which take the same pathway, and most statins are metabolized by CYP3A4. The higher the blood level, the higher the risk of adverse effects.[1]

Because the dosage of a statin could be decisive for the occurrence of side effects, it is very important how much of it is given. It depends on how high the initial value of LDL-C is. If LDL-C has to be decreased by more than 50%, this is called high intensity statin therapy, where the long-lasting statins like atorvastatin 40-80 mg or rosuvastatin 20-40 mg are prescribed. [62]

3.10 Drug interactions

Issues:

- Patients who need statins, usually need some other drugs. As we know, the risk of interactions rises with the number of medications a person needs.
- Lots of hospitalizations are due to drug interactions, which increases the risks of hospital infections, overtreatment and so on.
- Reducing hospitalizations could inhibit a way that leads to death.

When another drug needs CYP3A4 to be eliminated, the statin accumulates and the high level of it is mostly responsible for the appearance of adverse effects. Especially muscle tissue is susceptible for this. What all active substances have in common is their rapid absorption. The peak of the maximum serum concentration is reached after 4 hours. The systemic bioavailability is low as mentioned above.

Differences between statins lie in the elimination half-life (range from less than 5 h of simvastatin, up to 3 0h of atorvastatin) and in the pharmacokinetics, i.e. what the body does with the agent (CYP enzymes). The most important CYP enzyme for statins is CYP-3A4. Not just because most statins take this pathway, also the most popular one, atorvastatin, is metabolized by it. CYP-2C9 and -2C8 are important for fluvastatin and pitavastatin and CYP-2C9 and -2C19 are the enzymes which inactivate Rosuvastatin, which is also a very commonly prescribed statin. The exception is Pravastatin which did not need a CYP enzyme because it is eliminated in the cytosol of hepatic cells. There is a long list of agents inhibiting CYP3A4:

- atorvastatin, lovastatin, simvastatin, fluvastatin, pitavastatin
- amiodarone
- antidepressants
- azole antifungals

- calcium-channel blockers
- cyclosporine
- calcineurin inhibitors: tacrolimus, sirolimus
- macrolide- or mycin-antibiotics
- midazolam
- nefazodone
- protease inhibitors
- sildenafil
- tamoxifen[63,64]

Most drug interactions occur with statins and immunosuppressive drugs, as well as with antifungal or antibiotic drugs. [64]

3.11 Adverse effects

In a review about efficacy and safety of a statin therapy it is said that lowering LDL cholesterol with a daily dose of 40 mg of atorvastatin in 10,000 patients for 5 years achieves a benefit of 10% in secondary prevention and 5% in primary. So, 1,000 patients out of 10,000 did not get another major vascular event and 500 of 10,000 patients are saved from getting a first major vascular event at increased risk. A statin therapy decreases the risk year per year it is taken. Of 10,000 patients in 5 years, 5 patients will get myopathy which could end up in rhabdomyolysis. 50 to 100 will get new-onset diabetes during treatment and 5 to 10 a haemorrhagic stroke. Symptomatic adverse events like muscle pain will occur in 50-100 patients in five years with a statin treatment, is said in this review.[65]

3.11.1 Muscle symptoms

The most frequent adverse effect of statins are muscle symptoms. Every 10th to every 3rd taking a statin complains about symptoms like that. The huge issue is the resulting bad compliance of the patients with muscle symptoms, even though they know about their cardiovascular risks. Muscle symptoms related to a statin therapy are often difficult to detect, because there is mostly no elevation of creatinine kinase in plasma and there is a big range of these muscle symptoms. It goes from myalgia to rhabdomyolysis.

To summarize light muscle symptoms, the term SAMS (= statin-associated muscle symptoms) is used. It describes myalgias, cramps and weakness, which appear shortly after starting a statin therapy, or the dosage got elevated and after cessation it disappears quickly.[63]

A brief excursion into history. The first statin-related muscle symptoms appeared in 1988, one year after the Food and Drug Administration approved lovastatin in the United States. Just one year later a correlation of statin intake and exercise to increase the risk of SAMS was seen. More than 30 years later the mystery should have been resolved, but today we still do not know the mechanism behind the symptom, there are just hypotheses.[66]

As mentioned, the incidence of SAMS seems to be very high, but a myopathy with a huge elevation of plasma creatine kinase or rhabdomyolysis is very rare. 1 of 1,.000 gets a myopathy with an elevated level of CK of more than ten times the upper limit and 1 of 10,000 will get the adverse event of a rhabdomyolysis. After patients experienced a period of SAMS, it is tried to get them back on a statin therapy after a washout period, whether with a lower dose of the same statin or another one. If the lowest dose with three tried statins does not work, the long-acting statins should be used every other day. It is seen that a therapy like that can achieve the same LDL-C lowering effect than a daily intake.

Determining SAMS is very difficult because there is no labor value to check, there is just patients' history.

Several risk factors are found, which increase the risk of getting SAMS. The higher the dose, the higher the risk. Increased serum concentrations appear after a high intake of statins or a slow catabolism of them. Drugs who get catabolized in the same way as statins can inhibit the pathway, and statins accumulate as mentioned above.

Hypothyroidism as a cause of slow metabolism can also be the reason for a slow reduction of serum levels. Reduced muscle mass and increased physical activity are risk factors as well. People at an advanced age have a reduced muscle mass, and so do women compared to men. Being old and being a woman can therefore also be added to the list of risk factors.

Observational studies show a prevalence of SAMS of 10–29% whereas RCTs report a prevalence of 1–2%. The reason could be a nocebo effect because this possible adverse effect of statins is known well in society and leads patients to expect side effects. [63]

The main problem with occurring muscle symptoms is that due to that, patients do not continue to take their medication, as mentioned above. Most of the former statin users say that the main reason for not continuing the medication was due to muscle symptoms. Mortality and CVD risk were also investigated in patients with a high or low adherence. There was a significant lower mortality and CVD risk in the high adherence group.

Important facts to know about the adverse event muscle symptoms that are maybe statin related:

- The STOMP study showed no differences with or without muscle symptoms regarding strength of muscles or exercise.
- 90% who reported SAMS to a statin, tolerated another statin. It is doubted that the statin was the main cause of the muscle complaints.
- Discomfort and weakness occur within 4–6 weeks after starting therapy, increasing the dose or adding an interacting drug.

The muscles that are affected when talking about statin-associated muscle symptoms are mainly pain and weakness of large muscle groups like back muscles, thighs or calves.
If a patient complains about SAMS, the clinician should evaluate risk factors that increase the risk of getting it excluding secondary causes like slow metabolism due to hypothyroidism or other myopathies like polymyalgia rheumatica and should reevaluate the indication and dosage of the taken statin.
It is not always the statin which is to blame, it should be kept in mind that other commonly prescribed drugs can cause muscle-related side effects as well, like glucocorticoids, antipsychotic, immunosuppressant or antiviral agents, lipid modifying drugs or substances of abuse, like alcohol, opioids or cocaine.
Considering the CK level and the CVD risk, patients with a low CVD risk should be reassessed if a statin therapy is necessary. Patients with a high risk of CVD should get a possible tolerable lipid lowering therapy.
In high-risk CVD patients at a CK level above 4 times the ULN, with monitoring of CK the statin therapy can be continued. If CK rises to 10 times ULN the dose has to be lowered but the statin can be continued as well.
If CK rises above 10 x ULN, therapy must be discontinued because of the risk of developing rhabdomyolysis.
After weaning, CK should be monitored and if it does not drop, a secondary cause is more likely and other investigations should be done.
If CK levels decrease after stopping the statin therapy, another statin with a lower dose should be prescribed while monitoring CK.
In general, high intensity statins with a long half value period should in general be considered as first line statin therapy.
Patients who suffered from SAMS got the combination of ezetimibe plus fluvastatin which was well tolerated and reduced LDL-C by 46%.

A side effect, where statins are the known cause, is myositis. Myositis is defined as muscle symptoms and an elevated level of CK (creatine kinase).

Creatine kinase is an enzyme that comes from damaged muscle cells. Everyday muscle cells die, so there is a constant threshold value in our blood that should not get over a certain value. An elevation of CK of more than 10 times ULN appears in 1-10 per 10,000 people in one year. The frequency depends on the statin itself, the dosage and other accompanying risk factors.

A more severe condition is rhabdomyolysis. It is to suspect when severe muscle pain occurs with a general weakness and myoglobinemia or myoglobinuria. Patients with CK levels above 40x ULN are also very likely to suffer from rhabdomyolysis. The main issue of this condition is that damaged muscle cells could lead to acute renal failure. Urinalysis should be done and renal serum parameters should be evaluated. The treatment of a rhabdomyolysis is hydration i.v. and urine alkalinization. If CVD risk is high, non-statin LDL-C lowering agents should be used.[66]

There are many controverse studies. Some say there is significantly more SAMS in patients with statins, others say muscle pain is a very frequent condition and it appears also in many patients of the placebo group.

It has to be mentioned that detecting these undefined symptoms is very challenging. One reason why statin-induced muscle symptoms are discussed controversially is because of that. It is diagnosed based on patients' self-report, there is no detectable value, no helping diagnostic device, just listening to what the patient has to report. What could help is to organize the statin-related myotoxicity into seven stages ranging from myalgia, myopathy, severe myopathy, rhabdomyolysis to SINAM (statin-induced necrotizing autoimmune myopathy).

The "first" stage is stage 0 and it would be asymptomatic and there would be no or less CK elevation. Myalgia is muscle pain without an elevation of CK or the elevation stays below 4 times the ULN. It can be distinguished between tolerable and intolerable myalgia classified as stages 1 or 2. Myopathy, stage 3, contains muscle pain and weakness with no trauma and there is a CK elevation of more than 4 times to 10 times the ULN. Stage 4, the severe myopathy, has the same symptoms as usual myopathy but with a much higher level of CK (10 – 50x ULN). Rhabdomyolysis, stage 5, has a huge CK elevation, or at least over 10 times ULN in combination a decreased urination. Rhabdomyolysis is a severe but rare

disorder and affects 3.4 per 100,000 patients treated with a statin in one year and it depends on which statin is used.
The incidence for rhabdomyolysis seems to be higher with some types of statins than with others. Cerivastatin has been taken from the market, therefore.
SINAM, stage 6, occurs with symptoms of myopathy. The pathomechanism of this condition is developing auto-antibodies against HMG-CoA reductase. It is not the same as rhabdomyolysis, but it could lead to it.
Different hypotheses how statins could cause muscle pain:

- Lipophilic statins are getting more likely into muscle cells.

Statins vary in their chemical structure and as a result in clinical effects. Pravastatin and rosuvastatin are hydrophilic, whereas the other five statins are lipophilic. To get into the liver, hydrophilic statins need a carrier. Lipophilic statins can just go through the hepatic membrane and membranes of other tissues. It appears that the prevalence of SAMS in lipophilic statins is higher than in hydrophilic ones. But that supposition is not established yet.

- Cholesterol synthesis in muscle cells can be inhibited.

Statins initially inhibit the synthesis of cholesterol in the liver, but at very high serum concentrations, cholesterol synthesis in other tissues can also be inhibited. Because of this, statins can lower the cholesterol levels in muscle cells, but if this is responsible for muscle symptoms or damage to muscle cells remains to be seen.

- The impaired protein prenylation can be myotoxic.

Stains can impair the prenylation of proteins and that could lead to myotoxicity, statin-induced.

- Mitochondrial dysfunction

If mitochondria are not able to synthesize ATP, they increase the production of ROS (reactive oxygen species) which could end up in cell apoptosis.

- Oxidative stress

Oxidative stress ends up in hydrogen peroxide and this could be catalyzed into water or hydroxyl radicals, which causes irreversible damage.[67]

- Vitamin D deficiency

Patients under statin therapy with low Vitamin D levels develop SAMS more likely. Why patients under this therapy could have low levels of vitamin D is explained with the need of cholesterol in the endogenous synthesis of it. Why this deficiency could lead to symptoms like this may be because many cells have vitamin D receptors, including muscle cells, and a deficiency alone could cause myalgia. Other studies say a vitamin D deficiency may exacerbate a statin-induced muscle pain. [67] The hypothesis in 2011 when this was investigated was, that supplementing Vitamin D during a statin therapy may reverse a statin intolerance.[68]

Today there is still no clear answer to that and randomized controlled trials are not available. An association with an improved tolerance of statins and the supplementation of vitamin D was observed, but the placebo and nocebo effects could not be ruled out.[69]

- Coenzyme-Q10 deficiency

Statins do not only inhibit HMG-CoA-reductase, but they also reduce the endogen synthesized substance coenzyme-Q10. If the levels of CoQ10 are lower there is often a higher ratio of substances of the blood that are markers for mitochondrial myopathy. These substances could be a marker but they could also be the cause of the muscle symptoms.

There is no evidence that supplementing CoQ10 can reduce SAMS. What makes assessing complicated is, that CoQ10 in blood does not correlate with the level in the muscle.

An advantage of CoQ10 is that it is not known to cause any severe adverse events.[67]

Three trials that are randomized and controlled investigated how the prophylactic administration of CoQ10 affects myalgia in patients taking statins. There must be added that the sample sizes were low in these trials. No significant differences in CK levels were detected and also no significant differences in pain scores used. Five randomized controlled trials tried to find out if coenzyme Q10 could be helpful as treatment of SAMS. One nonrandomized and one meta-analysis did too. No beneficial effect was detectable either, which means a coenzyme Q10 supplementation for prophylaxis or treatment cannot be recommended.[70]

It has to be added that with statins and the adverse event of muscle symptoms a meta-analysis showed no significant dose dependent association.

Uncertainty remains also about the causality of statins to bring on myalgia. A meta-analysis found that 9.5% of statin patients developed myalgia, but this rate was statistically insignificant compared to the placebo group. Besides the placebo effect, a nocebo effect could occur as well. A nocebo effect is defined as adverse symptoms which occur because of negative expectations of the patient. Patients with occurring muscle pain who take it for primary prevention, do not show reduced strength or an impaired aerobic ability. So it can be assumed, that the muscle pain does not come from a statin-induced myotoxic effect.

But in some patients elevated CK were found under statin therapy, which suggests muscle injury.

Pharmacogenetics is a new field and it could points out patients at risk of muscular symptoms and maybe one day it will help in prescribing statins. For instance, patients with a polymorphism of an anion transporter gene may be more susceptible to develop SAMS.

But most often a statin intolerance can be explained with a nocebo effect, and most patients can get back to a statin therapy successfully, as is confirmed by placebo-controlled trials.

Patients should be told that these adverse events are not permanent and result in no permanent damage and that discontinuing the statin therapy could end up in a cardiovascular event or death. According to the authors of this paper, some patients think the statin therapy is more dangerous than the risk for cardiovascular disease.

It was seen that the ones who continued with a statin therapy after experiencing an adverse event had a better outcome. Within four years, they had less CV events and death combined (the incidence was 1,7% lower).[71]

A good management of people with muscle symptoms and a statin therapy is very important. After a confirmed SAMS, the statin needs to be discontinued. A holistically view should be established, i.e. looking for drug-drug interventions, assessing activity level or vitamin D deficiency and evaluating comorbidities like osteoarthritis or other conditions which may cause muscle pain. After that, the patient needs to be informed about risks and benefits of the therapy and alternatives should be offered. Other types of statins, a reduced dose or every other day dosing or other lipid lowering drugs need to be considered. What the patients also needs to know is, that these symptoms are reversible. A regular reassessment of patients with statin therapy should be done to keep the compliance of the

patients high. Gladly the incidence of SAMS is not very high and mostly mild pain occurs.[67]

3.11.2 New-onset diabetes

Statin use could lead to new-onset diabetes. This is what observations showed and what several studies wanted to prove. First, everyone thought it had to be the fact that the risk of the population who needs statins to develop T2D is just higher because of their lifestyle, but new studies consider statins could have an impact on insulin secretion and insulin sensitivity. What impact statins have on the glucose metabolism was investigated and three ways were discovered. Changes in the Ca-Channel system led to an impaired insulin secretion in ß-cells. In addition, they could reduce GLUT4 in target cells or statins make a condition of diabetes mellitus more likely by decreasing cholesterol products and thus intra-cellular signaling. More potent statins have an increased risk for developing NODM (new-onset diabetes mellitus), like atorvastatin or rosuvastatin. Statins with lower potency such as pravastatin and pitavastatin have less impact on the metabolism of glucose. A meta-analysis showed, pravastatin may improve the sensitivity for insulin, while pitavastatin has no impact on insulin sensitivity compared to placebo.

Prescribing low-potency statins to patients at increased risk of new-onset diabetes can be considered, but the risk of getting a CV events and mortality must be known and weighed against this. It is recommended not to avoid potent statins in patients at high and very high risk. The WOSCOP study ("West of Scotland Coronary Prevention") was among others one of the first studies to show that the intake of statin and a new onset of diabetes are associated with each other.

It can be considered to prescribe low-potent statins in patients at elevated risk for new-onset diabetes, but the risk of cardiovascular events and mortality must be weighed against it. It is suggested not to avoid high-potency statins in patients at high and very high risk of cardiovascular events and mortality. The WOSCOP (West of Scotland Coronary Prevention) study was one of the first studies which showed, statin use and new-onset diabetes correlate with each other. The publication of this study was in 2001. Several studies in the last twenty years showed that the risk could depend on which statin is used and how much of it. In addition, it must also be said that the evidence for some of these studies was not the best because the confidence interval was mostly too broad.[72]

A meta-analysis with randomized trials tried to find out the real risk of developing type 2 diabetes under statin treatment. 13 trials with 91,140 non-diabetic participants were

included and 4,278 of them developed diabetes in an average time of 4 years. In the statin group compared to the control group, 9% more diabetes patients occurred. Older participants had the highest risk of diabetes development but neither the body mass index at the baseline of the therapy nor changes in LDL-C could explain the variations in the risk. One of 255 people treated with a statin gained diabetes within 4 years. This could be called a mild increased risk. There was no difference seen in types of statins. In people with moderate or high cardiovascular risk, the treatment should not be changed because of this mild increased risk, the authors say, because the benefit of it outweighs the risk of getting diabetes. An interesting fact was, that when only trials were analyzed which used fasting glucose measurements, the results were not statistically significant anymore. In further analyses there was no difference seen between statins and the diabetic risk. [73]

The METSIM study should reject the conclusion that the other risk factors from patients who need statins cause diabetes. This study investigated the risk of getting type two diabetes mellitus (T2DM) from taking statins. Also, deterioration towards hyperglycemia, insulin resistance and insulin sensitivity were investigated. Only men were included, and it took 5 years. To prove the impact of statins on developing T2DM, they adjusted as much risk factors as possible like age, BMI, waist circumference, physical activity, smoking, alcohol consumption, family history, beta-blocker and diuretic drugs.

After adjusting all these factors, the risk to develop diabetes was 46% higher in the group with statin intake. This study also shows different effects of different statins and doses.

Most of the patients got simvastatin and atorvastatin. Compared with no statin treatment the risk of developing T2DM was higher with one of these. After adjusting the confounding factors, the risk developing T2DM decreased but remained significantly higher in the statin group. Another proof why statin use must have an impact on developing T2DM is, that with higher dosage of a statin the risk to get T2DM increases as well.[74]

Considering that atorvastatin (80 mg) had the highest rates of increasing new onset followed by rosuvastatin, there could be a difference between high to low intensity treatment. [75]

The assessment of the effect modification of statins in new-onset diabetes based on different medical backgrounds was investigated in a retrospective cohort study. In this study, they wanted to detect if different sex, age, medical history and current medication influence the risk of new-onset diabetes. As expected, the results showed that in the statin

group the number of new-onset diabetes was higher than in the non-statin group, but no significant subgroup interactions were assessed. So, you cannot make a statement about how different patients with different conditions or illnesses should be treated more individually, because it seems to have no significant effect.[76]

The effect of lowering insulin secretion is attributed to affect ATP potassium channels, voltage-gated Ca channels, stimulating muscarine receptors, inhibiting Ca release from ER and activating cAMP dependent signaling pathways. [72]

How statins affect insulin **sensitivity**:

The diabetogenic effect on the pancreatic ß-cells happens because of the cholesterol excess in the ß-cells. This effect depends on the cholesterol entry.

Not only the numbers of LDL-C receptors of liver cells gets increased, also ß-cells of the pancreas gets more LDL-C through receptors into the cells. That the prevalence of T2DM in patients with FH (familial hypercholesterinemia) is lower compared to general, supports this hypothesis. Reasons for FH are mutations in LDL receptors or apo B. Patients with absent LDL receptors have the lowest rate of T2DM.

How statins affect insulin **resistance**:

Statins affect the glucose uptake in human cells by inhibiting the expression of the glucose transporters (GLUT). This was observed in adipose tissue cells (GLUT4), skeletal muscle cells (GLUT4) and pancreatic islet b-cells (GLUT2).

The inhibition of HMG-CoA reductase is responsible for reduced cholesterol synthesis and leads to a reduced expression of coenzyme Q10, which is important for GLUT4 generation. This could be an explanation for the reduced expression of glucose transporters type 4, because adding coenzyme Q10 improves the simvastatin-induced reduction. The inhibition of coenzyme Q10 also plays a role in impaired insulin secretion because of reduction in the production of adenosine triphosphate.

Glucose uptake is also reduced in tumor cells, but the reason for that is not the inhibition of GLUT proteins, it is the changed cholesterol biosynthesis pathway independent of glucose transporters.

A decreased adiponectin level could affect insulin resistance and insulin sensitivity because adiponectin inhibits hepatic gluconeogenesis, stimulates fatty acid oxidation and glucose uptake.[77]

What is clinically relevant, is the most important question. The number of new-onset diabetes is not very high. It is estimated to be 10–20 patients out of 10,000 patients with

statin therapy. This new diabetes condition causes a doubling of the cardiovascular risk in these patients. 5–10 patients could get a major cardiovascular event from that adverse effect, but in 150 people out of 10,000 such a major cardiovascular event can be prevented.[72]

In contrast to statins, PCSK9 inhibitors do not show an association with the onset of diabetes. RCTs reported about new-onset diabetes or worsening of pre-existing diabetes under PCSK9 inhibitor therapy. 23 studies with 65,957 participants were included. PCSK9 inhibitors as a class were not associated with diabetes as adverse event. In addition to that a sub-analyses showed a significantly decreased risk of diabetes with alirocumab, where evolocumab or bococizumab showed no decrease. As a closing statement you can say PCSK9 inhibitors are not associated with a new onset of diabetes, in placebo controlled trials.[78]

As a difference to muscle symptoms, the possible risk of statin-induced diabetes is maybe age related and the development of diabetes happens nearly exclusively in individuals with metabolic syndrome. The additional therapy of type 2 diabetes can often be problematic in elderly patients. [44]

A BMI lower than 30, fasting blood sugar <100, HbA1c < 6% or no signs of a metabolic syndrome make a metabolic change to new-onset DM unlikely.

Therefore, one can say, a metabolic syndrome and increased age are two main risk factors for the adverse effect of developing type 2 diabetes with statins. But with or without risk factors for developing DM, the benefit of a statin therapy preventing ASCVD events outweighs the risk of progressing NODM in over 65-year-old patients, the authors say.[79]

3.11.3 Cataract

Statins could induce the development of cataracts. It is mostly a disease of the elderly, but with low incidence it can occur in less than 55-year-olds. Then it is called early onset cataract (EOC). There are differences in opacities in cataracts. Opacities can occur posterior subcapsular or anterior polar. In senile cataracts, both types mainly occur simultaneously. Beneath statin therapy there are many other known risk factors that could lead to early cataract. The hypothesis with statins is that epithelial cells need high cholesterol to provide the transparency of the lens. In a trial with dogs in the nineties, cataract developed with a cholesterol reduction by a statin therapy. In addition to that, lipophilic statins may be more likely to cause that adverse effect because of better migration properties. After recommendations to take statins for primary prevention,

concerns of more occurring early onset cataracts came up. This case control study showed an association between statin use and the early onset of cataract. There was a more positive association with a higher dose of statins and longer use. [80]

Patients with familial hypercholesterolemia have higher LDL-C levels since birth and a higher risk of a coronary disease. In heterozygous FH patients, statins are used for decades while in homozygous FH patients the effect of this therapy seems too small.

Because of the long duration of statin therapies in HeFH patients, long-term adverse events can be well investigated in this population. In this observational study elderly patients with HeFH and a prolonged statin therapy were assessed to find out if there is an association between statins and cataracts.

25.2% of people with HeFH had a history of a cataract surgery, where there were just 16.1% in the group of control. Further investigation showed, that age was higher in HeFH patients with cataract surgery. Therefore, the association between age and cataract was analyzed compared to the duration of a statin therapy and the level of LDL-C without a lipid-lowering therapy.

The results showed only a significant association with age and cataract. People with HeFH and a statin therapy were not at an elevated risk of a cataract, even with a statin therapy for more than 20 years. The authors of this paper say, that whether a statin use for a long time, nor a severe hypercholesterolemia are risk factors for the occurrence of cataracts.[81]

While a case control study evaluated a higher risk of cataract surgery in people with a prolonged use of fibrates but not of statins,[82] another analysis found an association between cataract and several lipid lowering drugs. Statins, fibrates, bile sequestrants, herbal drugs, nicotinic acid, ezetimibe or PCSK9 inhibitors were investigated in this analysis using the Individual Case Safety Reports database of the WHO. 3,049 out of 14,664 reports of cataracts were lipid lowering drug users over the age of 45 and 84% of them took statins. Atorvastatin, rosuvastatin, simvastatin or lovastatin were taken by the patients and there was a significant association with all of them. These findings support the hypothesis of the impact of low cholesterol in the pathogenesis of a cataract.[83]

There are genetic variations of HMG-CoA reductase which could help answering the question of statins and cataracts. The aim was to evaluate which impact the mevalonate pathway has in comparison to general LDL-C lowering. Data of 402,750 individuals showed a strong association between HMGCR (3-hydroxy-3methylglutaryl-coenzyme A reductase) genetic score and circulating LDL-C levels. This score combines all five genetic

variants of the inhibition of HMG-CoA reductase. There is a higher risk of getting cataract or having a cataract surgery in patients with a lifelong inhibition of HMGCR variants. RCTs did not show an increased risk of cataracts in people taking statins. However, these RCTs were mostly of short duration or had inadequate ophthalmic assessment.

The actual mechanism of why and how a cataract develops, is not fully clear as mentioned in this paper. Here it is said that in animals no relationship between low cholesterol and the appearance of cataract was detectable, however, a relationship between plasma levels of statins and cataract was established.

It is more likely that HMG-CoA reductase is important for sterol synthesis in the lens to ensure transparency, since no association with cataracts was found with other signaling pathways (NPC1L1 or PCSK9) nor with low LDL-C levels. This paper recommends educating patients about the adverse event and recommending a close follow-up, particularly in younger patients who suffers from FH and taking statins for a very long time.[84]

3.12 Familial Hypercholesterinemia

Familial hypercholesterolemia (FH) is very common and ends up in a disorder of the lipid metabolism. In around 95%, there is a loss-of-function mutation in the gene that codes the LDL receptor. In rare cases, there is the loss-of-function mutation in the apo-B gene, so this protein has a reduced binding to the LDL receptor. Not common but also possible is a gain-of-function mutation in the PCSK9 gene.[14]

Heterozygous familial hypercholesterolemia is a widespread common autosomal dominant inherited disorder. 1 of 220 individuals is affected and it ends up in an elevation of LDL-C levels. This mostly silent condition can end up in a higher risk of a CV event or death if untreated. In up to 30% it can show certain manifestations like xanthelasmas, tendon xanthomas or corneal arcus. A distinction must be made between heterozygous and homozygous FH. Homozygous FH is inherited in an autosomal recessive manner.

A defect in the LDL receptor was found in only 2% of cases in men under 50 and women under 60 with a cardiac event. However, 20% of heart attacks in younger men are attributed to FH. FH is underdiagnosed which is followed by undertreatment. This review recommends a screening in 9- to 11-year-old children. An earlier screening in children at two years of age is recommended when there is a history of early onset-CAD or high total cholesterol levels in the or if the child itself has risk factors. Big data from a FH registry demonstrated that the mean age of FH diagnosis is by the age of 50. Till then one out of

three already had an atherosclerotic cardiovascular event. This is one main reason why an early screening is needed, the authors say.

The diagnosis of FH is a combination of a look for physical findings, a family history, early onset of ASCVD and a higher LDL-C level than normal. To avoid misdiagnosis it is important to keep in mind that medications like cyclosporine, amiodarone or hydrochlorothiazide could increase LDL-C, and chronic illnesses like hypothyroidism or liver or renal impairment can do that too.

A further possibility of diagnosing would be genetic testing. Mortality rate in people with a monogenic FH seems to be higher compared to polygenic hypercholesterolemia.

Data from five prospective cohort studies and seven case-control studies including more than 26,000 individuals showed that people with a FH mutation are at higher cardiac risk with a certain LDL-C level compared to the general population which has a much lower risk with the same LDL-C level. As example, in individuals with LDL-C of more than 190 mg/dl, the risk in FH patients was 22-fold higher than in the reference group at LDL-C level below 130 mg/dl. However, in individuals without a FH mutation with an LDL-C of more than 190 mg/dl, the risk of CAD was just 6-fold higher than in the reference group with LDL-C below 130 mg/dl.

In addition to dietary and lifestyle modifications, lipid lowering therapies are needed. The importance of not smoking and regular exercise should be communicated. Besides the treatment of lipids, hypertension and diabetes mellitus must be treated as well.

All statins in a reduced dosage are recommended in children with FH. The treatment is supposed to start between the age of 8 and 10. Pravastatin and pitavastatin can be given to children at the age of eight, approved by the FDA where the other five statins are approved for 10-year-old children. Ezetimibe has no age restrictions for the treatment in people with HeFH. For adults with LDL-C of 190 mg/dl or more and the condition of FH, a lipid lowering treatment is recommended. A high dose statin therapy should be applied in FH patients, but if this intensive statin therapy is not tolerated the statin dose that is tolerated maximally could be given like a moderate or low intensity therapy.

- High intensity (>50% LDL-C reduction)
    - Atorvastatin 40-80mg
    - Rosuvastatin 20-40mg
- Moderate intensity (30-<50% LDL-C reduction)
    - Atorvastatin 10-20mg

    - Fluvastatin 40-80mg
    - Lovastatin 40mg
    - Pitavastatin 2-4mg
    - Pravastatin 40-80mg
    - Simvastatin 20-40mg
    - Rosuvastatin 5-10mg
- Low intensity (<30% LDL-C reduction)
    - Fluvastatin 20-40 mg
    - Lovastatin 20 mg
    - Pitavastatin 1 mg
    - Pravastatin 10-20 mg
    - Simvastatin 10 mg

Because many FH patients are treated after an event has occurred, the identification and early initiation of lipid-lowering drugs in these patients is important.

Statins are not indicated in pregnant women. However, some experts recommend a statin therapy in FH patients with prevalent ASCVD and in homozygote carriers. In a large cohort study of more than 880,000 pregnancies, 1,152 of them took a statin during pregnancy and there was no increased risk for organ malformations. [85]

In people with homozygous familial hypercholesterolemia there is a massive elevation of LDL-C. ASCVD starts in early childhood. A treatment in these patients is difficult because an aggressive reduction of LDL-C is needed and at the same time there is a reduced response to statins, because statins work mainly by increasing LDL receptors to get more LDL-C out of the blood. The activity of LDL receptors in people with HoFH is low due to the genetic variation. If statins are successful, depends on the present residual activity of LDL receptors. Interestingly, some lipid lowering effects are seen even in HoFH patients with no LDL receptors.[86]

The guideline recommends a screening in all individuals below 50 years of age with a first-degree relative with FH. Young and middle-aged adults with CVD do more often have FH compared to the general population. However, several studies showed, people with FH have the same life expectancy than other people. Why there is an elevation of CVD in FH patients could be because a subset of these people did inherit increases of coagulation factors too. In several studies, LDL-C did not differ significantly between those with or without cardiovascular disease. [27]

3.13 Treatment since childhood

People with familial hypercholesterolemia are advised to treat the significantly elevated cholesterol levels from childhood. A long-term observation shows that treatment protects patients from atherosclerotic disease up to an age of 40, even if target LDL-cholesterol levels are rarely reached. Due to various genetic defects, those affected already have significantly increased cholesterol levels as children. In a placebo-controlled study where pravastatin was used, it was seen that LDL-C levels of children from 8 to 18 can be restored without any negative effects on growth, muscle or liver enzymes, endocrine function parameters or pubertal development. After 2 years of treatment, there were slight advantages in carotid intima-media thickness compared to the placebo group. Since the trial ended for ethical reasons, all 214 participants have been advised to take cholesterol-lowering treatment. Most of them took a statin. [87]

20 years later, 184 of the participants were re-examined. The mean age was over 30 years, and the average LDL-cholesterol was slightly above 160 mg/dl. Compared to the start in childhood when the average LDL-cholesterol was 237 mg/dl, now it was 32% lower than before. The accelerated atherosclerosis which occurs early in those people could be prevented as shows the increase of the carotid intima-media-thickness of only 0,0056 mm per year. It must be added that the 95 siblings of the participants who were not suffering from familial hypercholesterolemia, had very similar results with 0,0057 mm increase of the intima media thickness of carotid per year. In relation to the generation of the parents of these children, only one “child” had a cardiovascular event by the age of 28.6 years while 41 of the parents with the same genetic defect had suffered a cardiovascular event at the same age. These two comparison groups are not ideal because siblings and parents could have a different cardiovascular risk due to a different lifestyle. But the authors firmly believe that this therapy saved the children from the fate of their parents.[88]

3.14 COVID-19

Statins gained attention early in the treatment of COVID-19 based on their many action mechanisms. A meta-analysis reported a benefit with a statin treatment during suffering from COVID-19 due to 35 observational studies. A reduced risk for a fatal or severe course of the illness was shown with statins compared to a non-use. The mechanism how statins are able to do that is unknown. Pleiotropic effects are suggested to be responsible, like

modulation of inflammation, immune response, antiviral effects and improved endothelial function.[89]

To confirm a lower infection rate in individuals with statins, researchers infected normal cells and cells treated with statins with a coronavirus which is closely related to SARS-CoV-2. The statin cells got less infected than the others. Afterwards it was tested with SARS-CoV-2 in a high security laboratory. Especially in cells treated with fluvastatin, there was a lower concentration of the virus. In cultures of respiratory epithelial cells these findings were confirmed.[90]

The pathophysiological mechanism of the test results from above did probably occur because of a lower cholesterol level. Lipid rafts are called areas in the plasma membrane with lots of cholesterol, and specific receptors for the Coronavirus like the ACE-2-receptor are concentrated in these areas. The statin-induced inhibition of cholesterol synthesis ends up in less cholesterol in the plasma membrane and an alteration of viral receptors. Due to this, the possibility of the Coronavirus to enter a cell is reduced. Another mechanism is an increase the activity of HMG-CoA-reductase and cholesterol synthesis after infection of the cell to support replication of the virus. A negative impact on viral replication with statins inhibiting HMG-CoA-reductase and therefore cholesterol-synthesis results out of that. In addition, statins suppress mevalonate synthesis and prenylation of proteins which are needed in the replication pathway or for assembly of the virus. The transmission of the virus is reduced by reducing ICAM-1 (intercellular adhesion molecule-1) levels and impair the binding to it. The improvement of the endothelial function is also a very important mechanism, because endothelial dysfunction is a common denominator of a severe course of COVID-19. Statins alone have significant antiviral effects, but combined with antiviral drugs the effect could be greater, at least trials in HCV patient showed results like that. But using statins as an additional therapy to antiviral drugs may increase the rate or severity of adverse effects because both are metabolized by CYP3A4 which could lead to an elevation of the plasma level. What is to prefer are the hydrophilic statins, which are not significantly metabolized by CYP enzymes (pravastatin, rosuvastatin).

Most clinical studies suggest a positive effect in virus infected cells due to known mechanisms, but some studies say that satins may be ineffective or, what would be worse, are harmful. For instance, different statins have shown insufficient antiviral effects in highly pathogenic influenza viruses, or viral replication of norovirus increased in piglets treated with simvastatin, suggesting an immunosuppressive effect. What has also been

observed is a possible reactivation of HBV (Hepatitis B Virus) or Herpes zoster by statins. If adverse events are more severe or more frequent in COVID-19 patients, was not considered in this meta-analysis. Facts from studies from the nineties were listed and it was said that there was no concern for muscle symptoms and rhabdomyolysis. Just 0.5% developed muscle symptoms and rhabdomyolyses defined by myonecrosis, while myoglobinuria and acute renal failure were a very rare event with a subsequent incidence of hospitalization of 0.44 per 10,000 patient years. These numbers are not relatable to patients suffering from COVID-19 and other possible comorbidities. Some were afraid of harms caused by them. A study investigated a higher risk for acute respiratory syndrome among patients with taking statins compared to those who do not. The assumed mechanism is that statins downregulate the expression of toll-like-receptors on immune cells. Therefore, NF-κB activity is downregulated as well and less inflammatory cytokines are decreased which ends up in an increased risk to develop an acute respiratory syndrome. [91]

However, large RCTs of individuals with ARDS (developed from other causes than COVID-19) have shown that rosuvastatin or simvastatin did not provide a significant benefit in overall mortality.[92,93]

A very important question is also in what dosage they should be taken. Only two studies included in this meta-analysis reported the used dosage, and in both atorvastatin was selected. In one trial 20 mg/day were used and in the other 40 mg/day. Another three studies investigated the difference between high and moderate/low intensity statin therapy. Two of these studies reported similar results of all-cause mortality and severe disease in both, high and moderate/low intensity therapy groups. The third study distinguished between three groups, high, moderate and low and came to conclusion that high or moderate therapy lowers the risk of mortality but low intensity therapy does not. Which type of statin leads to better outcomes needs to be further investigated. [91]

This meta-analysis includes 14 observational studies with almost 20,000 participants with COVID-19 taking statins before or in hospital. There was one case control study and the rest were retrospective cohort studies. Outcomes were mostly mortality or ICU (intensive care unit) admission or reporting severe and critical disease. Included studies showed that statin users had no improved clinical outcome compared to non-statin users and they had no elevated mortality either. In comparison to the other meta-analysis, preprint studies were included and there was no adjustment for confounding factors.[94]

One randomized controlled trial was accomplished regarding statins in COVID-19 patients in intensive care. Atorvastatin 20 mg are taken per day for 30 days. The primary outcome was venous or arterial thrombosis, need for extracorporeal membrane oxygenation or all-cause mortality in 30 days. 290 individuals got atorvastatin and 297 got placebo, the median age was 57 years and the portion of women was 44%. 31% of the people died in group with atorvastatin and 35% died in the group with placebo (CI 0.58 – 1.22). No significant findings in the reduction of all-cause mortality with statins in patients with COVID-19 and intensive care were detected.

As adverse events, myopathy did not occur, but raised liver enzymes were found, in both groups to 2%. Considering these adverse events, statins seemed to be safe in these patients.[95]

Maybe there is no grand benefit of statins in patients with COVID19, but there is apparently no harm either. It can be said that those who were treated with statins before infection, should continue the intake without worries.[90]

3.15 Conclusion

First the main focus was on how statins should be used individually in different patients and how adverse events could be avoided. During research questions came up like which benefit there is in different patients, how relevant is the age of the patients and how can risks be calculated, which role plays the risk factor LDL-C in different patients and how important is it to reduce the rates of it.

First the European guideline of 2019 was assessed followed by the European guideline of 2021. A review critically considered the recommendations of the guideline and pointed out some flaws. Some questions could not be answered.

Many, many trials are available with statins. There is not always an approvement in how big the benefit is and how frequently different adverse events occur. This paper tried to involve both sides, the one which does not see any disadvantage in a statin therapy i.e. saying that LDL-C cannot get too low and adverse events are very rare and mild, and the other side which sees statin treatment more critically and tries to figure out whether statin treatment in different patients is necessary, which benefit there is and which harm can be caused.

In the guideline of 2021, there were several adaptations. To elevate the risk, SCORE2 is used now for people under an age of 70 years. In those over the age of 70, SCORE-OP needs to be used. These adaptations are designed to provide a better and more specific risk

assessment to treat those who need a statin and to avoid unnecessary prescribing so that the balance between benefits and adverse events remains balanced. The new SCORES are based on new data, especially those in the elderly, and a new biomarker is taken to include all lipoproteins with the carrying protein apo-B, called non-HDL because HDL is the only one carrying apo-A. It is supposed that all lipoproteins carrying apo-B are artherogenic.

What must not be forgotten is that there are several risk factors which can cause a coronary artery disease or contribute to that condition. A screening of risk factors is recommended by the European guideline in men over 40 years of age and women over 50 years or postmenopausal. The guideline recommends different treatment goals at different risks.

In general, the first line lipid lowering treatment are statins. If statins work insufficiently in different patients, ezetimibe should be added, and if goals are not achieved PCSK9 inhibitors can be added too. No benefit occurs with adding a therapy regarding all-cause mortality, but there is a benefit in the prevention of non-fatal MIs or non-fatal strokes. PCSK9 inhibitors are able to prevent more non-fatal MIs or strokes than ezetimibe. It has to be added that the greatest benefit occurred in the very high-risk group compared to the high-risk group. Patients with a moderate or low cardiovascular risk did not benefit from any of these two therapies.

The next question to answer was if elderly people should be treated. They have the highest risk scores, but different trials denied the association between high LDL-C and mortality in this group of age. Those with the highest LDL-C lived the longest with or without a statin therapy as one trial demonstrated. In addition to that, a greater hospitalization with infections was seen in people with low LDL-C which led to the suggestion that a higher level of LDL-C is protective against infectious diseases. With increasing age, the individual risk of having a fatal or non-fatal major cardiovascular event rises. Total cholesterol, however, appears to be less of a risk factor for cardiovascular death or all-cause mortality in the elderly. What is also important to consider in elderly people is when the benefit does occur. If life expectancy is reduced, it is recommended to avoid a statin therapy. 2.5 years are needed for statin treatment to prevent one major CV event in 100 persons at an age of 50 to 75 years. The rate of adverse events is not increased in elderly, but the different metabolism has to be considered regarding the dosage.

Pravastatin is not metabolized via CYP3A4 like many other drugs which lowers the risk for drug-drug interventions. This is important especially in the elderly because of polypharmacy.

Considering primary prevention in the elderly, the European guideline of 2021 recommends a statin treatment at different ages with different scores. In apparently healthy people with a SCORE-OP risk evaluation of more than 15%, a statin therapy may be considered with a Class IIb recommendation.
There is no Class 1 recommendation to treat apparently healthy adults with statins. The guideline suggests the prescription for younger or older people at certain risk scores.
A steady relative risk reduction of 12% was detected in those at primary prevention, but there was no benefit in all-cause mortality. Regarding adverse events, with atorvastatin and lovastatin there was an increased risk of liver dysfunctions, but no increased risk in primary prevention of developing diabetes with statins.
The same dilemma occurs on the other side, with young patients. Which ones should be treated, is a prescription for primary prevention useful, what about the adverse events and what about the benefits? It might be helpful to evaluate the lifetime risk in these patients or to measure the Coronary Artery Calcium Score (CAC).
If you want to use a drug more individually, it needs to be cleared first what benefit there is when taking the drug. There are many data on the association between increased LDL-C and the development of ASCVD. It is well known that many other risk factors influence the cardiovascular risk as well, but the INTERHEART study said, the risk reduction with lowering LDL-C remains constant regardless of other risk factors.

Besides the question of whether statins should be prescribed, there is the question of whether the prescribed statins are taken by the patients. A lot of different reasons exist why people refuse to take them.

Many trials conformed the hypothesis of a reduction of ASCVD events which is proportional to the decrease of LDL-C. For every 1 mmol/l reduction of LDL-C which is equivalent to 39 mg/dl, the risk reduction to get an ASCVD event within five years is 22%. This value depends on the average baseline LDL-C level of 120 mg/dl and is not generalizable to people with a higher or lower LDL-C level.
Firstly, the mortality rate was not investigated in depth and some uncertainties appeared in the rate. Some trials had even results where mortality did not decrease at all. In addition to that, one trial showed no reduction in cardiovascular mortality with a more severe lipid lowering therapy compared with a less intensive therapy regime. But other trials showed

significant reductions with statins in all-cause mortality. Further investigation showed that the all-cause survival benefit is related to the baseline level of LDL-C. The greatest benefit was seen in people with LDL-C levels of 160 mg/dl and more and no all-cause survival benefit occurred in people with LDL-C levels below 100 mg/dl in one meta-analysis. However, the cardiovascular mortality rate decreased even in patients with LDL-C levels below 100 mg/dl in this group of patients, but the reduction was greater in people at higher LDL-C levels. In contrast to all-cause mortality, major vascular events seem not to be dependent on baseline levels, the reduction of events was even significant in those below 100 mg/dl baseline level of LDL-C. This supports the hypothesis the higher the baseline LDL-C level, the greater the benefit of the therapy.

Because of confirmed efficacy and safety of statins, the threshold to start a statin was lowered. After the WOSCOPS study a general prescription for everyone with LDL-C levels of over 190 mg/dl was suggested. A meta-analysis for primary prevention with statins showed significant reductions in non-fatal MIs, but the prevention of fatal MIs was just significant with atorvastatin. Non-fatal strokes were significantly reduced by atorvastatin and rosuvastatin, but fatal strokes were not significantly prevented by any statin. All-cause mortality was significantly reduced by atorva-, rosuva- and pravastatin, and CVD mortality was significantly lowered by rosuva- and pravastatin. Notable is the finding that there is no significant effect in reducing the risk of fatal MIs except for atorvastatin, but cardiovascular mortality was only significantly lowered by rosuvastatin and pravastatin.

The guideline says LDL-C should be lowered as much as possible, at least in high-risk and very high-risk patients. Due to the fact that major cardiovascular events get reduced with a more intensive lipid lowering therapy, the lower, the better is said. Furthermore, no increase in adverse events with a more intensive therapy was detected. Some trials detected an increased risk of haemorrhagic strokes as adverse event, but in one analysis no increased risk neither with statins nor with PCSK9 inhibitors was seen. Even levels of LDL-C of below 50 mg/dl are safe and there are greater benefits than harms, is said.

A significant absolute risk reduction with a more intensive therapy meaning a statin plus ezetimibe was seen in strokes. With a single therapy of a statin or a PCSK9 inhibitor no significant outcome was detectable. Only those with the evidence of atherosclerosis had a benefit, this supports the finding of no benefit in strokes for primary prevention.

In 2020 a review was published which pointed out limitations of the guideline of 2019. LDL-C is just a risk factor in young and middle aged, is said. As example they mention mental stress, which is very common in this group of age which can also lead to an increase in LDL-C but has several other abilities too.
A paper appeared with the name ”LDL-C does not cause cardiovascular disease“, which was published from authors from all over the world. They say that there are falsifications of the cholesterol hypothesis. Besides the fact that the Bradford Hill criteria for causality are not fulfilled, statistics are misleading and contractionary observations are ignored. They say people with low total cholesterol do get atherosclerosis as well. They refer to a study which detected the association with increased LDL-C and mortality of coronary heart disease in the elderly. In women over 50 years there was no association detectable and in men over 64 years a weak association was found. Another trial showed a lower LDL-C level or normal levels in patients after an acute myocardial infarction after hospital admission. The answer to that was that LDL-C needed to be lowered more, but in the follow-up of three years the total mortality of these patients was increased with LDL-C levels of lower than 105 mg/dl. The mortality rate was twice as high.

Since the first statin, its pleiotropic effects have been assumed. They should have an effect directly on the artery wall and reduce the thrombogenicity. They are said to diminish the levels of inflammatory markers, adhesion of macrophages, migration and proliferation of different cells and oxidation of LDL-C. Furthermore, they are supposed to enhance endothelial NO synthase and the apoptosis of different cells. It is not clear which impact pleiotropic effects have on the prevention of cardiovascular diseases. What outweighs the presumption about pleiotropic effects are trials with other lipid lowering drugs that show similar outcomes.

Gender medicine is a young branch in medicine. Currently the differences between men and women are further investigated to establish a gender specific medicine in the future.
The guideline recommends a screening of hypertension and diabetes mellitus in women with a history of certain illnesses. Untreated mental disorder and migraine with aura also seem to have an impact on the risk of CVD. Hormonal contraceptives may be avoided in women with migraine with aura and the CVD risk should be assessed in men with erectile dysfunction.

Women get CVDs 7 to 10 years later than men do. The reason is possibly the protective effect of oestrogen during reproductive years. But what is observed in the USA is that the rate of coronary heart disease and mortality in younger women (35-54 years) rises. Women who smoke and women with diabetes have a greater relative risk of CVD compared to men, but there are other risk factors for women that need to get attention: Pre-eclampsia, gestational diabetes, polycystic ovary syndrome, early menopause and autoimmune diseases. The European guideline is aware of the unique cardiovascular risk factors in women. The reason for the lack of information among women is that most trials involve only men.

People with T2DM are high- or very high-risk patients. The risk is elevated in them because of the diabetic condition, therefore to lower the risk, LDL-C should be decreased in them as is mentioned in the guideline.
A recent retrospective matched-cohort study assessed the association between statins and diabetes. A progress of the diabetes occurred significantly in nearly 56% of the statin group compared to 48% of active comparators. In a sub-analysis a more intensive lipid lowering therapy was associated with a greater progression of the diabetes.
These findings need to be considered in the application of statins in patients with diabetes mellitus.

People who suffer from HIV are at increased CV risk. A higher rate (30%) of coronary plaques was found in the group with patients with HIV at a very low ASCVD risk (<2,5%). Below the risk of 7.5% of ASCVD, nearly half of the HIV patients had vulnerable plaques. The risk factors in HIV patients are the prolonged immunosuppression, antiretroviral therapy, chronic inflammation and dyslipidaemia. Antiretroviral drugs are metabolized the same pathway as most statins are, via CYP3A4. This could result in a greater risk for adverse events due to drug interactions like myopathy and rhabdomyolysis. When pitavastatin is chosen in HIV patients, no significant drug interactions are expected and no dose adjustment is needed with PI (proteinase inhibitors).
No difference was seen in hsCRP levels in participants with or without plaques, but considering vulnerable plaques, hsCRP values were higher in them. The JUPITER trial showed that anti-inflammatory effects of statins in reducing hsCRP might be more important in those with elevated levels than LDL-C reduction. Because CAD occurs much

earlier in people with HIV, a treatment in people at younger age is recommended. Further studies are needed to determine how the plaque phenotypes relate to major cardiovascular events. Which role a statin therapy plays in these patients, if or how statins are able to reduce plaques, needs also further investigations.
Because of drug-drug interactions between statins and immunosuppressant drugs, a prescription needs to be well thought and adjusted. Special attention should be paid to calcineurin inhibitors and cyclosporin with statins, because some combinations need to be avoided and some need a dose restriction.

A meta-analysis demonstrated that pitavastatin and pravastatin are able to reduce albuminuria too, as atorvastatin does. So, these three substances are currently considered as the medication of choice in CKD patients with proteinuria. The one that is mainly renally eliminated, is pravastatin. Pravastatin is the one that is mostly recommended in elderly patients due to safety reasons, but in patients with CKD the dose has to be adjusted, especially in those with an eGFR below 30. No dose adjustment is necessary with atorvastatin and fluvastatin.
All-cause mortality and cardiovascular mortality is not increased if eGFR and albumin-to-creatinine ratio show levels in a normal range. The lower eGFR (estimated glomerular filtration rate) gets and the more albumin is excreted though urine, the higher the risk of cardiovascular mortality.

There are two different types of heart failure patients. The ones with a “preserved ejection fraction” (HFpEF) and the other ones with “reduced ejection fraction” (HFrEF).
Studies with rosuvastatin 10 mg did not show any benefit in HFrEF patients, where data from observational studies show a higher one-year-survival rate in HFpEF patients with a statin treatment.
Special attention needs the rising incidence of heart failure patients. A hypothesis is that low coenzyme Q10 levels could cause diastolic dysfunction.
In a small clinical trial, a reverse of diastolic dysfunction was seen with 300 mg CoQ10 per day in statin treated patients with developed heart failure.
The hospitalization rate was lowered in HF patients with statins was seen in a meta-analysis, but a larger meta-analysis showed that just the rate of non-fatal hospitalizations for HF patients was reduced and not fatal hospitalizations.

The European guideline of 2021 recommends statins in ischemic HF patients for secondary prevention. For HFrEF or HFpEF patient there is no recommendation. Data with good evidence suggest that there is no sufficient benefit of a statin therapy for HF patients as the guideline says.

Recent findings support the hypothesis that statins are safe and even beneficial in patients with a chronic liver disease. In a meta-analysis was seen, that the progression of liver fibrosis is significantly reduced with statins. Simvastatin decreased the portal pressure in a study of half of the patients. A huge meta-analysis found a lower rate of HCC with statins which is one main cause of death in these patients. There was a 37% risk reduction in patients developing HCC with statins.
80 mg/day of atorvastatin should have a beneficial effect in patients with NAFLD. Supporting that hypothesis, in a small study 19 of 20 participants with NASH had a complete resolution with rosuvastatin for 12 months. In contrast to that, a trial with pitavastatin did not show beneficial results, and the use of simvastatin or pravastatin in patients suffering from NASH was found to increase the risk of myopathies. More adverse events occurred in patients with decompensated cirrhosis at a higher dose of simvastatin compared to a lower dose. Statins are unable to decrease the re-bleeding rate of esophageal varices. There is no indication for statins in patients with decompensated cirrhosis or acute liver failure.

Pharmacokinetics is an important topic because of polypharmacy. How drugs are metabolized and which drugs can interact with each other is relevant to avoid adverse events. All statins are metabolized via CYP3A4 except pravastatin and rosuvastatin. Most drug interactions occur with statins and immunosuppressive drugs, as well as with antifungal or antibiotic drugs.

The most frequent adverse effect of statins are muscle symptoms. Muscle symptoms related to a statin therapy are often difficult to detect, because there is mostly no elevation of creatinine kinase in plasma and there is a big range of these muscle symptoms. It ranges from myalgia to rhabdomyolysis.
After patients experienced a period of SAMS (statin-associated muscle symptoms), an attempt is made to get them back on a statin therapy after a washout period, either with a

lower dose of the same statin or another one. If the lowest dose with three tried statins does not work, a long-acting statin should be used every other day. It is seen that a therapy like that can achieve the same LDL-C lowering effect than a daily intake.

Different risk factors like a high dosage from drug-drug interaction or slow catabolism like hypothyroidism can increase the risk of muscle symptoms. Reduced muscle mass (women, older people) and increased physical activity are risk factors as well. Observational studies showed a prevalence of SAMS of 10-29%. RCTs, however, report a prevalence of 1–2%. The reason could be a nocebo effect because this possible adverse effect of statins is well known in society and ends up in the expectation of side effects on the side of the patients. There is not always the statin to blame, it should be kept in mind that other commonly prescribed drugs can cause muscle-related side effects as well.

Patients with adverse events and low CV risk should be reevaluated if a treatment with statins is required, and patients at high CV risk should receive the possible tolerable lipid-lowering therapy.

In high-risk CVD patients with a CK level above 4 times the normal upper level, statin therapy should be continued with CK monitoring and it should even be continued but with a lower dose, if CK rises till 10x ULN. If CK gets above 10x ULN, the therapy needs to be stopped because of the potential risk of rhabdomyolysis. After weaning, CK should be monitored and if it does not drop, a secondary cause is more likely and other investigations should be done. The treatment of a rhabdomyolysis is to stop the statin treatment, hydration i.v. and urine alkalinization. If CVD risk is high in statin intolerant patients, non-statin LDL-C lowering agents should be used.

It is not clear how statins cause muscle pain, but there are several hypotheses.

Patients with a deficiency of vitamin D should develop muscle symptoms more likely. An association with an improved tolerance of statins and the supplementation of vitamin D was observed, but the placebo effect and nocebo effect could not be ruled out. People taking statins develop a deficiency of coenzyme-Q10. Adding this coenzyme to the treatment of a statin could have a preventive effect, it was hypothesized, but there was no beneficial effect detectable. This means, a coenzyme Q10 supplementation for prophylaxis or treatment cannot be recommended.

There are significant findings of statins contributing to the development of T2DM. In addition to that, there is a correlation between a higher dose of a statin and a higher risk of T2DM.
Statins affect the sensitivity of insulin and the insulin resistance. The results of hydrophilic and lipophilic statins were very similar. It could be called a slightly increased risk. There were no different findings in patients at different sex, age, medical history and current medication. But the development of diabetes happens nearly exclusively in individuals with a metabolic syndrome. A BMI lower than 30, fasting blood sugar <100, HbA1c < 6% or no signs of a metabolic syndrome make a metabolic change to new-onset DM unlikely.
With statins the risk of T2DM was increased, generally independent of the observed co-factors. The estimated incidence of new-onset diabetes is 10 – 20 patients of 10,000 patients with statin therapy. This new diabetes condition causes a doubling of the cardiovascular risk in these patients. 5–10 patients could get a major cardiovascular event from that adverse effect, but in 150 people out of 10,000 such a major cardiovascular event can be prevented. So, the benefits of statins clearly outweigh the risk of diabetes. PCSK9 inhibitors as a class are not associated with diabetes as adverse event.

Early onset cataract (EOC) can occur in less than 55-year-olds with statins. Risk factors for the occurrence of cataracts may be the use of statins for a long time or a severe hypercholesterolemia, one paper points out.
People with HeFH and a statin therapy were not at an elevated risk of a cataract, even with a statin therapy for more than 20 years. The results showed only a significant association with age and cataract. But in contrast to that finding, there was found a significant correlation between cataracts and the use of statins, a meta-analysis showed. In animals no relationship between low cholesterol and the appearance of cataract was detectable, a relationship between plasma levels of statins and cataract was established, however. Informing the patients about this possible side effect and a close follow-up in patients who take statins for a long time is recommended.

Familial hypercholesterolemia (FH) is inherited in an autosomal co-dominant manner and causes a disorder of the lipid metabolism. FH is underdiagnosed which is followed by undertreatment. A screening in 9- to 11-year-old children is recommended. In patients who

have one relative who suffers from familial hypercholesterolemia, an early screening should be done is recommended in the European guideline.
The diagnosis of FH is a combination of a look for physical findings, a family history, early onset of ASCVD and a higher LDL-C level than normal. It has to be kept in mind that other causes can elevate the level of LDL-C too. Another option would be genetic testing.
People with an FH mutation are at higher cardiac risk with a certain LDL-C level compared to the general population which has a much lower risk with the same LDL-C level. In addition to dietary and lifestyle modifications, lipid lowering therapies are needed. For adults with LDL-C of 190 mg/dl or more and the condition of FH, a high dose statin therapy should be applied.
Statins are contraindicated during pregnancy, but a large cohort study did show no increased risk for organ malformations with statins in pregnant women.
A treatment in homozygous FH patients is difficult because the response to statins is mostly low. If statins are successful, depends on the present residual activity of LDL receptors. Interestingly, some lipid lowering effects are seen even in HoFH patients with no LDL receptors.
Some studies showed that people with FH have the same life expectancy than other people. Other inheritances could be responsible for the elevation of CVD in these patients, is said.
Treatment since childhood is a long-discussed topic. In a placebo-controlled study where pravastatin was used, it was seen that LDL-C levels of children from 8 to 18 can be restored without any negative effects on growth, muscle or liver enzymes, endocrine function parameters or pubertal development. All statins in a reduced dosage are recommended in children with FH. The treatment is supposed to start between the age of 8 and 10.

Because of different action mechanisms statins are supposed to have, they gained attention in the early treatment of COVID19.
A meta-analysis of 35 observational studies reported a benefit of statin treatment in COVID-19 disease. One hypothesis is that the possibility to enter a cell of the virus is reduced by statins. Another hypothesis is that the inhibition of HMG-CoA-reductase impairs the replication of the virus.

Besides these mechanisms, statins should improve the endothelial function and a dysfunction of the endothelium which is a common denominator of a severe course of COVID-19. Pravastatin and rosuvastatin are preferred as additional therapy to antiviral drugs because they are not metabolized via CYP3A4. A study investigated a higher risk for acute respiratory syndrome among patients while taking statins compared to those who do not. Large RCTs of individuals with ARDS (developed from other causes than COVID-19) have shown that rosuvastatin or simvastatin did not provide a significant benefit in overall mortality. No significant findings in the reduction of all-cause mortality with statins in patients with COVID-19 and intensive care were detected.

There was no increased rate of adverse events either. In summary it can be said that there is no benefit of statins in patients with COVID-19 but no harm either. Those already on statins can continue the treatment.

4 Discussion

4.1 Primary prevention

The screening of risk factors including the lipid status should be done in men over 40 years and in women over 50 years or post-menopausal. Women develop ASCVD 10 years later than men, the hormone oestrogen is said to have a protective impact on the endothelium.

For a long time, SCORE was used to assess the CV risk in people with different risk factors. Lipids of the blood are one risk factor of ASCVD and the Interheart study[10] said, also a main risk factor. The new European guideline of 2021 uses a new score to evaluate the individual risk, called SCORE2. The main difference between SCORE and SCORE2 is the biomarker taken for lipid levels. SCORE used LDL-C while SCORE2 uses non-HDL now. It calculates the 10-year risk of a fatal or non-fatal event. [12]

There is a broad use of statins in secondary prevention. However, in primary prevention it is not fully clear when to start with a statin therapy.

The following table lists the facts about statins in primary prevention this paper detected:

First, lifestyle recommendations, smoking cessation and lowering systolic blood pressure under 160mmHg are suggested.[12]
A reduction of LDL-C of below 100 mg/dl can be recommended in: - <50 years: > 7.5% SCORE2 - 50-69 years: > 10% SCORE2

<table>
<tr><td colspan="2">- Over 70 years: > 15% SCORE-OP (Class IIb recommendation)[12]</td></tr>
<tr><td colspan="2">In adults with a borderline risk score, it is usually uncertain whether therapy should be started or not. The CAC (coronary artery calcium) score could help to answer this question. Due to costs and availability, this score cannot be determined for all.[12]</td></tr>
<tr><td>Mortality benefit</td><td>A big meta-analysis with RCTs showed a 12% risk reduction in CV events with statins in primary prevention. No benefit was seen in all-cause mortality but the follow-up time of many trials was short.[40]
CV death were significantly lower in those taking statins for primary prevention. No evidence in a reduction of CV death was seen for secondary prevention. The same was seen regarding all-cause mortality. These results indicate a possible benefit from primary statin therapy for all-cause mortality. Other RCTs with a population at lower risks are needed to confirm these suggestions.[19]
Another meta-analysis investigated also cardiovascular and all-cause mortality, when taking statins for primary prevention but there were combined endpoints and the trial duration was very short to assess mortality. Non-fatal CV events were significantly reduced by all types of statins but only with atorvastatin fatal MIs were reduced and no statin reduced the rate of fatal strokes significantly in this analysis.[23]</td></tr>
<tr><td>Safety</td><td>In primary prevention, it is always important not to cause harm in apparently healthy people. Muscle disorders and liver dysfunction were the most common side effects, other adverse events such as renal insufficiency, type 2 diabetes or ocular side effects were rare.
- There is no association between statins and the development of diabetes in primary prevention.
- With clinically confirmed muscle symptoms, there was no significant association with statins.
- Liver dysfunction: the highest risk was seen with atorvastatin and lovastatin at higher dosages.

Observational studies recommend the use of statins for primary prevention, the benefits outweigh the potential harms, is said.
The WOSCOPS study says that statins are safe for a long-term use for</td></tr>
</table>

	primary prevention and there are detectable benefits over a period of 20-years.[22]
Compliance	Beside of prescribing statins for primary prevention, compliance is a major concern. Fear of side effects is just one of many reasons to stop a statin therapy.[43]
Primary prevention and age	No increased rate of adverse events is detected in over 65-year-old with statins for primary prevention. Pravastatin is recommended because of decreased risk of drug-drug interactions. In very old and frail patients, statins should be avoided because they have no long-term benefit with limited life expectancy. [44] When the life expectancy is limited to less than 2.5 years patients do not benefit enough (within years) to outweigh harms that could occur within weeks.[46] A randomized clinical trial showed, that in patients with a life expectancy of under one year who continued to take a statin, the self-reported quality of life was worse than in those who were withdrawn from the therapy. [47]

Table 1 Primary prevention with statins

4.2 Cholesterol hypothesis

Some authors from different countries doubt the cholesterol hypothesis and have arguments against it, but there is different evidence from different trials supporting the cholesterol hypothesis.

Supporting the cholesterol hypothesis:

- Atherosclerotic changes were detected in all mammalian species after increases of apo-B containing lipoproteins.
- The Interheart study: elevated LDL-C is significantly associated with myocardial infarction without the appearance of other risk factors.
- There is an association between the level of LDL and the risk of ASCVD. Many studies including randomized intervention trails demonstrated that.
- Lifelong LDL elevations have a higher lifetime risk for ASCVD.
- ASCVD decreases independently of how LDL is lowered, whether by statins, PCSK9 inhibitors or ezetimibe.

- Results of different trials say that the proportional reduction decreases by 22% to get a major cardiovascular event in five years. This reduction occurs in all patients independent of the baseline level of LDL-C.
- If an LDL-C level of below 70 mg/dl is reached, measurements with intravascular ultrasound demonstrated that atherosclerotic plaques show no further progression.
- A PCSK9 inhibitor achieves together with a statin a 20% relative risk reduction for myocardial infarctions, stroke or cardiovascular death (combined endpoint) within 2.2 years. [16]

Against the cholesterol hypothesis:

- In 19 cohort studies, even an inverse association with LDL-C and mortality was observed, the lower LDL-C got, the higher was mortality. [24]
- In a trial where saturated fat was replaced, serum cholesterol was decreased but the rate of all-cause mortality stayed the same. Older patients had even a higher risk of death when serum cholesterol was reduced up to 30 mg/dl. [25]
- A paper pointed out limitations of the European guideline. They say that there are many studies with many included participants of elderly people where there was no survival benefit seen in them. They say that LDL-C is mainly a CV risk factor of the young and middle-aged. Mental stress could be responsible for a raise of LDL-C with lots of other effects. [27]
- In another publication with the title "LDL-C does not cause cardiovascular disease", the authors claim that there are falsifications of the cholesterol hypothesis. The Bradford Hill criteria are not fulfilled for causality, statistics are misleading, unsuccessful trials are excluded and contradictory observations are ignored, they say. After they talked about trials with total cholesterol also trials with LDL-C were discussed.[32]

4.3 LDL-C below 100 mg/dl

Some studies have found a reduction in mortality, others have not. It is important to distinguish between total mortality and cardiovascular mortality.

Six RCTs confirm the reduction in CV and all-cause mortality with a statin treatment in the long term.[3] However, a meta-analysis including eight trials showed a reduction of CV mortality during the trials but not afterwards. This leads to the suggestion that mortality

rates assessed during trial periods do not reflect empirical evidence or the participants stopped the treatment after the trial.[19]

Upon further research, it was seen that the reduction in total mortality appeared to be dependent on baseline LDL levels. The greatest reduction in all-cause mortality and CV mortality was seen in patients with a LDL-C baseline level of more than 160 mg/dl. All-cause mortality was not reduced in patients at a LDL-C level of lower than 100 mg/dl and even the CV mortality rates were lower at baseline levels of above 100 mg/dl than below 100 mg/dl.[28]

In contrast to cardiovascular events, no significant difference was detected between a less or more intensive LDL-C lowering therapy for cerebrovascular events. The risk reduction of strokes with a lipid lowering therapy remains steady at 21% independent of baseline LDL-C levels or with different ranges of LDL-C lowering.[18]

As adverse event an increased risk of haemorrhagic strokes was seen in major LDL-C lowering trials, but neither with statins nor with PCSK9 inhibitors a significant association was found. [28]

A meta-analysis with RCTs with people taking statins and PCSK9 inhibitors or ezetimibe showed a decrease in non-fatal stroke or MI, a greater risk reduction was seen with PCSK9 inhibitors but even with ezetimibe a further lowering than with a monotreatment of statin was achieved. However, no significant reduction in CV or all-cause mortality was seen. This might be because of the short follow-up time of only two years, or because of the average LDL-C level of the participants of 105 mg/dl. These findings support the finding mentioned above, the survival benefit is dependent on baseline LDL-C and below 100 mg/dl no benefit in all-cause mortality is detectable. [26]

There is the question of why no survival benefit occurs in people with a LDL-C lower than 100 mg/dl.

One explanation therefore is that cancer and infections lower LDL-C. The mortality could be increased in people with low LDL-C because of these conditions.

Another explanation is that infections could cause cardiovascular diseases and that LDL inactivates microorganisms and toxic products. The observation that healthy people with low LDL-C are more likely to get infectious diseases and cancer supports this hypothesis. [32] An increased survival is detected in NAFLD patients taking statins as well as a lower rate of hepatocellular carcinoma, infections and decompensating events. A lower rate of

infections does not support the hypothesis about low LDL-C as a risk factor of infections, to refer to the mentioned topic. [61]

Why are LDL-C levels of below 100 mg/dl are recommended if there is no benefit in all-cause mortality? Because there is a broad consensus about the relative reduction of the cardiovascular event rate (21-22% in 5 years per 39 mg/dl LDL-C reduction).

Therefore, the European guideline recommends in very high-risk patients levels below 55 mg/dl of LDL-C and in high risk patients 70 mg/dl. If this goal values are not achieved with statin, other lipid lowering drugs should be added like ezetimibe or PCSK9 inhibitors.

Because these lipids are needed to produce hormones for instance, there were concerns about adverse events caused by too low LDL-C levels, especially when administered to children with FH.

Studies with intensive lipid lowering showed no increased adverse events. Even with LDL-C levels down to 21 mg/dl they are safe, a meta-analysis points out but the duration of the trials were short and the number of participants was low. [29]

Observational studies show as mentioned above, that diseases which are caused or aggravated by microorganisms seem to occur more often in people with low levels of LDL-C.

19 cohort studies demonstrated that mortality of respiratory or gastrointestinal diseases of mostly infectious origin were significantly inversely associated with total cholesterol.

In addition to that, many types of cancer have their origin in viruses. If a high cholesterol could protect from infection, it is as follows also protective against cancer. [24]

This hypothesis is questionable because no increased risk of cancer was detected in studies with many participants and long follow-up times. For example, one million women with statins were assessed to evaluate the risk of breast cancer and there was no association. [28]

The suggestion that HCC do occur less in people taking statins does not support this hypothesis, but HCC could be caused by many reasons, an infectious disease like hepatitis is only one possible cause.

There is also the question of how long to take a statin. Randomized studies have shown that longer exposure to lower LDL-C levels reduces the risk of having a cardiovascular event compared to shorter exposure. These findings support a cumulative effect. [12]

Adverse events can occur within a therapy with statins, that is confirmed but the relation between benefit and possible harm needs to be kept in mind.

On the one hand, clinical myopathy occurs with an incidence in 0.5 of 1,000 statin-treated patients in 5 years, a rhabdomyolysis happens in 0.1 of 1,000. To get diabetes during a statin therapy is estimated with 10%. On the other hand, 43 people are prevented from a major vascular event per 1,000 people treated in a period of 5 years and 11 of the prevented ones had a 5-year risk below 10%. [15]

What needs to be kept in mind as well is that mostly the rate of the relative risk reduction is stated. These numbers are mainly between 10% or 20%, so the actual risk is reduced by that percentage and the amount of the reduction of the actual risk by the relative risk is the absolute risk reduction. [32] These numbers are usually much smaller. Numbers like that allow a better vision to the actual benefits of a treatment.

4.4 Age

Another important risk factor beneath LDL-C is the age. The risk evaluation with SCORE is also adapted to age with the SCORE2-OP for older people (above 70 years of age).

With increasing age, the individual risk of having a fatal or non-fatal major cardiovascular event rises. Total cholesterol, however, seems to become less of a risk factor for cardiovascular death or all-cause mortality. [12]

In 19 cohort studies, even an inverse association with LDL-C and mortality was observed, the lower LDL-C got, the higher was mortality. [24]

The issue of the lack of data of over 70-year-olds has been addressed and data from many older patients was collected and a different score for over 70 year-olds was established.

Only a class IIb recommendation is given for lipid-lowering therapy for primary prevention in people > 70 years, regardless of the risk score. Due to the cumulative effect, younger people seem to benefit more than older ones. [12]

The very old are defined as >75 years to 84 years. In this group of age, everyone has a greater risk than 10% of having a major cardiovascular event and it is not recommended to prescribe for cardiovascular risk.[12] There is little data on primary prevention in the very old and the benefit is unclear. The rate of side effects compared to placebo is not increased in this age group many investigations showed but statins should not be used in very old, frail patients. [46]

Due to polypharmacy in older patients and especially in those who are often in need of a statin too drug-drug interactions could lead to more and more severe side effects. Therefore pravastatin is recommended in older comorbid patients because it is independent of the CYP-P450 system the chance of drug-drug interactions is reduced. [44]

With a limited life expectancy, the benefit of a statin therapy may be not occur and it makes no sense to prescribe statins then. In patients with a very short life expectancy, it is recommended to remove the statin because a better quality of life without this therapy was seen in a randomized study. [47]

4.5 Attention to women and comorbidities

- Attention to women
    - Women who smoke and women with diabetes seems to have a higher relative risk of cardiovascular disease compared to men. [52]
    - there are other risk factors for women that needs to be considered: preeclampsia, gestational diabetes, polycystic ovary syndrome, early menopause, and autoimmune diseases. [52]
    - The European guideline considers the unique cardiovascular risk factors in women but it is especially important that the primary physicians are aware of these risk factors in women and recognize them. [12]

Gender medicine gets more popular nowadays and helps in better treatment of women. Because women are often excluded from trials due to many reasons, there was an imbalance. Many recommendations were made from trials with men for the general population were individual risk factors for women like mentioned above got too little attention. In future treatment of CV risk factors this has to be changed with an increased awareness.

- Attention to comorbidities
    - Diabetes
        - In well-controlled type 2 diabetes that does not last longer than 10 years (short standing DM), does not show any organ damage and no other risk factors are present, no lipid-lowering therapy is recommended. [14]
        - For diabetics with other risk factors, however, more or less intensive lipid-lowering therapy is recommended, depending on whether organ damage is present or not or there is already an established ASCVD.

- T2DM with risk factors but without established ASCVD or TOD (target organ damage):
    - Step 1: LDL-C < 100 mg/dl and a lower goal is set in Step 2 (70 mg/dl and 50% reduction)
- T2DM with established ASCVD and/or severe TOD:
    - Step 1: LDL-C < 70 mg/dl and a lower goal is set in Step 2 (55 mg/dl and 50% reduction)[14]
- Statins can contribute to the progression of the disease in diabetics, a large study showed, which should be considered. [55]
- Atorvastatin is able to rise the level of HbA1c were no difference was seen with the other types of statins and pitavastatin may even reduce HbA1c moderately. [54]

Statins can worsen the condition of diabetes which increases the CV risk, but in relation to the risk reduction of statins in these patients, this elevated risk is negligible.

- HIV
    - People with HIV are at increased risk of a cardiovascular event. Despite good treatment, there is still residual inflammatory activity that represents a cardiovascular risk factor. Since statins should also have anti-inflammatory effects, they could be recommended as primary prevention in HIV patients. [57] Because coronary artery disease occurs more quickly in HIV patients, early statin therapy is recommended. What have to be considered is that antiretroviral drugs are metabolized via CYP3A4 as many statins are. Simvastatin and lovastatin should be avoided with treatment of proteinase inhibitors, and dose adjustment is necessary for statins other than pitavastatin. Pitavastatin is therefore the drug of choice in HIV patients on this treatment. [56]

There needs to be awareness for the early onset of ASCVD in people with HIV. An early treatment is recommended and to avoid possible adverse events or harm it must be known that statins interact with immunosuppressant drugs.

- CKD

- In people with a chronic kidney disease, it must be known that the lower the eGFR and the higher the albumin in the urine, the higher gets the risk of cardiovascular death. [58]
- The benefit appears to be greater in patients when statins are used earlier in chronic kidney disease. However, this hypothesis needs to be confirmed in further studies. But the benefit decreases rapidly in patients with an eGFR below 30 ml/min or patients requiring dialysis. It is also important to adjust the dose below an eGFR of 30 ml/min. In CKD patients with proteinuria, pitavastatin, pravastatin, and atorvastatin are recommended because they have been shown to reduce albuminuria. [58]

With a progress of chronic kidney disease, the CV mortality rate gets higher is important to know.

- Heart failure
  - Discussing heart failure and statins is difficult because of different views: Some say statins are helpful in at least a part of heart failure patients and others have the assertion statins may even cause heart failure, they speak of statin-associated cardiomyopathy.[59]
  - In HFrEF patients there seems to be no benefit with statins, but a meta-analysis showed a reduced hospitalization rate of an acute exacerbation of the heart failure but not fatal MIs, stroke or cardiovascular mortality.[58]

    One meta-analysis including six RCTs showed a lower hospitalization rate with an intensive statin therapy, but in a larger meta-analysis it was seen that statins do just reduce the rate of non-fatal hospitalizations for heart failure but not the rate of heart failure deaths.[60]
  - In HFpEF patients there was seen a benefit with statins in hospitalization rate and mortality. A risk factor for CAD is an elevated LDL-C level, but it must be taken into account that heart failure patients with low plasma cholesterol levels have a poorer prognosis. The reasons for this have yet to be explored.[58]

It is uncertain if patients with heart failure should be treated with statins or not. It is said statins could also cause heart failure, but in HFpEF patients the hospitalization rate and mortality rate was decreased with statins. The European guideline has no statement to this issue. It is said that there is probably no possible benefit of statins in HF patients.

- Liver diseases
  - An increased survival is detected in patients with a liver disease and the treatment of a statin as well as a lower rate of hepatocellular carcinoma, infections and decompensating events. [61]
  - Statins may influence key points of fibrogenesis. Many trials and a meta-analysis report from a reduced progression of fibrosis with statins, significantly. Four RCTs showed a small to moderate benefit with statins in these patients. [61]
  - Even the portal hypertension was lowered with statins, but there was no detectable benefit in the rate of oesophageal rebleeding. [61]
  - Non-alcoholic steatohepatitis is an advanced form of non-alcoholic-fatty-liver-disease. It is a very frequent cause of liver diseases nowadays and there is no effective treatment for that except weight loss. 80 mg/day of atorvastatin should have a beneficial effect in patients with NAFLD, as three major prospective RCTs showed. [61]
  - Patients with NASH should be treated with 10 mg of rosuvastatin, is the recommendation due to those findings, starting at 5mg and when there are no occurring adverse effects, the dose could be elevated. [62]

Statins should reduce the rate of HCC and infections in patients with a liver disease. Also there was an improvement seen of hepatic tissue were a reduced progression of fibrosis was detected. No benefit was seen in the rate of oesophageal rebleeding, which is a common cause of death in these patients.

- Statins should be avoided in patients with following conditions
  - Patients with a limited life expectancy
  - CKD patients with dialysis
  - HFrEF patients

4.6 Adverse events

4.6.1 Muscle symptoms

- Muscle symptoms are very common, where an elevation of CK of more than 10 times the upper limit is very rare. If an elevation like this occurs, the statin needs to be stopped. [67]
- These symptoms and CK elevations occur within 4 to 6 weeks of the statin prescription or an elevation on the dose, otherwise secondary causes of muscle pain must be considered like polymyalgia rheumatica or other drugs which may cause muscle pain. [67]
- After SAMS (statin associated muscle symptoms) the statin should be washed out and another statin should be given or the same statin could be prescribed at a lower dose. If that does not work, a long-acting statin should be used every other day. 90% who had muscle symptoms then tolerated another statin. [67]
- SAMS occurs more in the larger muscles, bilaterally primarily the calf and thigh. [67]
- Risk factors could be a high dose, a slow catabolism like in older patients or with hypothyroidism. Reduced muscle mass and increased physical activity could be other risk factors. Therefore, older people and women who have reduced muscle mass are at higher risk. In a large study, however, no connection was found between muscle symptoms and increased activity. [64]
- When it comes to muscle symptoms, there is a large gap between observational studies and RCTs. Observational studies indicate a prevalence of SAMS of up to 30%, whereas RCTs only found prevalences of 1-2%.[64]
- The explanation could be a nocebo effect, which describes the occurrence of a side effect when you expect it or know about the possibility of occurence. [72]

Why these muscle symptoms occur is not fully understood, there are several hypotheses.

Cholesterol synthesis in muscle cells is inhibited	The cholesterol deficiency in the cells could lead to symptoms like that. [68]
Impaired protein	It could be myotoxic. [68]
Mitochondrial dysfunction	Impaired cell organelles or free radicals are thought to cause muscle symptoms. [68]
Oxidative stress	
Vitamin D deficiency	It is not clear how vitamin D affects muscle symptoms. A supplementation could maybe improve muscle symptoms.

	[70]
Coenzyme Q10 deficiency	Supplementing CoQ10 does not cause any severe adverse events but no difference in muscle pain assessed by scores or in CK levels were detected and there was also no detected benefit in a use for prophylaxis. This means whether as treatment nor as prophylaxis a supplementation with CoQ10 can be recommended. [71]

Table 2 Causes of muscle symptoms

It is not quite understood why these muscle symptoms occur. Likely muscle symptoms with an increase of CK are rare. Like RCTs showed, compared to observational studies the rate of muscle symptoms with statins is placebo controlled not very high. Because of the nocebo effect, it might be better patients would not know about this adverse event. But nowadays many people know and otherwise get to know about it. It is not clear how a supplementation of vitamin D could be helpful, but it is quite clear that the supplementation of CoQ10 is whether suitable for treatment nor for prophylaxis of muscle symptoms.

Pharmacogenetics could identify patients at potential risk for muscular adverse events. It is a new field, but maybe one day it will help in prescribing statins. For instance, patients with a polymorphism of an anion transporter gene may be more susceptible to develop SAMS. [72]

4.6.2 New onset diabetes

- The WOSCOP (West of Scotland Coronary Prevention) study was one of the first studies which showed, statin use and new-onset diabetes correlate with each other. [73]
- As adverse event statins can cause new-onset diabetes but only in those who take statins for secondary prevention. This could be explained by larger populations, older patients and higher doses.[49]
- More potent statins have an increased risk for developing NODM (new-onset diabetes mellitus), like atorvastatin or rosuvastatin. Statins with lower potency such as pravastatin and pitavastatin have less impact on the metabolism of glucose. There is also the correlation between a higher dose of a statin and the increased risk of T2DM. [73]

It can be considered to prescribe low-potent statins in patients at elevated risk for new-onset diabetes, but the risk of cardiovascular events and mortality must be weighed against it. It is suggested not to avoid high-potency statins in patients at high and very high risk of cardiovascular events and mortality. [73]

A big meta-analysis with randomized controlled trials found a 9% increased risk to develop diabetes with statins within 4 years. Even after adjusting for various risk factors, the association between statins and new onset diabetes remains constant. [74]

What is clinically relevant, is the most important question. The number of new-onset diabetes is not very high. It is estimated to be 10–20 patients out of 10,000 patients with statin therapy. This new diabetes condition causes a doubling of the cardiovascular risk in these patients. 5–10 patients could get a major cardiovascular event from that adverse effect, but in 150 people out of 10,000 such a major cardiovascular event can be prevented. So, the benefits of statins clearly outweigh the risk of diabetes. PCSK9 inhibitors as a class were not associated with diabetes as adverse event.

A metabolic syndrome and increased age are two main risk factors for the adverse effect of developing type 2 diabetes with statins. [73]

4.6.3 Cataract

Cataract is mostly a disease of the elderly, but with low incidence it can occur in less than 55-year-olds. Then it is called early onset cataract (EOC).

The hypothesis with statins is that epithelial cells need high cholesterol to provide the transparency of the lens. In a trial with dogs in the nineties, cataract developed with a cholesterol reduction by a statin therapy. In addition to that, lipophilic statins may be more likely to cause that adverse effect because of better migration properties. [81]

In patients with HeFH with prolonged statin therapy the occurence of a cataract was studied. The results showed only a significant association with age and cataract.

People with HeFH and a statin therapy had no increased risk of cataracts for more than 20 years. [82]

In contrast to that collected reports within 40 years show a significant association with atorvastatin, rosuvastatin, simvastatin or lovastatin and the occurrence of cataract.

These findings support the hypothesis of the impact of low cholesterol in the pathogenesis of a cataract. [84]

To analyze the association of genetic variations in HMG-CoA reductase, the key enzyme in the synthesis of cholesterol and cataract should provide new evidence of the hypothesis

that statins may cause cataract. There are five genetic variants of the inhibition of HMG-CoA reductase. There is a higher risk of getting cataract or having a cataract surgery in patients with a lifelong inhibition of HMGCR variants. [85]

RCTs did not show an increased risk of cataracts in people taking statins. However, these RCTs were mostly of short duration or had inadequate ophthalmic assessment.

The actual mechanism of why and how a cataract develops, is not fully clear. In animals no relationship between low cholesterol and the appearance of cataract was detectable, however, a relationship between plasma levels of statins and cataract was established. It is more likely that HMG-CoA reductase is important for sterol synthesis in the lens for transparency because no association with other pathways (NPC1L1 or PCSK9) was detected. This paper recommends informing patients about the possible side effects and suggests a close follow-up especially in younger patients with familial hypercholesterolemia who take statins for a very long time. [85]

Summary of the common adverse events with statins

Muscle symptoms	Muscle symptoms occur often in people in general. RCTs found an increase of 1-2% of muscle symptoms with statins. A nocebo effect, which means the expectation of this adverse event from statins seems to be responsible for the raised levels of complaints about muscle symptoms in these patients. The severe adverse event of rhabdomyolysis is very rare.
New onset diabetes	There is an elevated risk of developing T2DM with statins, but only for secondary prevention. In people with T2DM the risk of getting a CV event is doubled, where much more CV events could be prevented with statins.
Cataract	Early onset cataract can occur in people below the age of 55 years with statins.

Table 3 Adverse events

4.7 Familial Hypercholesterinemia

Heterozygous familial hypercholesterolemia is a widespread common autosomal dominant inherited disorder where homozygous FH is inherited in an autosomal recessive manner and is much rarer.

20% of heart attacks in younger men are attributed to FH, is said and is underdiagnosed which is followed by undertreatment.

With a family history of early onset-CAD or high total cholesterol levels a screening in 2-year-olds is recommended or if the child itself has risk factors like diabetes mellitus or obesity and 9- to 11 year old children should be generally screened for FH.

Big data from a FH registry demonstrated that the mean age of FH diagnosis is by the age of 50. Till then one third of these FH patients already experienced an atherosclerotic cardiovascular event.

The diagnosis of FH is a combination of a look for physical findings, a family history, early onset of ASCVD and a higher LDL-C level than normal. A further possibility of diagnosing would be genetic testing.

There is a big difference in the risk in patients with FH mutation compared to those without a mutation and the same LDL-C levels. The risk in people with FH mutation is 22-fold higher with a LDL-C level of more than 190 mg/dl where the risk in people without the mutation is 6-fold higher.

All statins in a reduced dosage are recommended in children with FH. The treatment is supposed to start between the age of 8 and 10. For adults with LDL-C of more than 190 mg/dl and FH a lipid lowering treatment is recommended. [86]

The activity of LDL receptors in people with HoFH is low due to the genetic variation. If statins are successful, depends on the present residual activity of LDL receptors. [87]

The guideline recommends a screening in all individuals below 50 years of age with a first-degree relative with FH. Young and middle-aged adults with CVD do more often have FH compared to the general population. However, several studies showed, people with FH have the same life expectancy than other people. Why there is an elevation of CVD in FH patients could be because a subset of these people did inherit increases of coagulation factors too. In several studies, LDL-C did not differ significantly between those with or without cardiovascular disease. [27]

Is treating children successful and harmless? A long-term observation shows that treatment protects patients from atherosclerotic disease up to an age of 40, even if target LDL-cholesterol levels are rarely reached.

It was seen that LDL-C levels of children from 8 to 18 can be restored without any negative effects on growth, muscle or liver enzymes, endocrine function parameters or pubertal development. [88]

In a trial where children got compared to their parents with high LDL-C levels, the children which were treated with statins had a much lower rate of CV events by a certain age, than their parents. These two comparison groups are not ideal because parents could have a different cardiovascular risk due to a different lifestyle. But the authors firmly believe that this therapy saved the children from the fate of their parents. [89]

4.8 COVID-19

Because of pleiotropic effect, statins were thought to be helpful in COVID-19 patients.

A meta-analysis reported a benefit with a statin treatment during suffering from COVID-19 due to 35 observational studies. [90]

Opposite to that finding a study investigated a higher risk for acute respiratory syndrome among patients with taking statins compared to those who do not. [92]

Large RCTs of individuals with ARDS (developed from other causes than COVID-19) have shown that rosuvastatin or simvastatin did not provide a significant benefit in overall mortality. [93,94]

Maybe there is no grand benefit of statins in patients with COVID19, but there is apparently no harm either. It can be said that those who were treated with statins before infection, should continue the intake without worries. [91]

4.9 Thoughts of other ways to prevent CV events

Inflammation also appears to play a major role in the development of atherosclerosis.

The Jupiter study included patients with elevated CRP. In these patients, lowering CRP was more important than lowering LDL-C. Healthy patients with elevated CRP have a three-fold increased risk of a cardiovascular event, while the risk of a stroke is doubled. Statins are said to have an anti-inflammatory effect. This study showed a 20-30% reduction in CRP with statins. [41]

A therapeutical approach would be anti-inflammatory drugs. CANTOS, which is short for canakinumab anti-inflammatory thrombosis outcome study, was the first study which examined how reducing inflammation affects cardiovascular events. The lipid levels in these patients remained unchanged. Because of concerns of high costs and huge infections there was no further development for this indication. Methotrexate was also investigated for this reason but did not provide any benefits in reducing CVD.

COLCOT, Colchicine cardiovascular outcomes trial, was published in 2019. A significant reduction in CVD outcomes with a low-dose of colchicine was found in patients who had a

recent event of an acute myocardial infarction. In contrast to positive results there was also an increase detected in non-cardiovascular mortality, which needs further investigations. [12]

Due to knowledge of the mechanisms of how plaques develop, it would be an approach to try to stop the vanish of smooth muscle cells of the plaque to keep them stable this way. [12]

I think that statins can be effective to some extent in preventing cardiovascular events, however, in my opinion, the benefits of this therapy are not sufficient when considering the absolute risk reduction.

Damage to the vascular wall is a multifactorial event that is in most cases not caused by an increase of blood lipids alone. Besides lowering blood pressure and anticoagulation therapy, statins are drugs that can reduce the risk of cardiovascular events or, to a lesser extent, mortality, but cannot be considered as a cure.

With regard to preventive medicine, according to the current state of knowledge, it is difficult to say what benefit early statin therapy can show.

One possibility would be to stop to hold on to statins and look for alternatives that could have a better effect on stabilizing plaques or preventing atherosclerosis and its consequences.

It is possible that other drugs that prevent atherosclerotic changes in the vessels via a different pathway than lipid lowering could achieve better results.

On the other hand, we know that a healthy diet, sufficient exercise and abstinence from smoking is most effective in reducing the risk of a cardiovascular event or death.

People should be motivated to become active and to take care of their health. That should be started in school. In addition to regular lessons on healthy nutrition and cooking, children should be taught to enjoy movement.

Exercise in particular appears to be most effective against atherosclerosis. An idea would also be to shorten the working week or to introduce the already discussed 4-day week in order to have more time for activities. There could also be more seminars on how to live healthy for adults.

Investing in preventative medicine could save many from a cardiovascular event or death while saving many healthcare costs.

Drugs such as statins should then only be used by a minority who are genetically higher in lipid levels or by those who fail to reach certain target levels.

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