UNIVERSITAT DE BARCELONA

Final degree project

Lipid-lowering drugs in Acute Myocardial Infarction prevention

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Main area: Pharmacology and Therapeutics

Secondary areas: Physiology and Physiopathology

Biochemistry and Molecular Biology

FACULTAT DE FARMÀCIA I CIÈNCIES DE L'ALIMENTACIÓ

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Abbreviations

ACS: Acute coronary syndrome

AMI: Acute myocardial infarction

CAD: Coronary artery disease

CHD: Coronary heart disease

cTn: Cardiac troponin

CV: Cardiovascular

DAPT: Dual antiplatelet treatment

ECG: Electrocardiogram

ECM: Extracellular matrix

HDL: High-density lipoprotein

HMG-CoA: 3-hydroxy-3-methylglutarylcoenzyme A

IMPROVE-IT: The Improved Reduction of Outcomes: Vytorin Efficacy International Trial

LDL: Low-density lipoprotein

LDLR: Low-density lipoproteins receptor

Lp(a): Lipoprotein a

LPL: Lipoprotein lipase

mAb: Monoclonal antibodies

MI: Myocardial infarction

MMP: Metalloproteinases

NO: Nitric oxide

NPC1L1: Niemann-Pick C1-like protein 1

NSAID: Nonsteroidal anti-inflammatory drugs

NSTEMI: Non-ST elevation myocardial infarction

oxLDL: oxidized low-density lipoproteins

PCI: Percutaneous coronary intervention

PCSK9: Proprotein convertase subtilisin/kexin type 9

P.O.: Per Os

PPAR-α: Peroxisome proliferator-activated receptor α

STEMI: ST elevation myocardial infarction

TG: Triglyceride

T2DM: diabetes mellitus type 2

URL: Upper reference level

UFH: Unfractionated heparin

VLDL: Very-low-density lipoprotein

VSMC: Vascular smooth muscle cell

1. Abstract

Acute myocardial infarction (AMI) is defined as myocardial cell death caused by prolonged myocardial ischemia. Although advances in both acute and secondary prevention treatment in recent years have improved the prognosis of the disease, it continues to have a great impact on society, as 14% of individuals with AMI will die because of it in the following year. First, this project seeks to contextualize, through epidemiological studies, the relevance of type 1 AMI worldwide, as well as the acute treatment of the disease. Finally, it delves into the pathophysiology involved and focuses on prevention. Accumulation of low density lipoproteins (LDL) in the arterial wall is one of the major risk factors for developing atherosclerosis, the main trigger for type 1 AMI. Statins are currently established as the reference treatment for AMI prevention, both in monotherapy and in combination with other lipid-lowering drugs. Combined therapies have shown to induce major reductions in cardiovascular risk, but research must be continued to improve outcomes. Statins have traditionally been used together with cholesterol absorption inhibitors, bile acid sequestrants and fibrates. A new lipid-lowering drug family, monoclonal antibodies inhibiting PCSK9 proteins, has been developed recently, showing promising results for the disease prevention, awaiting further safety and efficiency studies.

Resum

L'infart agut de miocardi (AMI) es defineix com la mort del miocardi causada per una isquèmia prolongada. Tot i que els avenços en el tractament tant agut com de prevenció secundària dels últims anys han millorat la prognosi de la malaltia, aquesta segueix tenint un gran impacte en la societat, ja que el 14% dels individus que pateixin un AMI en moriran com a conseqüència abans d'un any. En primer lloc, aquest treball busca contextualitzar, mitjançant estudis epidemiològics, la rellevància global de l'AMI tipus 1 així com el tractament agut de la malaltia. Finalment, aprofundeix en la fisiopatologia involucrada per després centrar-se en la prevenció. L'acumulació de lipoproteïnes de baixa densitat en la paret arterial és un dels principals factors de risc per a desenvolupar aterosclerosi, el desencadenant principal de l'AMI tipus 1. Actualment les estatines estan establertes com el tractament de referència per a la prevenció de l'AMI, tant en

monoteràpia com en teràpia combinada amb altres fàrmacs hipolipemiants. Les teràpies combinades han demostrat induir majors reduccions del risc d'esdeveniments cardiovasculars, però s'ha de continuar la recerca per a millorar els resultats. Tradicionalment les estatines s'han utilitzat conjuntament amb inhibidors de l'absorció del colesterol, segrestadors d'àcids biliars i fibrats. Recentment s'ha desenvolupat una nova família d'hipolipemiants, els anticossos monoclonals inhibidors de la PCSK9, els quals mostren resultats prometedors en la prevenció de la malaltia, a l'espera de nous estudis de seguretat i eficiència.

2. Integration of different fields

Acute myocardial infarction (AMI) has a great impact on society nowadays. Though survival rates have increased along the last years due to new treatment techniques, incidence is still high worldwide, causing plenty of both personal and economic costs. Therefore, finding improved treatment and mainly primary and secondary prevention therapies are key points for AMI management.

Lipoprotein accumulation in the arterial wall is one of the most important risk factors for the atherosclerotic plaque formation and further reduction in the blood flow to the heart, causing AMI. This project is focused on primary and secondary pharmacological prevention of hyperlipidaemia to reduce AMI risk. Successful prevention of AMI would be reflected in greater quality of life for the patients and economic costs reduction for the sanitary system. Thus, the main area herein treated is Pharmacology and Therapeutics.

In order to understand how classic therapies operate, why some are more effective than others, and to lead research towards new prevention treatments to these events, it is necessary to fully understand the processes involved in the pathogenesis of the disease at a molecular and biochemical level. This objective will be achieved through the secondary areas involved in this project, Physiology and Physiopathology and Biochemistry and Molecular Biology.

3. Introduction

Acute myocardial infarction (AMI) is defined as myocardial cell death caused by prolonged myocardial ischemia (1). Ischemia is the initial step of AMI development, and can be both identified by diffuse chest or upper zone pain, epigastric discomfort, dyspnea or fatigue present in the clinical history; or from the electrocardiogram (ECG). AMI is classified into atherosclerotic (type 1 AMI) or non-atherosclerotic (including types 2-5 AMI).

3.1. Acute Myocardial Infarction types

3.1.1. Atherosclerotic Acute Myocardial Infarction. Type 1

Type 1 AMI is a chronic inflammatory disease of the arterial wall defined as spontaneous myocardial infarction related to atherosclerotic plaque rupture. It has traditionally been divided into ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI).

STEMI entails abruptly complete blockage of the vessel lumen after the disruption of an atherosclerotic plaque and its release to the blood, favouring thrombogenesis and artery occlusion. ST-segment elevation appears during the initial stage because of a total occlusion of an epicardial coronary artery, and most patients ultimately evolve Q waves on the ECG (Figure 1) (2). Instead, NSTEMI implies partial blockage of the arterial lumen resulting from thrombus forming on a disrupted atherothrombotic coronary plaque or eroded coronary artery endothelium. NSTEMI implies ischemic discomfort, without ST-segment elevation (Figure 1). In both STEMI and NSTEMI appear variations in serum cardiac biomarkers of necrosis like cardiac troponins (cTn). (3).

cTn are contractile regulatory proteins widely used for the diagnosis of acute coronary syndrome (ACS), which includes patients presenting stable angina and those with AMI. They are only mildly elevated in other cardiac conditions other than AMI and highly specific for myocardial injury. Therefore, quantification of cTn levels is required.

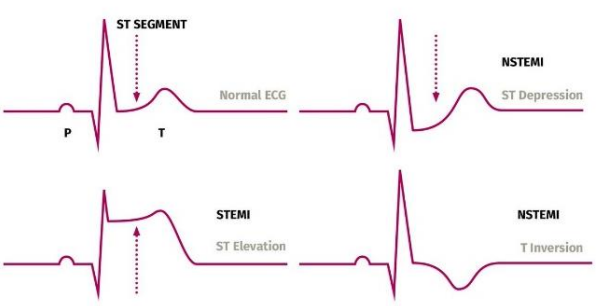

Figure 1. Schematic representation of electrocardiogram patterns *(2)*

Type 1 AMI is characterized by the detection of a rise or fall of cTn values with at least 1 value above the 99th percentile upper reference level (URL) and at least one of the following:

- Symptoms of acute myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy

This review will focus on type 1 AMI since it is the most common one. Therefore, it is briefly described in this section to be extensively discussed later.

3.1.2. Non-atherosclerotic Acute Myocardial Infarction. Types 2-5

Type 2 AMI: Myocardial infarction secondary to an ischemic imbalance

The ischemic imbalance between the oxygen supply and demand of this AMI can be attributed to different systemic causes, none of which may be of atherosclerotic origin. Among these causes we can find conditions like hypoxemia, severe bradyarrhythmia, severe hypotension, hypertension or anemia, myocardial perfusion reduction, spontaneous coronary artery dissection, vasospasms, coronary embolism and microvascular dysfunction (1, 4).

Type 2 AMI is characterized by the detection of a rise or fall of cTn values with at least 1 value above the 99th percentile URL and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis and at least one of the following:

- Symptoms of acute myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new pattern consistent with an ischemic etiology

Type 3 AMI: Myocardial infarction resulting in death when biomarker values are unavailable

Diagnosing this type of AMI may be challenging. Patients suffer cardiac death, with symptoms suggestive of myocardial ischemia, ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained or increases in cardiac biomarkers can be identified. It can also be detected by autopsy examination (1, 4).

Type 4a AMI: Myocardial infarction related to percutaneous coronary intervention (PCI)

Coronary intervention-related AMI is arbitrarily defined as an elevation of cTn values >5 times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn levels are stable (≤20% variation) or falling, the post-procedure cTn must rise by >20% (1, 4). However, the absolute post-procedural value must still be at least 5 times the 99th percentile URL. Type 4a AMI is characterized by the detection of the above mentioned cTn variations and at least one of the following:

- New ischemic ECG changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Angiographic findings consistent with a procedural flow-limiting complications such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow or distal embolization

Type 4b AMI: Myocardial infarction related to stent thrombosis

A subcategory of PCI-related AMI is stent/scaffold thrombosis, as documented by angiography or autopsy using the same criteria utilized for type 1 AMI. In this AMI type, it is important to consider the time of occurrence of the stent/scaffold thrombosis in relation to the timing of the PCI procedure (1, 4).

Type 5 AMI: Myocardial infarction related to coronary artery bypass grafting (CABG)

During a CABG procedural, myocardial injury is related to numerous factors, such as any potential ischemic injury, the extent of the direct traumatic injury to the myocardium or the details of the cardiac preservation, causing a rise in the cTn levels. CABG-related AMI is arbitrarily defined as elevation of cTn values >10 times the 99th percentile URL in

patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤20% variation) or falling, the post-procedure cTn must rise by >20% (1, 4). However, the absolute post-procedural value still must be >10 times the 99th percentile URL. Type 5 AMI is characterized by the detection of the above mentioned cTn variations and at least one of the following:

- Development of pathological Q waves
- Angiographic documented new graft occlusion or new native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

3.2. Type 1 spontaneous Acute Myocardial Infarction

3.2.1. Epidemiology

Cardiovascular diseases are the leading cause of death worldwide (1). With an increasing frequency, although with large variations between countries, they mostly result from ischemic heart and cerebrovascular diseases (Figure 2).

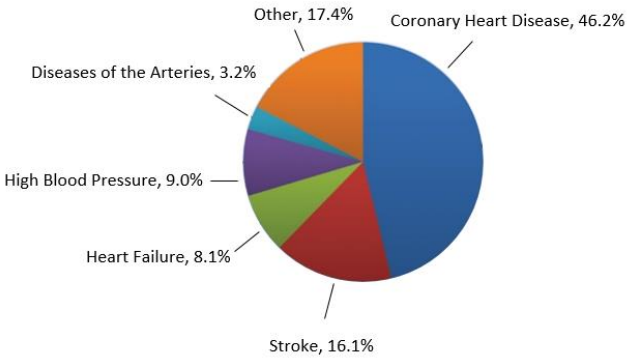

Figure 2. Percentage breakdown of deaths attributable to cardiovascular disease (5).

According to recent data retrieved from Eurostat, the statistical office of the European Union, in EU-28 there were 1.83 million deaths reported in 2016 as diseases of the circulatory system, corresponding to the 35.7% of all deaths. 118,824 of these deaths were in Spain and, among them, 14,908 were due to acute myocardial infarction. Between 2013 and 2016, the coronary heart disease (CHD) prevalence in America was approximately 6.7% among the Americans ≥20 years, 7.4% corresponding to men and 6.2% to women (6). Regarding AMI, the prevalence was also bigger among men (4%) than women (2.3%) except among those in the range of 20-39 years old. The estimated annual incidence of AMI was 605,000 new attacks and 200,000 recurrent attacks. The average age at which AMI occurs among women is 72.0 years and among men 65.6 years.

3.2.2. Prognosis

Of all the people who experience a coronary event, 35% of them will die as a result of it in the following year, as well as 14% of those experiencing an AMI (6). Furthermore, the median survival time after the first AMI in people ≥45 years old is 8.2 years for men and 5.5 years for women, and within 5 years after the AMI, 17% of men and 21% of women will have a recurrent AMI. According to the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, the risk of suffering a recurrent cardiovascular (CV) event is around 20% in the following three years after an ACS (7).

If successful early reperfusion or preserved left ventricular function among other factors are proceed, it will be associated with a better prognosis, although it is highly variable. In contrast, if the patient suffers from previous vascular diseases, diabetes mellitus type 2 (T2DM) or poorly preserved left ventricular function among other factors, it will be associated with a poorer prognosis. Elderly and diabetic patients can present AMI without symptoms, making its diagnostic and, therefore, its treatment harder, reflected in aggravated prognosis.

3.2.3. Signs and symptoms

AMI symptoms can be varied and differ between men and women. In addition, we must take into consideration that they can occur with different severities in each patient, though they are the same between STEMI and NSTEMI. The first symptom usually is deep, visceral pain, often radiating to the back, jaw, left or right arm, shoulders or any of the upper body areas that lasts more than a few minutes or that goes away and comes back. This discomfort is usually diffuse, and accompanied with nausea and vomiting, dyspnea or diaphoresis (8).

While chest pain is among both men and women the most commonly reported symptom, women are more likely than men to have jaw and upper back pain, shortness of breath, nausea and vomiting.

3.2.4. Pathophysiological mechanisms of type 1 Acute Myocardial Infarction

Type 1 acute myocardial infarction is most commonly due to the disruption of a vulnerable atherosclerotic plaque or erosion of the coronary artery endothelium, leading to the decrease of the myocardial blood flow with ensuing myocyte necrosis (9).

Atherosclerotic plaques are usually formed in the lumen of medium sized and large arteries curvatures, branch points and bifurcations. Dyslipidaemia, together with T2DM, is one of the most firmly established risk factors for atherosclerosis and, therefore, type 1 AMI. Elevated LDL levels are the main risk factor for atherosclerotic plaque formation. However, diabetic dyslipidaemia is mostly characterized by increased levels of large very-low-density lipoprotein (VLDL) particles, which generate atherogenic remnants, small and dense LDL particles and triglyceride (TG), as well as dense high-density lipoprotein (HDL) particles. Tobacco consumption, hypertension, turbulent flow and inflammatory diseases are also other risk factors for type 1 AMI because of their ability to trigger lesions in the intima, damaging the blood vessels wall and, therefore, favouring atherosclerosis (3).

These lesions in the intima, the innermost layer of the vessels wall, will cause its dysfunctionality. Tunica intima consists of an endothelial cells monolayer that provides the interface between circulating blood and the rest of the vessel wall. In a normal state produces nitric oxide (NO), a signalling molecule with important functions on the vessel wall as relaxation and inhibition of proliferation of vascular smooth muscle cells (VSMC), inhibition of activation and aggregation of platelets and inhibition of inflammation caused by cell adhesion and migration (10).

Endothelial dysfunction causes a reduction in NO production while stimulates adhesion molecules production, attracting inflammatory cells to the intima, and resulting in an environment conductive to the development of atherosclerosis (10). It also causes an increase in lipoproteins permeability and favours their retention in the intima by extracellular matrix molecules (11). Then, LDL particles can undergo oxidative modifications becoming oxLDL, which stimulate monocytes and adhesion molecules recruitment into the intima (Figure 3) (10).

Monocytes will differentiate into macrophages via macrophage colony-stimulating factor (M-CSF) and engulf oxLDL becoming foam cells that potentiate the inflammatory response.

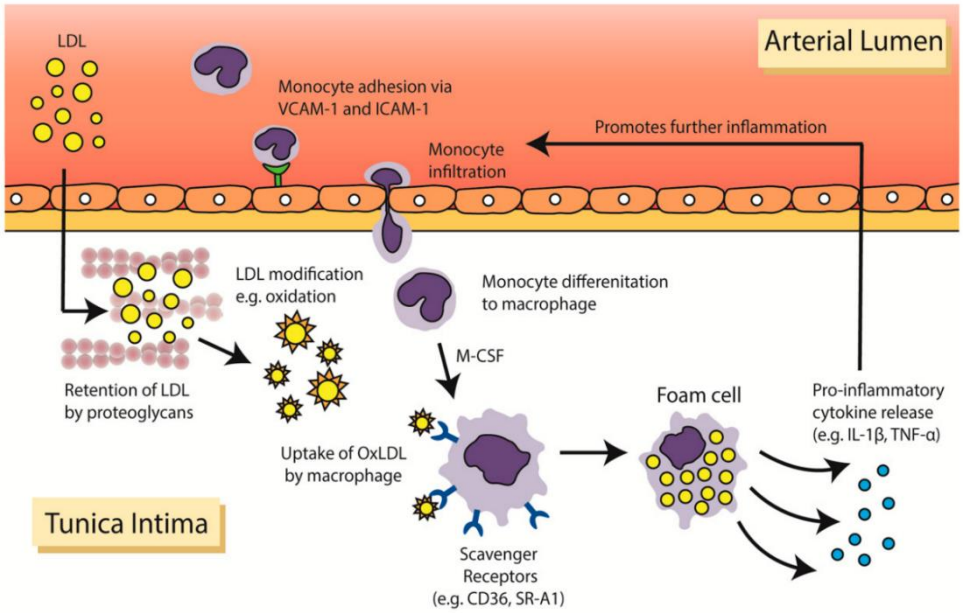

Figure 3. Infiltration of low-density lipoprotein (LDL) and formation of macrophage foam cells in the arterial wall. LDL particles are prone to infiltration and retention in the arterial wall, where they will undergo oxidative modifications becoming oxLDL, which promote monocyte recruitment to the arterial wall. These monocytes will differentiate into macrophages, engulf the oxLDL and become foam cells, which will stimulate inflammation by the release of pro-inflammatory cytokines (12).
LDL: low-density lipoprotein; oxLDL: oxidized low-density lipoproteins; M-CSF: macrophage colony-stimulating factor; VCAM-1: Vascular Cell Adhesion Molecule 1; ICAM-1: Intercellular Adhesion Molecule 1; CD36: cluster of differentiation 36; SR-A1: Scavenger Receptor; IL-1β: Interleukin-1β; TNF-α: Tumor Necrosis Factor-α.

If the circulating level of lipoproteins is bigger than the phagocytic capacity of the monocytes, macrophages will act chemotactically upon more monocytes and smooth muscle cells, which in turn will phagocyte more lipids and become foam cells.

Macrophages synthesize pro-inflammatory cytokines, which recruit VSMC from the media layer to the intima (13). Extracellular matrix increase in dense by VSMC replication and production of collagen and elastin, contributing to the development of the fibrous cap. A strong fibrous cap that will isolate the lipid core from circulating blood is formed, stabilizing the plaque but also narrowing the vessel lumen.

End result lesion is a subendothelial fibrous plaque composed of lipid core surrounded by VSMC and connective tissue fibres. Unstable plaques have thick lipid core but thin

fibrous cap, making them more susceptible to rupture than stable plaques, with low lipid contend but thick fibrous cap (14).

Many of the involved macrophages undergo apoptosis and are removed by other macrophages. If this process happens successively, macrophage death occurs with its consequent release of lipids, pro-inflammatory mediators and metalloproteinases (MMPs) in the intimal lesion (13), increasing collagen degradation and rending the cap susceptible to rupture (3). T-lymphocytes enter the intima and regulate functions of the innate immune cells. Activated T-helper cells secrete cytokine interferon gamma (IFN-γ) which inhibits the production of the new interstitial collagen that is required to repair and maintain the fibrous cap that protects the plaque.

Gradual loss of VSMCs and collagen-rich cap matrix degradation lead to fibrous cap thinning and rupture with subsequent release of its thrombogenic material into the blood flow. These events will result in platelet adhesion and thrombus formation, triggering inflammation.

AMI arises from an atherosclerotic plaque rupture and following clot formation, but rather than with vessel stenosis itself, it is related with plaque enlargement. Likelihood of plaque rupture is increased with thick necrotic core, thin fibrous cap, positive remodelling and large plaque burden. Thus, an increase in necrotic core volume and fibrous cap attenuation turns out to be a major risk factor for plaque rupture. Contrarily, necrotic core volume diminution and calcification, even if it implies heightened luminal stenosis, leads to plaque regression. Therefore, plaque stabilization becomes a key target in atherosclerosis prevention and regression and, consequently, for AMI prevention.

According to the American Heart Association (AHA), atherosclerosis can be divided into six types of lesion depending on their progression level (Figure 4).

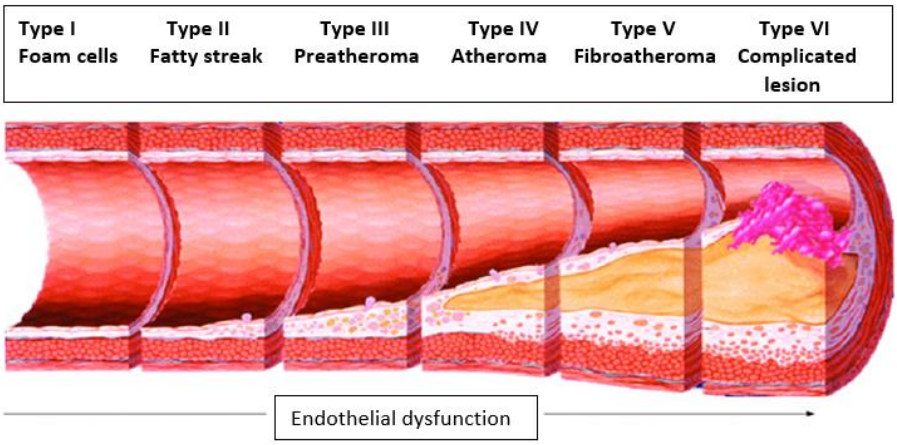

Figure 4. Evolution and progression of atherosclerosis lesion. **Type I lesion**: First microscopically detectable lipid deposits in the intima. Monocyte recruitment from the vessel lumen into the intima and evolution to macrophages. These macrophages engulf lipoproteins becoming foam cells and begin to produce pro-inflammatory and adhesion molecules. **Type II lesion:** Macrophage foam cells stratify in adjacent layers forming a fatty streak. **Type III lesion:** Intermediate lesion with extracellular lipid accumulation defined as preatheroma. **Type IV lesion:** First advanced lesion defined as atheroma. With high lipid contend (lipid core formation), intimal disorganization and arterial deformity. **Type V lesion:** Reparative connective tissue (mainly composed by collagen and elastin) and fibrous plaque formation around the lipid core defined as fibroatheroma. **Type VI lesion:** Fibrous plaque rupture with consequent thrombus formation and lumen vessel occlusion (15, 16, 17).

3.2.5. Diagnosis

Patients with ischemic heart disease are divided into two groups: those with chronic coronary artery disease (CAD) presenting stable angina and those with ACS. The latter includes patients with STEMI and NSTEMI, with evidence of myocyte necrosis, and patients with unstable angina without myocyte necrosis evidence (3). It is important to differentiate between unstable angina and AMI, as their treatment will be different. A patient experiencing AMI will not relief his/her symptoms while resting as it is owing to ischemic necrosis due to prolonged lack of blood flow and oxygen during a prolonged period. Instead, a patient suffering from angina will feel chest pain during exercise or emotional stress, with relief of symptoms while resting.

A patient with suspected AMI should have an initial evaluation that includes physical examination, focused clinical history, cardiac biomarkers quantification and electrocardiogram. This will help the physician to assess the severity of AMI and to distinguish between different ACS events, such as STEMI and NSTEMI, as well as unstable angina. For instance, AMI presents with a rise or fall in cTn levels, whereas the last one displays normal cardiac biomarker values.

3.2.6. Acute treatment

In this section, acute treatment after Type 1 AMI is discussed, both for STEMI and NSTEMI. Even though both are classified as Type 1 AMI and have an atherosclerotic origin, there are some differences in their pathophysiology as it has been previously described in this review. Therefore, their treatment must be differentiated. Primary and secondary prevention, focused on lipid-lowering therapies, will be further discussed in section 6.

3.2.6.1. ST Elevation Acute Myocardial Infarction

Myocardial necrosis in AMI begins 15-30 minutes after severe ischemia. At present, the main treatment strategy is revascularization by percutaneous coronary intervention (PCI) within the first 120 minutes since the symptoms presentation (18). It is essential that initial assessment and management be rapid to be able to start the treatment as soon as possible to increase the myocardial salvage tissue and reduce mortality. Thereby, a patient diagnosed with STEMI should be referred to a PCI-capable hospital to reach a performance goal of ≤90 minutes from the first medical contact.

PCI performance is preferred over fibrinolytic therapy because of its lower rates of haemorrhage, early death and reinfarction. When patients arrive to the PCI-capable hospital 12-24 hours after the symptom onset, PCI is only recommended if ischemic symptoms persist. After 24 hours, if symptoms persist and PCI is not available, the elected therapy is fibrinolytic (18).

Initial interventions

Once STEMI diagnostic is made, continuous ECG monitoring should be proceed. Supplementary oxygen should be administered to patients with an arterial saturation below 90% (19). However, it has been proved that routine administration of oxygen once achieved 90% saturation does not decrease the individual risks of recurrent cardiac events and makes no difference in the rate of the primary endpoint of death or rehospitalization with AMI within one year (20).

Pharmacotherapy should be started after the first medical contact to relive ischemic pain, and nitrates administration is widely used; 0.4 mg of sublingual nitroglycerin is administered to improve symptoms and lower blood pressure (21). In patients with an unacceptable level of pain, intravenous morphine is the therapy of choice. Otherwise,

morphine therapy is not recommended because it is associated with higher adjusted risk of death than those not treated, and neither nonsteroidal anti-inflammatory drugs (NSAID) are recommended, since prothrombotic events are associated with their use (22).

Antiplatelet treatment

According to the AMI code in Catalonia, antiplatelet treatment should be started as soon as possible, consisting in Aspirin administration together with a P2Y12 antagonist, as it has established benefit in primary and secondary prevention of AMI, whether later PCI or fibrinolytic strategy will be proceed (21).

The combined treatment with Aspirin and a P2Y12 inhibitor is defined as dual antiplatelet treatment (DAPT) (23). Aspirin is a thromboxane A2-dependent platelet aggregation inhibitor, and it is administered with a per os (p.o.) dose of 250 mg (21). P2Y12 is a Gi-coupled receptor which reduces cAMP intracellular levels, essential to platelet activation. Platelet activation can be inhibited with a P2Y12 antagonist, rather irreversibly with clopidogrel or prasugrel, or reversibly with ticagrelor (23).

To achieve maximum efficacy, prompt initiation of P2Y12 inhibitor should be proceed. Clopidogrel, ticagrelor or prasugrel will be administered previously to the PCI according to the criteria described in Figure 5. If the patient will later undergo fibrinolytic treatment instead of PCI, he/she should receive 300 mg p.o of clopidogrel for patients <75 years old or 75 mg p.o for patients >75 years old. Prasugrel and ticagrelor have a more rapid onset of action and greater potency than clopidogrel. Therefore, its use is inadvisable for high haemorrhagic risk patients or for the elderly.

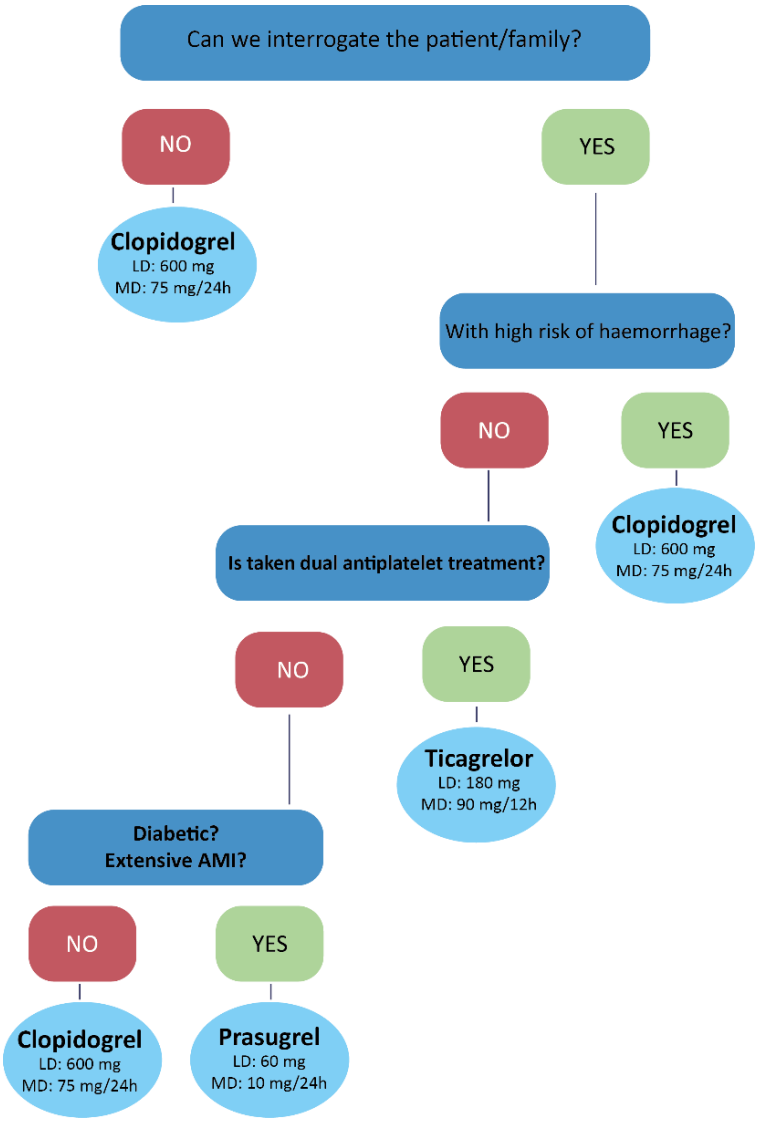

***Figure 5. Antiplatelet therapeutic options*.** If the patient or a family member cannot be interrogated to know about the patient history or he/she suffers from known high risk haemorrhage, 600 mg p.o of clopidogrel will be administered. Patients without high risk for haemorrhage but under DAPT will receive a loading dose of 180 mg p.o of ticagrelor. Diabetic patients or with extensive AMI will receive 60 mg p.o of prasugrel. Finally, if he/she does not meet any of the above conditions, 600 mg p.o of clopidogrel will be administered**. Adapted from AMI code in Catalonia** (21)**:**
http://canalsalut.gencat.cat/web/.content/_AZ/I/infart_de_miocardi/codi_iam/documents/triptic_iam_def.pdf

Anticoagulant treatment

Anticoagulant treatment is recommended for all patients experiencing an AMI in addition to antiplatelet treatment, before PCI or fibrinolytic procedure. Anticoagulant alternatives include unfractionated heparin (UFH), low-molecular-weight heparin or enoxaparin, and the synthetic drug bivalirudin.

While the ATOLL (Acute myocardial infarction Treated with primary angioplasty and intravenous enOxaparin or unfractionated heparin to Lower ischaemic and bleeding events at short- and Long-term follow-up) trial showed significant reductions in

mortality and major bleeding over UFH, the MATRIX (Minimizing Adverse haemorrhagic eEvents by TRansradial access site and systemic Implementation of angioX) trial showed no improvements of bivalirudin over UFH (24). Therefore, enoxaparin is preferred over the other options, with greater safety and efficacy, administrating 70 international unit (i.u)/kg dose with a maximum of 5,000 i.u (21).

Fibrinolytic treatment

Fibrinolytic therapy enhances blood clot elimination after an AMI, but it will only be administered if PCI performance is not available, since its combination is related with higher haemorrhage risk. Tenecteplase is a fibrin-specific tissue plasminogen activator. It promotes the degradation of plasminogen into plasmin, which in turn degrades the fibrin matrix of the thrombus. Tenecteplase is the drug of choice since it is has comparable efficacy to the other fibrinolytics commercialized but it is related with less non-cerebral bleeding. It is administered as a single bolus up to 50 mg, according to the patient's weight (25).

3.2.6.2 Non ST Elevation Myocardial Infarction

The protocol treatment for NSTEMI after the first medical contact is similar to the one set for STEMI treatment. Supplementary oxygen and nitroglycerin should follow the same administration recommendations, and NSAIDs are also misadvised. In the same way, DAPT with 250 mg of Aspirin and the chosen P2Y12 inhibitor is administered (26). In NSTEMI patients managed with an invasive strategy, UFH is the recommended anticoagulant, but for patients managed with a conservative strategy, the synthetic anticoagulant fondaparinux or the low-molecular-weight heparin enoxaparin are preferred (27).

Prospective trials have demonstrated that fibrinolytic therapy may increase haemorrhagic risk in patients with NSTEMI (28) and, therefore, its use is misadvised. In unstable patients urgent PCI is performed, but given the residual perfusion in the ischemic zone, revascularization can be delayed for patients at lower immediate risk. However, timing can vary depending on the presence or absence of high risk features. If initial treatment with DAPT and ischemic pain relieve therapy stabilized the patient, PCI can be delayed (18).

4. Objectives

Cardiovascular diseases, including acute myocardial infarction, still remain the leading cause of death worldwide, with a great incidence and impact on society. Benjamin *et al.* state that 35% of those experiencing a coronary event will die as a result of it in the following year. According to Schiele *et al.*, the risk of suffering a recurrent cardiovascular event is around 20% in the following three years after an acute coronary syndrome. Therefore, therapeutic alternatives need to be found to diminish this recurrence, as well as to reduce primary events.

The main objective of this review is to summarize the current mainly used lipid-lowering therapies for primary and secondary prevention of AMI, in order to be able to understand the actual management of the disease.

The main currently used lipid-lowering therapies are statins, cholesterol absorption inhibitors, PCSK9 inhibitors, bile acid sequestrants and fibrates. Statins are established as the leading therapy for primary and secondary prevention of AMI, but are sometimes related with severe adverse effects like myalgias. In this case, a dose reduction or even the treatment interruption is needed. Alternately, combined therapy of another lipid-lowering drug on top of the current statin treatment, although with lower doses, shows improved outcomes. This review aims to perform an exhaustive bibliographic research to understand its physiopathology and to assess the current management, to be able to direct research in the future towards new perspectives.

To be able to do so, secondary goals complementary to the main one are established to reach a global vision of the disease:

- Distinguish the different features that characterize acute myocardial infarction types, focusing on type 1.
- Contextualise through epidemiological studies the relevance of the disease worldwide.
- Comprehend the pathophysiology involved in the atherosclerosis process.
- Display the current protocol for acute treatment of the acute myocardial infarction.

5. Material and methods

In order to perform an updated bibliographic inquiry, an exhaustive research has been carried out mainly in PubMed and Uptodate databases, focusing in reviews from the past 5 years. Keywords for strategic research were: “acute myocardial infarction”, “prevention”, “treatment”, “atherosclerosis pathophysiology”, “dyslipidaemia”, “lipid-lowering”, “statins” and “adverse effects”. However, some older reviews regarding mainly the pathophysiology of the disease have been used. In this case, also the textbook *Harrisons – Principles of internal medicine* (3) was useful. The core of this review is based on information obtained from guidelines of *la Generalitat de Catalunya (Canal Salut*) to be fully adapted to our geographic scope; and from *The European Society of Cardiology, Eurostat, the American College of Cardiology and the American Heart Association* to have a global viewpoint. Moreover, all the literature used to write this project is referenced with Mendeley®.

6. Results and discussion

Plasma lipoproteins, responsible of cholesterol and triglycerides transport in blood, can be divided, according to their size and density, into six different classes: chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and lipoprotein (a) (Lp(a)) (29).

LDLs are the lipoproteins with higher capacity of cholesterol transport and, therefore, the most representative indicator of atherosclerotic plaque formation risk. VLDL particles, synthetized in the liver, carry most of the circulating TG, also associated with increased atherogenic risk. A patient suffering from hypertriglyceridemia will have abnormal VLDL particles, which will difficult their catabolism through hepatic LDL receptor (LDLR) and cannot be properly hydrolysed by lipoprotein lipase (LPL). The result are small and dense LDL particles, highly atherogenic, more susceptible to oxidation and recognition by macrophages, which will engulf this oxLDL and become foam cells. Instead, HDL is the only lipoprotein with anti-atherogenic properties, transporting cholesterol to the liver.

Over time, large clinical trials have shown that lipid-lowering treatment has a great impact on AMI risk reduction in patients with dyslipidaemia (30) by both reducing progression and inducing regression of the atherosclerotic plaque (29). Dyslipidaemia

can be classified into hypercholesterolemia (elevated LDL levels), hypertriglyceridemia (elevated TG levels) and mixed hyperlipidaemia (elevated LDL and TG levels, usually accompanied by decreased HDL levels) (31). Accordingly, the lipid-lowering treatment will vary depending on the therapeutic goal, whether it be to reduce LDL, TG or both.

Data have proved a direct relation between the concentration of circulating LDL and the atherosclerotic plaque initiation with its consequent thrombus formation and blood flow obstruction, leading to AMI. Meta-analyses have confirmed a dose-dependent reduction in CV risk with the absolute LDL reduction (32). Furthermore, increases in HDL are associated with atherosclerosis reduction, at the same time that decreases in HDL are related with increased AMI risk, even though having low LDL levels (29).

At a population level, the risk factors modification has shown an important decrease in the hospitalization rates for AMI. Aiming to improve treatment benefits, the European Society of Cardiology (ESC) establishes specific objectives for each patient. LDL reduction goals are established according to the initial risk stratification (Table 1).

Recommendations for treatment goals for low-density lipoprotein cholesterol	
In secondary prevention for patients at very-high risk	An LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended
In primary prevention for individuals at very-high risk	An LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered
For patients with atherosclerotic cardiovascular disease (ASCVD) who experience a second vascular event within 2 years while taking maximally tolerated statin-based therapy	An LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered
In patients at high risk	An LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended
In individuals at moderate risk	An LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered
In individuals at low risk	An LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered

Table 1. Recommendations for treatment goals for low-density lipoprotein cholesterol. Adapted from Mach et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (29).

For primary and secondary prevention of atherosclerotic CV diseases, The American College of Cardiology and American Heart Association (ACC/AHA) stratifies patients according to their risk of suffering a CV event. This classification is based on baseline LDL levels, history of previous events and the presence or absence of comorbidities like diabetes mellitus or metabolic syndrome. Pursuant to this classification, treatment options and intensity will be recommended.

Below are shown the most efficient and, therefore, prescribed lipid-lowering therapies used nowadays for primary and secondary prevention of AMI. For that reason, these five therapeutic families are discussed in this review (Figure 6):

1. 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors or statins
2. Niemann-Pick C1-like protein 1 (NPC1L1) or cholesterol absorption inhibitors
3. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
4. Bile acid sequestrants
5. Peroxisome proliferator-activated receptor α (PPAR-α) agonists or fibrates

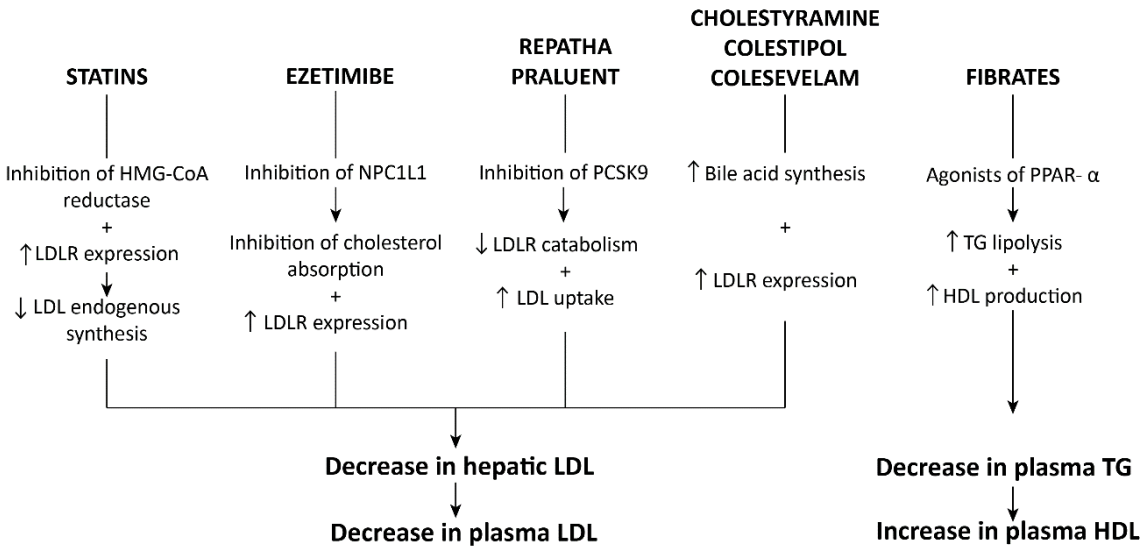

Figure 6. Mechanisms and main effects on lipid parameters of the different lipid-lowering treatments described in this review.

6.1. 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors or statins

Statins are reversible competitive 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors. In addition to competing with cholesterol for binding to the enzyme, they alter its conformation, thus preventing HMG-CoA reductase from attaining a functional structure. HMG-CoA reductase is the rate-limiting enzyme responsible for the conversion of HMG-CoA into mevalonic acid, a cholesterol precursor. Thus, statins reduce endogenous cholesterol synthesis (33). When cholesterol production in hepatocytes decreases, hepatic expression of LDLR increases, leading to the reduction of circulating LDL and its precursors (34).

Patients suffering from previous AMI, T2DM or chronic kidney disease are considered individuals with very high risk for another CV event. To be able to achieve the objective of ≥50% reduction from baseline LDL levels, high intensity statin therapy is recommended. Two drugs are considered in this situation: atorvastatin with a daily oral dose of 40-80 mg and rosuvastatin with a daily oral dose of 20-40 mg (35).

Statins do not only reduce CV risk by reducing endogenous cholesterol synthesis, but they also display pleiotropic effects (Table 2).

Additional effects of statins	
HDL increases	Statins show cardioprotective effects by increasing HDL levels, usually by a 5% to 10%. Although it is very modest compared with the LDL levels reduction, it is of great importance
Effects on endothelial cell functions	Hypercholesterolemia treatment also enhances endothelial functionality. This is essential to be able to produce NO, which inhibits VSMSC proliferation, the activation and aggregation of platelets and the inflammation caused by cell adhesion and migration (10)
Effects on the inflammatory process	GTPases are key proteins for the cytokines receptors functionality. Statins can prevent their isoprenylation and, therefore, inhibit cytokine function, reducing the inflammatory response
Effects on proliferation and migration of smooth muscle cells	Statins reduce vascular smooth muscle cells proliferation and migration into the intima

Effects on the stability of the atherosclerotic plaque	Statins reduce both MMP production and activity, responsible of the fibrous cap degradation. Thus, they enhance plaque stability, a key factor in plaque rupture and consequent AMI prevention
Effects on platelet activation	Increased levels of LDL are related with increased platelet reactivity after the fibrous cap rupture. Statin therapy showed a reduction of platelet aggregation induced by ADP
Effects on the coagulation process	Statins have also proven to reduce thrombus formation through mevalonate pathway inhibition

Table 2. Additional effects of statins (33).

Although atorvastatin and rosuvastatin are the most potent statins available for LDL levels reduction, there are other statins recommended for patients with a lower CV risk. Table 3 shows the effect of different doses of statins over total cholesterol and LDL reduction.

Dose (mg of agent)							**% Reduction**	
Atorvastatin	**Rosuvastatin**	**Pitavastatin**	**Simvastatin**	**Lovastatin**	**Pravastatin**	**Fluvastatin**	**TC**	**LDL-C**
			20	20	20	40	22	27
10	5	1	40	40	40	80	27	34
20	10	2	80	80	80		32	41
40	20	4					37	48
80	40						42	55

Table 3. Commercialized statins and therapeutic dosages. TC: total cholesterol. LDL-C: LDL-cholesterol (36).

Clinical trials outcomes have positioned statins as the leading treatment for primary and secondary prevention of AMI (37). A meta-analysis of randomised trials published in June 2009 shows the benefits of statins in patients with cardiovascular risk factors but without established cardiovascular diseases (38). Even though different statins at different doses were evaluated during a mean follow-up of 4.1 years, statin treatment was clearly associated with a 30% risk reduction in CV events. Furthermore, the CTT (Cholesterol Treatment Trialists') meta-analysis showed a 23% reduction in mortality of CV disease and non-fatal MI over five years after statin treatment, achieving a 38.7 mg/dL reduction in LDL levels (39).

Maximum risk reduction of CV events by 30% at the higher tolerated statin doses, suggest that CV risk is not only conditioned by high plasma LDL concentrations, but shows the implication of other lipoproteins. Furthermore, statins effect is limited in obese and T2DM patients, characterized by small and dense LDL, high TG levels and low HDL levels, largely related with increased CV risk. These findings suggest that the hyperlipidaemia treatment and subsequent AMI prevention relies not only in LDL lowering therapies but also in cardioprotective approaches (40). This topic will be further discussed in section "6.5. Residual risk".

Adverse effects

Statins are safe and well tolerated drugs. However, their use have been related with myotoxicity, mainly with high statin doses (41). While myopathy is the most clinically adverse effect reported, rhabdomyolysis is the most severe (29). Myopathy is defined as muscle symptoms and creatine kinase levels elevation. According to the PRIMO (Prediction of Muscular Risk in Observational Conditions) study (42), myopathy occurs with myalgia, muscle tenderness, heaviness, stiffness, cramps or weakness and is usually intensified with exercise. Rhabdomyolysis is characterized by severe muscular pain, muscle necrosis and myoglobinuria, potentially leading to renal failure and death (29). It is most commonly due to interactions with other drugs. Its incidence may vary according to the different statins usage, since they are metabolized by different cytochrome P450 isoforms, which can be inhibited by different drugs. Thus, many patients cannot tolerate a dose sufficient to reach their LDL goal, showing the benefits of a combined therapy (43). Currently, the only way to avoid this toxicity is the reduction of doses or the interruption of the administration.

6.2 Niemann-Pick C1-like protein 1 (NPC1L1) or cholesterol absorption inhibitors

Plasmatic LDL levels can also be reduced by inhibiting intestinal cholesterol absorption. Ezetimibe is a drug capable of inhibiting Niemann-Pick C1-like protein 1 (NPC1L1), the major cholesterol transport protein in enterocytes. NPC1L1 inhibition causes a reduction in intestinal cholesterol absorption but without affecting the absorption of fat-soluble nutrients. Thus, delivered cholesterol amounts to the liver are reduced, causing an upregulation of LDLR expression and increasing LDL clearance from the blood (29). However, inhibition of cholesterol absorption is usually followed by an increase in hepatic cholesterol synthesis, thus limiting the efficacy of these drugs. LDL levels can be

reduced about a 15 to 20% with the NPC1L1 inhibition by ezetimibe (29). Given that ezetimibe is not usually prescribed as monotherapy and there are no studies on the cardiovascular benefits of using ezetimibe alone, this review focuses only on its beneficial effects in combination with other lipid-lowering drugs.

When maximum or maximum tolerated statin doses are not enough to achieve LDL reduction goals, addition of a complementary agent can be beneficious for the patient. Ezetimibe has a mechanism of action supportive to that of statins. Therefore, it is well combined with statins in hypercholesterolemia treatment. It has been proved that 10 mg of ezetimibe added to the ongoing statin treatment has 22-26% LDL levels reduction beyond statins monotherapy (44). As secondary prevention, the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial has demonstrated that, after a median follow-up of seven years, patients with ACS treated with the association of ezetimibe and simvastatin had lower rates of CV events than those with simvastatin alone (45). An absolute risk reduction of 2% was observed in the combined therapy group above the simvastatin monotherapy group. Contrarily, there were no observed reductions in cardiovascular death rates in neither group. This trial showed, in the diabetic subgroup, a 5.5% absolute risk reduction and a 14% relative risk reduction in CV events after a combined therapy of 40 mg p.o of simvastatin with 10 mg p.o of ezetimibe over 40 mg p.o of simvastatin monotherapy. Thus, the IMPROVE-IT trial showed greater reductions in CV events risk in diabetic patients than in non-diabetic (46).

The PRECISE-IVUS (Plaque Regression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound) study showed a 2.3% plaque regression after ezetimibe on top of statin treatment in patients with ACS. With statin monotherapy, only a 0.2% plaque regression was observed (39).

People with chronic kidney disease are considered high risk patients for CV events, and they are most likely to be intolerant to high statin doses. The SHARP (Study of Heart and Renal Protection; available at clinicaltrials.gov and registered as NCT 00125593) study analyses the benefits of simvastatin plus ezetimibe combined therapy in patients with chronic kidney disease. Results showed a one-sixth fewer major atherosclerotic events in patients under 20 mg p.o of simvastatin and 10 mg p.o of ezetimibe compared with those under placebo. Outcomes were similar among all types of patients studied. Large

number of studies show the effectiveness of lipid-lowering treatments in CV risk reduction, but this trial was the first one to demonstrate its benefits in patients with kidney disease.

Thereby, besides decreasing CV events rates and improving outcomes, the combined therapy of ezetimibe on top of low-dose statin treatment can be helpful to patients intolerant to high statin doses.

Adverse effects

Ezetimibe has been shown to be safe, tolerable and effective at lowering LDL levels, either alone or in combination with statins (43). Combination therapy of ezetimibe plus statins has shown to achieve the LDL reduction goals with an overall safety similar to the respective monotherapies. During the SHARP study, no severe adverse effect was reported, in the muscles, as high statin doses showed, in the liver or any of the other organs.

6.3. Proprotein convertase subtilisin/kexin type 9 inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are the most novel lipid-lowering drugs available. PCSK9 are circulating proteins responsible of LDLR catabolism. PCSK9 proteins have become a therapeutic target, since their inhibition leads to an increase in LDLR expression and, therefore, a rise in LDL uptake and plasma concentrations reduction (29). Monoclonal antibodies (mAb) have been developed targeting these proteins. Currently, the only drugs approved are alirocumab, commercialized as Praluent, and evolocumab, commercialized as Repatha. In clinical trials, they have shown average LDL reduction by 60%, achieving LDL reduction goals. A small TG reduction and HDL increase has also been related with these mAb (29).

The GLAGOV (Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial assessed the effects on plaque reduction by evolocumab after statin treatment. LDL levels were diminished to 36.6 mg/dL after the mAb treatment and the coronary plaque volume was reduced by a 64.3%, compared with LDL levels of 93.0 mg/dL and a 47.3% reduction in coronary plaque volume after placebo treatment (39).

The FOURIER (Further Cardiovascular Outcome Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial assessed the effects of the injection of 140 mg of evolocumab every 2 weeks after statin treatment for secondary prevention of CV diseases. For primary endpoint risk, namely cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, after one year of treatment with evolocumab, a 12% risk reduction was observed, which was further reduced up to 19% over time (47). In terms of individual outcomes, MI risk was reduced by a 27%, but there were no observed reductions in cardiovascular death rates.

Furthermore, the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) study showed, after a follow-up of 12 months, a reduction in mean LDL levels from 92 mg/dL to 48 mg/dL (29). Primary outcomes, namely CHD death, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization, experienced a 15% relative reduction after a median follow-up of 2.8 years. However, this study did not show effects on CV death rates either.

Interestingly, the best effect of PCSK9 inhibitors was observed in a combined therapy with statins. PCSK9 inhibitors on top of the maximum tolerated statin dose can reach up to a 40 to 70% LDL levels reduction (39). Furthermore, the CREDO Kyoto (Coronary Revascularization Demonstrating Outcome study in Kyoto) trial assessed the efficacy of 140 mg of evolocumab administered every 2 weeks on top of a high-intensity statin treatment compared with the statin monotherapy (48). The combined therapy showed, after one year of treatment, a 20% reduction in mortality rates, in contradistinction to the evolocumab monotherapy, which showed declines in MI risk but had no effect on cardiovascular death rates.

Thereby, although achieving LDL reduction goals, PCSK9 inhibitors do not diminish primary endpoint risk as monotherapy. Contrarily, combined therapy with statins showed improvements in all primary endpoints, including cardiovascular death risk.

Adverse effects

As PCSK9 inhibitors are subcutaneously administered, the interaction risk with orally absorbed drugs is reduced. According to the IMPROVE-IT study, until now they have not been related with any clear adverse effects, but since they are only commercialized since 2015, further trials are needed to ensure their safety (29).

6.4. Bile acid sequestrants

Cholesterol in the liver can be either packaged into lipoproteins, mainly VLDL, and returned to the bloodstream or excreted to the enterohepatic circulation as the main component of bile acid. Part of this cholesterol can be later reabsorbed to the liver. Bile acid sequestrants bind to bile salts, forming an insoluble complex that will be removed from the enterohepatic circulation, preventing the reabsorption of both cholesterol and the resin, reducing the bile flow. Thus, new bile acid will be synthetized in the liver from new cholesterol particles, decreasing hepatic LDL levels and causing LDLR upregulation (29).

With a maximum daily dose for the exchange resins cholestyramine and colestipol of 24 g and 20 g respectively or 4.5 g of the synthetic drug colesevelam, it has been proved an 18 to 25% reduction in LDL levels, being a good alternative to statin intolerant patients with hypercholesterolemia but not with hypertriglyceridemia (49). They can also be administered in combination with either statins or ezetimibe to achieve the LDL reduction goals when they are not reached with statin monotherapy. Additional 10-16% reduction in LDL levels were observed when compared with statin monotherapy. Ezetimibe on top of the current bile acid sequestrant treatment showed an additional 10-20% reduction in LDL levels when compared with bile acid sequestrant monotherapy. The CV risk reduction has been proved through clinical trials to be proportional to the LDL levels reduction.

Furthermore, the LRC-CPPT (Lipid Research Clinics Coronary Primary Prevention Trial) study assessed the effects of cholestyramine after an average of 7.4 years versus placebo. The cholestyramine group experienced on average a 19% reduction in primary endpoint, namely CHD and nonfatal MI. LDL reduction was 12.6% greater than that of the placebo group. Contrarily, all causes of death rates were not significantly reduced (50).

According to the below presented studies, bile acid sequestrants prove to be effective lipid-lowering drugs, mostly in combined therapy with statins, improving CV outcomes, MI included.

Adverse effects

The most common adverse effects reported are gastrointestinal disturbances, including constipation, flatulence, stomach pain, vomiting, heartburn, loss of appetite and indigestion, and they can be diminished by a gradual dosage increase procedure. They can cause a slight TG increase and, therefore, are not indicated for patients with hypertriglyceridemia.

6.5. Residual risk

As stated above, the CV risk despite LDL-lowering treatment is still high. This is commonly referred as residual risk, and includes high TG rich lipoprotein and Lp(a) levels, low HDL levels and inflammation (51). It has been previously reported that elevated TG levels, low HDL levels and small and dense LDL particles, present in high-risk patients, can lead to atherosclerosis and, eventually, to AMI. Therefore, additional lipid modifying intervention may be needed (52), which will be briefly discussed in the following sections.

6.5.1. Peroxisome proliferator-activated receptor α (PPAR-α) agonists or fibrates

Fibrates are peroxisome proliferator-activated receptor α (PPAR-α) selective agonists prescribed to reduce plasma TG (53). PPAR-α are predominantly expressed in the liver, where they regulate gene transcription of enzymes involved in lipid metabolism. One of the genes modified by PPAR-α is that codifying for the LPL. Therefore, LPL activity is increased upon fibrate treatment, which reflects in a TG plasma levels diminution (54). Moreover, fibrates increase apolipoproteins A (ApoAs) expression, necessary for HDL assembling and functioning. Nowadays, three fibrates are available in the European Union: the selective PPAR-α agonists gemfibrozil and fenofibrate, and the pan-agonist alpha, beta and gamma bezafibrate. Clinical trials have proven the effectiveness of fibrates decreasing plasma TG by a 30% and increasing plasma HDL levels about 9% in patients with mixed dyslipidaemia and high TG baseline levels. Nonfatal MI odds were reduced by 22% (40). Some fibrates have also proven to decrease LDL but they are much less powerful than statins. Therefore, fibrates can be used as monotherapy for hypertriglyceridemia treatment and in combination with statins for mixed dyslipidaemia (55). Fenofibric acid on top of the current statin treatment shows greater reductions in TG, increases in HDL and LDL particles size shift from small to intermediate and large than statin monotherapy (52).

Sharma *et al.* (56) assessed the TG levels reduction after fenofibric acid or statin treatment and after their combination with different statin doses. After 12 weeks follow-up, fenofibric acid combined with low-dose statin resulted in 52.7% TG levels reduction, whereas low-dose statin monotherapy resulted in only 28.5% TG levels decrease. Treatment with moderate-dose statin showed a similar trend. The combined therapy showed a 53.8% TG levels reduction, and the statin monotherapy a 34.1%. Also, the TG levels reduction in this study after fenofibric acid was 39.6%.

As it has been previously mentioned in this review, T2DM is an important risk factor for AMI and ACS in general. Patients with T2DM also display a defective catabolism of TG, which reflects in elevated TG levels in plasma and, therefore, increased CV disease risk about two-fold on average and increased mortality risk after an ACS (29), worsening their prognosis. As an alternative to statin monotherapy, research has been made to analyse the benefits of fibrates in AMI risk reduction. The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial showed, after 5 weeks under 200 mg fenofibrate p.o., a 10% decrease in LDL levels, a 26% decrease in TG levels and a 6.5% increase in HDL levels (57).

Adverse effects

Fibrates are generally safe and well tolerated. They can cause increases in creatinine and homocysteine serum levels, though these have not been associated with an increased risk for renal failure in clinical trials (29). The main side effects reported are gastrointestinal disturbances and skin rashes. Myopathy is rarely associated with fibrates, but when it occurs, treatment must be discontinued. Otherwise, it can lead to rhabdomyolysis with its consequent kidney failure and death (58). Fenofibric acid is the only fibrate currently used in association with statins due to its lower intervention in their metabolism. It does not increase plasma statin concentrations, which could cause myopathy.

6.5.2. Other lipid-lowering drugs

Fasting TG levels proved effectiveness in long and short-term prediction of CV events in patients with ACS under statin treatment, suggesting a relation between fasting TG and residual CV risk. In addition, non-fasting TG levels are associated with ischemic disease and MI risk. In this regard, icosapent ethyl is an omega-3 polyunsaturated fatty acid

(PUFA) derivative which decreases the availability of non-esterified fatty acids in the circulation and, therefore, in the liver. Thus, VLDL synthetized in the liver will have less TG content. The REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention) trial showed, after one year under 4 g daily of icosapent ethyl on top of statin treatment, an 18% reduction in plasma TG. After 5 years follow-up, a 26% reduction in the secondary endpoints were observed, namely cardiovascular death, MI and stroke (51).

Matsuura *et al.* (51) analysed a large number of studies proving an inverse correlation between HDL and CV disease risk. This study revealed that, whereas small HDL particles were the most effective lipoproteins removing cholesterol, large HDL particles had the highest capacity of containing cholesterol. Furthermore, they also demonstrated that the function of both small and large HDL are altered in patients with ACS, suggesting that new strategies to rise HDL efflux capacity should be considered besides to increase its levels (51). Cholesteryl ester transfer protein (CEPT) is a protein that transfers the cholesteryl ester group from HDL to VLDL, chylomicrons, and their remnants, decreasing concentrations of the first while increasing concentrations of the last. Anacetrapib is a CEPT inhibitor, which leads to LDL depletion and the formation of larger HDL particles with increased content of cholesteryl ester (59).

Statin treatment generally do not diminish Lp(a) levels, making them a potential CV disease risk factor. Recent studies suggested that Lp(a) levels <50 mg/dL have beneficial impact on CV disease risk reduction, and this might be achieved with PCSK9 inhibitors, apo(a) antisense oligonucleotides or the CETP inhibitor anacetrapib (51). Furthermore, elevated levels in patients with chronic renal insufficiency proved to be related with higher MI and death rates, signalling them as an interesting lowering target for these individuals (51).

7. Conclusions

1. Statins are currently established as the leading treatment for primary and secondary prevention of AMI. High-dose statin treatment can reach up to a 55% LDL levels reduction, achieving LDL levels goal, but it is associated with only a 30% risk reduction in CV events and a 23% reduction in mortality of CV disease and non-fatal MI.
2. The current alternatives for patients intolerant to high-dose statin treatment are cholesterol absorption inhibitors, PCSK9 inhibitors and bile acid sequestrants, which also demonstrated to have improvements in CV risk reduction when added on top of the basal statin treatment.
3. Combined therapy of statins with ezetimibe, a cholesterol absorption inhibitor, has shown 22-26% LDL levels reductions beyond statins monotherapy, with an additional 2% absolute risk reduction in CV events.
4. Monotherapy with the mAbs alirocumab or evolocumab inhibiting PCSK9 have shown average LDL reductions by 60%. It has been related with a 12% risk reduction in primary endpoint risk, and further reductions up to 19% over time. Clinical trials have shown up to 27% reductions in MI risk, but there were no observed reductions in cardiovascular death rates. Contrarily, combined therapy with statins can reach up to a 40 to 70% LDL levels reduction, related with a 20% reduction in mortality rates.
5. Bile acid sequestrants monotherapy has shown an 18 to 25% reduction in LDL levels, reflected in an average 19% reduction in CHD and nonfatal MI, but all causes of death rates were not significantly reduced. Combined therapy with statins reflected an additional 10-16% reduction in LDL levels when compared with satin monotherapy. There are no data about the effects of the combined therapy on mortality rates, but it seems reasonable to deduce that it will induce comparable reductions in mortality.
6. Beyond LDL levels reduction, many patients still remain at high risk of having a CV event because of the residual risk, which includes high TG rich lipoprotein and Lp(a) levels, low HDL levels and inflammation.

7. Fibrates are established as the leading treatment for those patients with residual risk. Fibrates decrease plasma TG by a 30% and increase plasma HDL levels about 9% in patients with mixed dyslipidaemia and high TG baseline levels, which reflected a 22% reduced odd of nonfatal MI. These figures are even improved when fibrates are combined with statin treatment.
8. Until now, combined therapy with a lipid-lowering drug on top of statin treatment has helped improve outcomes, but results show that further improvements are needed. The recent discovery of monoclonal antibodies as lipid-lowering therapy is showing promising results in CV events risk reduction. New research focused on this approach should be developed to obtain more information about the antibodies safety and the benefits-cost relation.

8. Bibliography

1. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012 Oct 16;60(16):1581-98.
2. Pleister A, Selemon H, Elton SM, Elton TS. Circulating miRNAs: novel biomarkers of acute coronary syndrome? Biomark Med. 2013 Apr;7(2):287-305.
3. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's principles of internal medicine, 19th ed. New York: The McGraw-Hill Companies, Inc.; 2015
4. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018 Oct 30;72(18):2231-2264.
5. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ,et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016 Jan 26;133(4):e38-360.
6. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019 Mar 5;139(10):e56-e528.
7. Schiele F, Ecarnot F, Chopard R. Coronary artery disease: Risk stratification and patient selection for more aggressive secondary prevention. Eur J Prev Cardiol. 2017 Jun;24(3_suppl):88-100.
8. Version P. Acute Myocardial Infarction (MI) Pathophysiology. 2020;(Mi):1–13.
9. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. Lancet. 2017 Jan 14;389(10065):197-210. doi: 10.1016/S0140-6736(16)30677-8. Epub 2016 Aug

5. Erratum in: Lancet. 2017 Jan 14;389(10065):156.
10. Douglas G, Channon KM. The pathogenesis of atherosclerosis. Pathogenesis, risk factors and prevention. 2010;38(8): 397-402.
11. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Prim. 2019;5(1):1–18.
12. Nguyen MT, Fernando S, Schwarz N, Tan JT, Bursill CA, Psaltis PJ. Inflammation as a Therapeutic Target in Atherosclerosis. J Clin Med. 2019 Jul 26;8(8):1109.
13. Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. J Intern Med. 2014 Dec;276(6):618-32.
14. Ahmadi A, Argulian E, Leipsic J, Newby DE, Narula J. From Subclinical Atherosclerosis to Plaque Progression and Acute Coronary Events: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Sep 24;74(12):1608-1617.
15. Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W Jr, Rosenfeld ME et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation. 1994 May;89(5):2462-78.
16. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W Jr et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation. 1995 Sep 1;92(5):1355-74.
17. Granér M. Determinants of Coronary and Carotid Atherosclerosis in Finnish Patients with Clinically Suspected Coronary Artery Disease . A Quantitative Angiography and Ultrasound Study. 2007 May. 13
18. Anderson JL, Morrow DA. Acute Myocardial Infarction. N Engl J Med. 2017 May 25;376(21):2053-2064.
19. Siemieniuk RAC, Chu DK, Kim LH, Güell-Rous MR, Alhazzani W, Soccal PM et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018 Oct 24;363:k4169.
20. Abuzaid A, Fabrizio C, Felpel K, Al Ashry HS, Ranjan P, Elbadawi A et al. Oxygen Therapy in Patients with Acute Myocardial Infarction: A Systemic Review and Meta-Analysis. Am J Med. 2018 Jun;131(6):693-701.
21. Grup de Treball en Síndrome Coronària Aguda (SCA) del SEM. Codi IAM [Internet]. Generalitat de Catalunya Dep Salut; 2014 Mar [cited 2020 Feb 13]. 2p. Available from: http://canalsalut.gencat.cat/web/.content/_A-Z/I/infart_de_miocardi/codi_iam/documents/triptic_iam_def.pdf
22. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. Version 2. BMJ. 2011 Jan 11;342:c7086.
23. American Heart Association. What is Dual Antiplatelet Therapy? (DAPT)

[Internet]. Answers by Heart; 2017 [cited 2020 Feb 19]. 2p. Available from: https://www.heart.org/-/media/data-import/downloadables/a/b/d/answers-by-heart---dapt-ucm_493120.pdf

24. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018 Jan 7;39(2):119-177.
25. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators, Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet. 1999 Aug 28;354(9180):716-22.
26. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the management of patients with non-st-elevation acute coronary syndromes: Executive summary: A report of the American college of cardiology/American heart association task force on practice guidelines. Vol. 130, Circulation. 2014. 2354–2394 p.
27. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet. 2000 Jun 3;355(9219):1936-42.
28. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation. 1994 Apr;89(4):1545-56.
29. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-188.
30. Kinlay S. Early statin therapy in acute coronary syndromes. Minerva Cardioangiol. 2003 Oct;51(5):577-84.
31. Thompson GR. Management of dyslipidaemia. Heart. 2004 Aug;90(8):949-55.
32. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. JAMA. 2016 Sep 27;316(12):1289-97.
33. Stancu C, Sima A. Statins: Mechanism of action and effects. J Cell Mol Med. 2001;5(4):378–87.
34. Sehayek E, Butbul E, Avner R, Levkovitz H, Eisenberg S. Enhanced cellular metabolism of very low density lipoprotein by simvastatin. A novel mechanism

of action of HMG-CoA reductase inhibitors. Eur J Clin Invest. 1994 Mar;24(3):173-8.
35. Zhang X, Hu D. [Comments for 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults]. Zhonghua Nei Ke Za Zhi. 2015 Jan;54(1):9-12.
36. Mandeep S. Practical Approach to Managing Dyslipidemia: Role of Statins. Cardiol Advis. 2018;1–9.
37. American Diabetes Association. 9. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes-2018*. Diabetes Care. 2018 Jan;41(Suppl 1):S86-S104.
38. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. Version 2. BMJ. 2009 Jun 30;338:b2376.
39. Fujisue K, Tsujita K. Current status of lipid management in acute coronary syndrome. J Cardiol. 2017 Aug;70(2):101-106.
40. Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease--a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J. 2007 Nov;154(5):943-53.
41. Tomaszewski M, Stępień KM, Tomaszewska J, Czuczwar SJ. Statin-induced myopathies. Pharmacol Rep. 2011;63(4):859-66.
42. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovasc Drugs Ther. 2005 Dec;19(6):403-14.
43. Khanderia U, Regal RE, Rubenfire M, Boyden T. The ezetimibe controversy: implications for clinical practice. Ther Adv Cardiovasc Dis. 2011 Aug;5(4):199-208.
44. Gagné C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, et al. Ezetimibe Study Group. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol. 2002 Nov 15;90(10):1084-91.
45. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 18;372(25):2387-97.
46. Vavlukis M, Vavlukis A. Adding ezetimibe to statin therapy: latest evidence and clinical implications. Drugs Context. 2018 Jul 9;7:212534.
47. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017 May 4;376(18):1713-1722.
48. Kodera S, Morita H, Kiyosue A, Ando J, Takura T, Komuro I. Cost-Effectiveness of

PCSK9 Inhibitor Plus Statin in Patients With Triple-Vessel Coronary Artery Disease in Japan. Circ J. 2018 Sep 25;82(10):2602-2608.
49. Wiklund O, Pirazzi C, Romeo S. Monitoring of lipids, enzymes, and creatine kinase in patients on lipid-lowering drug therapy. Curr Cardiol Rep. 2013 Sep;15(9):397.
50. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017 Oct 3;70(14):1785-1822.
51. Matsuura Y, Kanter JE, Bornfeldt KE. Highlighting Residual Atherosclerotic Cardiovascular Disease Risk. Arterioscler Thromb Vasc Biol. 2019 Jan;39(1):e1-e9.
52. Goldfine AB, Kaul S, Hiatt WR. Fibrates in the treatment of dyslipidemias--time for a reassessment. N Engl J Med. 2011 Aug 11;365(6):481-4.
53. Grupo de trabajo de la Guía de Práctica Clínica sobre el manejo de los lípidos como factor de riesgo cardiovascular. Guía de Práctica Clínica sobre el manejo de los lípidos como factor de riesgo cardiovascular [Internet]. Donostia-San Sebastián: Ministerio de Sanidad, Servicios Sociales e Igualdad. OSTEBA; 2017 Apr [cited 2020 Feb 18]. 195p. Available from: https://portal.guiasalud.es/wp-content/uploads/2018/12/GPC_567_Lipidos_Osteba_compl.pdf
54. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation. 1998 Nov 10;98(19):2088-93.
55. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010 May 29;375(9729):1875-84.
56. Sharma A, Joshi PH, Rinehart S, Thakker KM, Lele A, Voros S. Baseline very low-density lipoprotein cholesterol is associated with the magnitude of triglyceride lowering on statins, fenofibric acid, or their combination in patients with mixed dyslipidemia. J Cardiovasc Transl Res. 2014 Jun;7(4):465-74.
57. Scott R, Best J, Forder P, Taskinen MR, Simes J, et al. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: baseline characteristics and short-term effects of fenofibrate [ISRCTN64783481]. Cardiovasc Diabetol. 2005 Aug 22;4:13.
58. Jacobson TA, Zimmerman FH. Fibrates in combination with statins in the management of dyslipidemia. J Clin Hypertens (Greenwich). 2006 Jan;8(1):35-41; quiz 42-3.
59. Tall AR, Rader DJ. Trials and Tribulations of CETP Inhibitors. Circ Res. 2018 Jan 5;122(1):106-112.