SCHOOL OF BIOLOGICAL SCIENCES

BSc (Hons) Biology

Analysing the regressive effects of statins on coronary plaques: A detailed insight into coronary artery disease

JOHN BONAPOS
UP887399

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Supervisor: Dr Alessandro Siani

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Contents

Abstract

Coronary artery disease (CAD/CHD) is a condition that occurs when the blood vessels supplying oxygen to the heart become damaged or narrowed as a result of atherosclerosis, a disease characterised by the accumulation of fatty plaque composites within the blood vessels. The narrowing of these vessels results in significantly reduced blood flow which can lead to acute coronary syndromes including ischemia or heart failure. This systematic review provides an insight on the use and effectivity of statins on regressing plaque accumulation towards the treatment of CAD. All papers used were sourced from PubMed and strictly assessed based on their relevance to statins, cholesterol, and coronary plaques. The chosen criteria narrowed the articles to that of those specifically analysing the effects of statins upon plaque deterioration. The main findings concluded that all statin types either stabilised or significantly lowered plaque development in patients. Although, not all studies were 100% successful and higher doses were required for more effective treatments.

1 Introduction

1.1 Coronary Artery Disease/Coronary Heart Disease (CAD/CHD)

Coronary Arteries are arterial blood vessels situated around the heart which continuously provide the organ with oxygenated blood. CAD is the resulting disorder that is caused when these blood vessels become damaged mainly due to narrowing. There are various recognised associated risk factors such as sex, genetic predispositions, lifestyle choices and general ageing, making CAD the most prevalent category of heart diseases worldwide. It is estimated to be responsible for roughly 370,000 deaths annually, accounting for 1 in 7 US deaths. (J. Adam Leigh et al, 2016) It occurs as a result of the narrowing of the lumen due to plaque accumulation and inflammation resulting in obstructed blood flow to the heart. This can lead to more serious coronary events such as superimposed thrombosis or complete coronary blockages which could induce a myocardial infarction potentially causing death. In fact, approximately 76% of all fatal coronary thrombi are precipitated by plaque rupture. (Erling Falk MD, 2006)

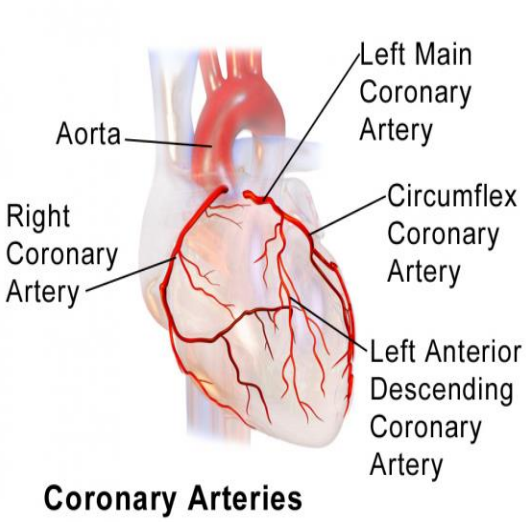

Figure 1- Heart diagram showing annotations of artery locations (The society of Thoracis Surgeons, 2015)

The symptoms can vary between individuals, but they predominantly consist of shortness of breath, general weakness, nausea, and pains in heart area followed by angina which is a tight sensation in the chest usually triggered by physical and emotional stress.

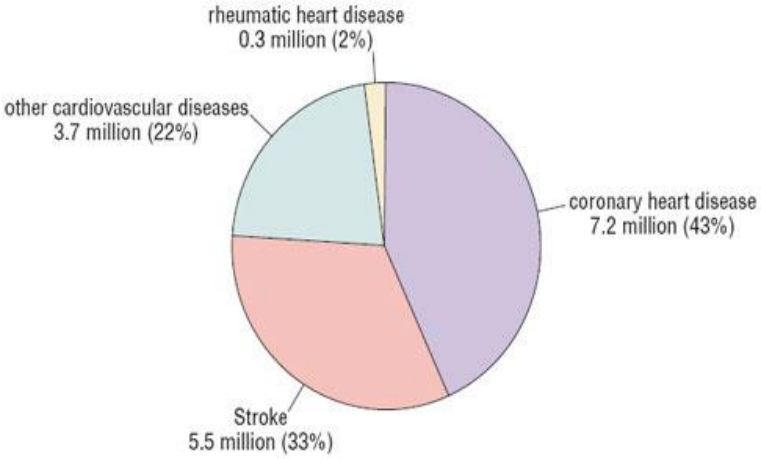

Figure 2 - Pie chart depicting global deaths from various cardiovascular diseases in 2002 (Mackay J & Mensah G, 2004)

1.2 Atherosclerosis & Atherosclerotic Plaque (Atheroma's)

Atherosclerosis is a disease affecting large and medium-sized arteries, they are generally characterized by endothelial dysfunction, vascular inflammation, and plaque formation within the arterial wall. Essentially it is a disease characterised by the accumulation of plaques (Atheroma's) within the arteries causing blockages. (Gillian Douglas, Keith M. Channon, 2014)

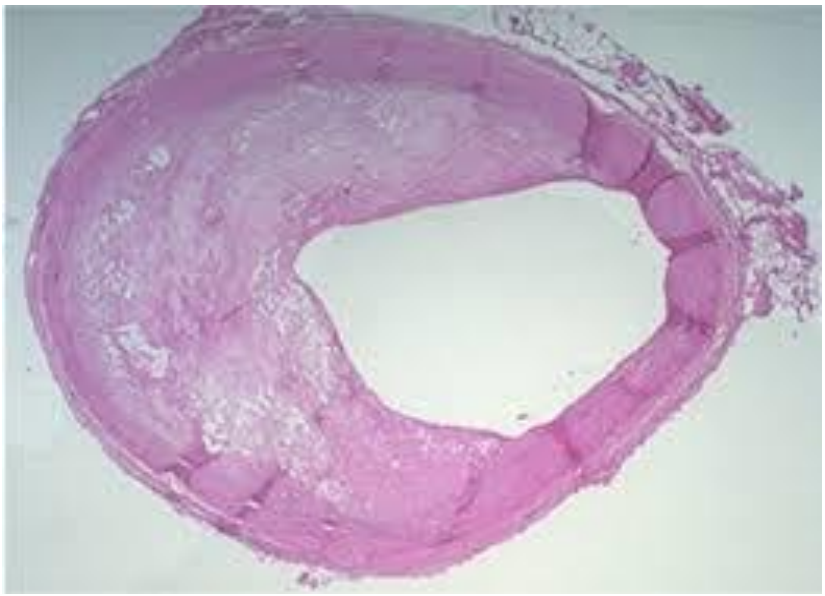

Figure 3 - Histology showing an atheroma mass on the left side occupying the majority of the lumen. Note that the right side appears normal. Boston University School of Public Health (2016)

Initial assumptions idealised atherosclerosis as a degenerative consequence of ageing, however we now know that it is a chronic inflammatory condition with potential to become an acute clinical event by plaque rupture and thrombosis. (A J Lusis, 2000) Furthermore, existing studies on children with this condition of course rules out the idea that atherosclerosis excludes younger individuals. Atherosclerosis is unlikely to be fatal alone, it is the potential superimposed thrombosis that can lead to strokes, heart attacks and acute coronary syndromes that can cause death.

Atheroma's are abnormal accumulations of debris, fatty composites, foam cells and other material within the inner wall of the artery and are widely associated with CAD. Characterised as raised protruding lesions in the lumen consisting of a cholesterol core and a fibrous cap. They are mainly composed of macrophages, lipids, calcium, tissue, and other debris. In the event of a rupture all this material can be released causing thrombosis and restricting blood flow potentially causing acute infarction in associated arteries. In western countries, Atherothrombotic complications are the leading causes of disability and mortality. (C Camaré et al, 2017)[5]

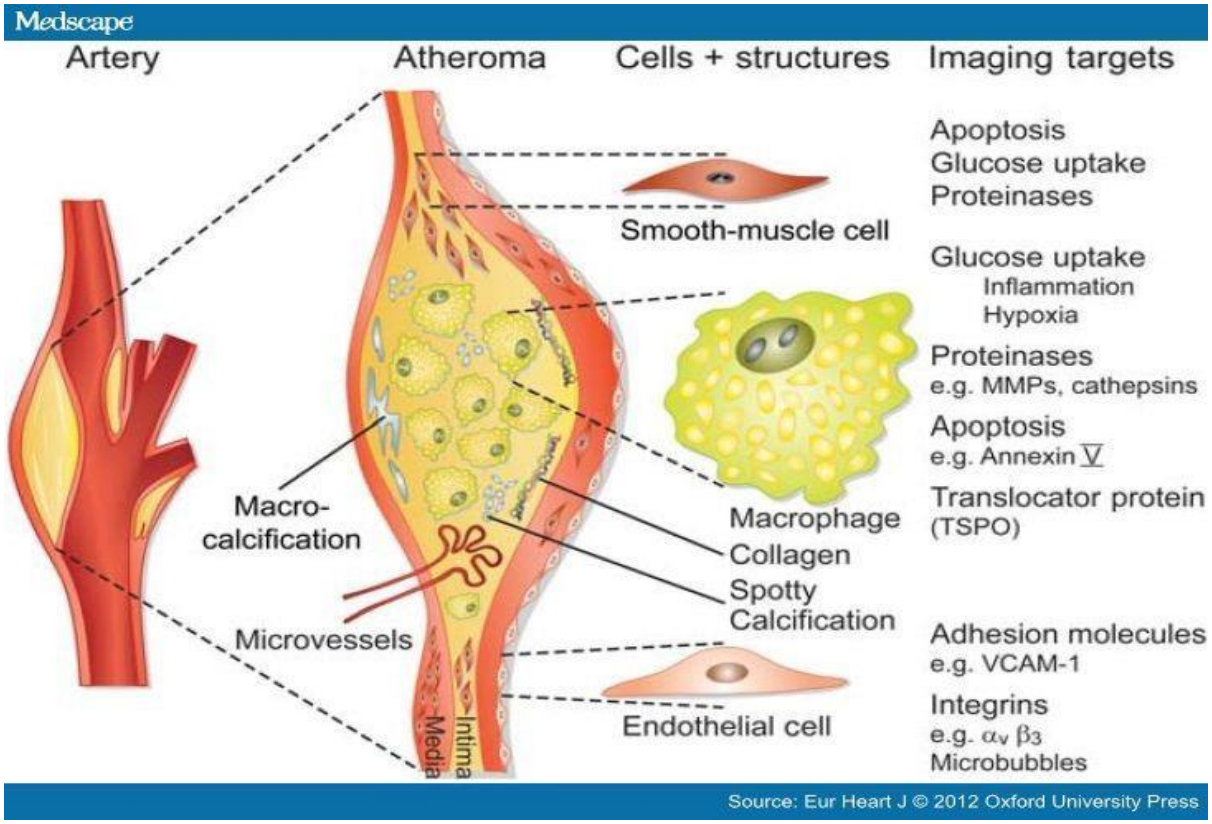

Figure 4 - An annotated micro-environment of an atheroma showing the cells, molecules and structures involved in its development and stability. Eur Heart J (2012) Oxford University Press

1.3 Pathogenesis

The main causes for atherosclerosis are established however some elements still hold unfamiliarity. We know that the process for development involves a series of complex molecular and cellular interactions. It has been observed that plaque formation is a disease process associated with elevated low-density lipoprotein (LDL) cholesterol levels. This along with increased concentration of apolipoprotein-B molecules and their accumulation at selected sites can be a sufficient enough cause for the development of atherosclerosis (Erling Falk et al, 2014) These LDL molecules and other apoB-containing proteins can readily enter and exit the arterial intima allowing for efficient transfer and accumulation of necrotic core components. (Eur Heart J. 2014)

The diseases' progression starts with the damaging of the endothelial layer of cells that line the arterial wall, this can be caused by numerous factors such as hypertension, smoking, hyperglycaemia hypercholesterolemia and increased LDL concentration. Endothelial cell damage increases the permeability of the arterial wall allowing LDL accumulation in the tunica intima. Compromised endothelial cells express adhesion molecules that capture monocytes. This firm attachment of monocytes to the endothelium is mediated by interactions with intercellular adhesion molecule 1 (ICAM1) or vascular adhesion molecule 1 (VCAM1) and integrin VLA-4 between the endothelium and monocytes. (Z. Chi, A J. Melendez, 2008) This attachment allows for the monocyte to squeeze between the endothelial cells, moving from the bloodstream into the intima in a process known as diapedesis. These monocytes then produce free radicals that in turn oxidise LDL producing OxLDL (oxidised LDL) particles which attract and activate more monocytes. They then engulf these LDL particles producing more OxLDL particles establishing a positive feedback of OxLDL accumulation and white blood cell migration. OxLDL directly activates endothelial cells to stimulate monocyte

migration towards the tunica intima of the artery where they differentiate into macrophages. The cytokine M-CSF plays a significant role in stimulating this differentiation (M E Rosenfield et al, 1992) The Macrophages in the tunica intima also engulf these OxLDL particles ultimately leading to the production of a foam cell saturated in modified LDL particles. This is what gives the cytoplasm a foamy appearance. These particular cells are what enhance the inflammatory response, their accumulation is what leads to fatty streak formation – the first stage in plaque development. (Gillian Douglas, Keith M. Channon, 2014) Foam cells then die releasing their contents which are engulfed by other macrophages further reinforcing the positive feedback loop for OxLDL production. Eventually the accumulation of lipids and dead cells produce an area with a lipid core which soon becomes a plaque. Endothelial cells cover the plaque, and the plaque continues to accumulate dead cells and also calcium salts causing it to harden forming an atheroma. Atherosclerosis is what occurs as a result of this plaque build-up and is the most common underlying cause of coronary artery disease. Elevated plasma cholesterol levels are probably the most sufficient unique cause for driving atherosclerosis development. While risk factors such as diabetes, hypertension, smoking, and sex (being male) are also associated with this and could contribute alongside its development. (Erling Falk, 2006)

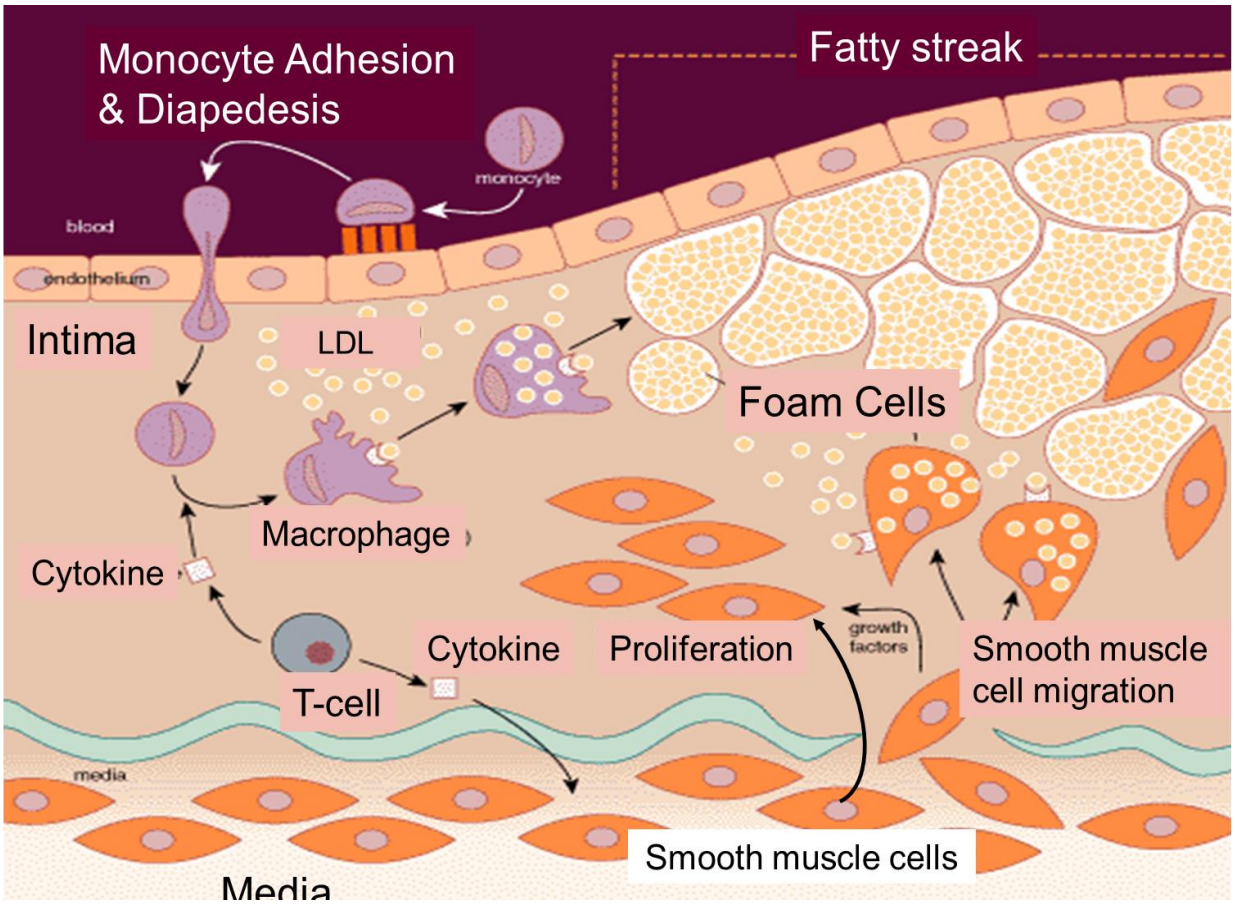

Figure 5 - A microenvironment showing the stages involved in foam cell development (Boston University School Public Health, 2016)

1.4 Aetiology and Prevalence

The aetiology of CHD is multifactorial, it can arise from a combination of genetic, lifestyle and environmental factors. Poor lifestyle choices are seemingly estimated to account for one third of all deaths from CHD in the UK. Atherosclerosis is much more likely to occur in older individuals, possibly due to the association between ageing and the increased chances of developing disorders with atheromatic predispositions e.g., obesity, and diabetes. (Br Med J, 1951) Surprisingly ethnicity has been known to be associated with this disease development. Certain ethnic minority groups in the USA were observed to have higher rates of CAD risk factors, excess morbidity, and CHD mortality when compared to the non-Hispanic white population. (J. Adam Leigh, M Alvarez, C. J Rodriguez, 2016)

Cardiovascular diseases (CVDs) are so prevalent that they were the leading cause of mortality and a major cause of morbidity in the 20th century with coronary artery disease being the most common cause accounting for around 42% of all CVD-related deaths(M. Jolly, L. Cho 2004). Prevalence is higher in lower socio-economic groups and as mentioned before ethnic minority groups. One example being South Asians in the UK who have a notably higher premature death rate from CHD (46% higher for men; 51% higher in women) Reasonable assumptions include migration, lower socio-economic status, poorer diets, and biological factors such as high levels of homocysteine, lipoprotein, and enhanced plaque. (Dr Colin Tidy, 2014)

1.5 Risk Factors

Age

Older individuals have higher chances of developing CAD for reasons mainly to do with greater likelihoods of developing medical conditions such as diabetes, obesity, decreased HDL/cholesterol level, increased blood pressure and decreased vessel elasticity (P. Jousilahti, E. Vartiainen, J. Tuomileehto, P. Puska, 1999) Furthermore, abnormalities in cholesterol metabolism play a role in atherosclerosis development through the promotion of LDL accumulation, that being said it is not uncommon for an increased cholesterol level in elderly individuals especially men as a result of this.

Lifestyle

Lifestyle choices such as a person's diet, habits e.g., smoking and/or drinking and exercise can greatly influence their susceptibility to developing coronary heart diseases. For example, smoking causes multiple events that can increase the risk of acute coronary syndromes like CAD. These things can include platelet clumping, coronary spasms, arrythmias, decreased HDL and reduced oxygen intake. (Healthwise University of Michigan, 2020)

Diets high in saturated fats (high level of triglycerides), sugar and alcohol are associated with premature CAD. This likely occurs in overweight individuals which increases the chance of having high blood pressure, diabetes, and hypertension. Being physically active can improve this drastically and can help control weight gain, blood pressure and fat accumulation.

Genetics

Coronary artery disease has significant genetic underpinnings deemed equivalent to that of environmental factors with an estimated heritability of around 40%-60%. (R. Mcpherson, A.

Tybjaerg-Hansen, 2016) First-degree relatives of patients with premature myocardial infarction were observed to have double the risk themselves.

In 2007 the first genome wide association study was published with the main finding being that a locus on chromosome 9p21 being widely associated with coronary artery disease. (Wl Lieb, R.S, Vasan, 2014) Even further studies have found that this particular locus is related to a wide range of vascular phenotypes such as myocardial infarction, aortic aneurysms, artery calcification and peripheral artery disease aswell as CAD. In addition, experimental studies have found a susceptibility to atherogenic stimuli in mice in which the inactivation of genes coding for MCP-1, its macrophage receptor CCR2 and macrophage colony-stimulating factor has contributed to atherosclerosis development. (Erling Falk MD, 2006)

Sex

Coronary artery disease is remarkably more common in men then woman. A study on cardiovascular disease risk factors on Finnish participants found that CAD prevalence was three times greater in men than woman and mortality was also five times higher. (P. Jousilahti, et al. 1999) This may be because men are more likely to experience and endure physical stress compared to women while also being more prone to obesity in their lifetime. Holding more fat around the abdominal area makes a person more prone to heart disease, high blood pressure, high cholesterol, and diabetes. (Brenda Goodman, 2011)

Table 1 – Presenting the mortality and societal impact rates of cardiovascular disease within the continents and worldwide (source unknown)

	AFR	AMR	EUR	SEAR	WPR	EMR	World
Mortality in thousands							
Ischemic (CAD)	346	925	2,296	2,011	1,029	579	7,198
Cerebrovascular	425	461	1,364	1,074	2,128	254	5,712
Rheumatic	11	10	30	129	93	25	298
Hypertensive	78	151	179	156	316	103	987
All CVDs	1,175	1,969	4,767	3,875	4,094	1,163	17,073
Societal impact in millions of DALYs							
Ischemic (CAD)	3.51	6.52	16.83	21.58	7.88	6.15	62.59
Cerebrovascular	4.88	3.99	9.53	9.60	15.84	2.70	46.59
Rheumatic	0.32	0.14	0.41	2.49	1.23	0.59	5.19
Hypertensive	0.82	1.11	1.14	1.69	2.30	0.94	8.02
All CVDs	14.24	15.22	34.76	14.24	31.78	13.10	151.38

1.6 Treatments & Diagnosis

Initial objectives are to identify thrombosis-prone plaques early in patients and providing immediate treatment to reduce the risk of acute coronary syndrome. (Erling Falk MD, 2006) According to the NHS diagnosis usually involves a risk assessment and then further examinations if required. The assessment usually involves genetic background, blood cholesterol and blood pressure checks, while further would involve the use of more sophisticated methods such as

ECG's, X-rays, MRI, and CT scans. CT Angiography is the most commonly used method for plaque identification in the majority of the studies. It involves the combination of a CT scan and injection of a dye to create pictures of the targeted areas such as blood vessels. Slightly newer methods for instance intravascular ultrasonography (IVUS) can be used to examine atherosclerotic plaques for the characterization and early staging of CAD.(E. Escolar et al, 2006)

The main treatments are lifestyle changes and drugs especially those that specifically lower cholesterol. Adopting a healthier and fitter lifestyle it probably the greatest way to promote healthier arteries and combat all heart diseases. Changes like quitting smoking, healthier diets, regular exercise, and reduced stress can all contribute to improved blood circulation, heart function and vessel elasticity.

Administrative drugs are another alternative option and there are various options for these to be used depending on the patient's condition.

- Cholesterol-modifying medications such as statins being the most popular. These medications reduce the level of material deposits that accumulate in coronary arteries especially decreasing the concentration of LDL cholesterol.

- Aspirins may be used to promote blood thinning to reduce the risk of blood clotting.

- Beta-blockers can be used to slow the heart rate and decrease blood pressure, which can be useful to patients who have recently experienced acute coronary syndromes. Beta blockers reduce the chances of future attacks.

- Calcium channel blockers and Ranolazine can be used along side betablockers to relieve symptoms of chest pain

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBS) These drugs are used to decrease blood pressure and assist in prevention of CAD development.

Statin side effects

Statin therapy although extremely beneficial, it also carries some potentially dangerous side effects.

Muscle aches or pains

- Although this may not be anything to be concerned about, you should tell your doctor about it. This is because there is a rare but serious side-effect of atorvastatin which is a severe form of muscle inflammation

Headache

- Drink plenty of water and ask your pharmacist to recommend a suitable painkiller. If the headaches continue, let your doctor know

Constipation

- Try to eat a well-balanced diet and drink plenty of water each day

Diarrhoea

- Drink plenty of water to replace any lost fluid

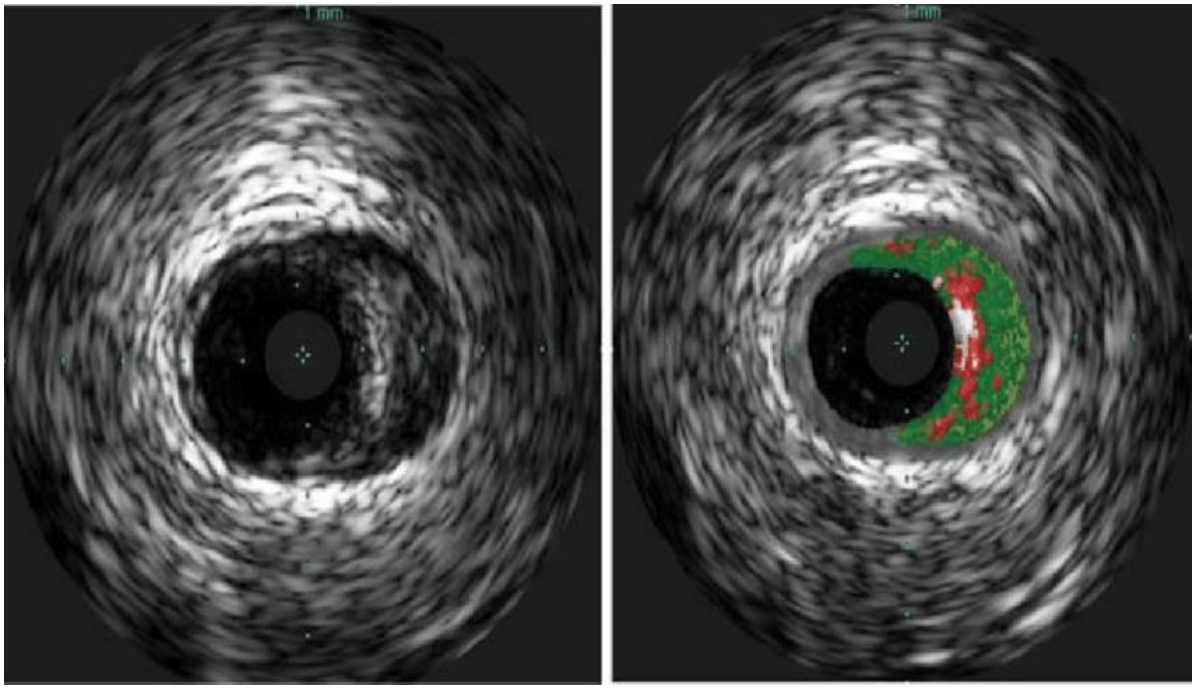

Figure 6 - A plain IVUS image (left), IVUS + Virtual Histology (right) with both depicting a plaque situated on the right-hand side of the imaging catheter (grey circle) Image on the right displays' plaque characteristics, calcification as white, necrotic core as red, fibrous tissue as dark green, and fibro fatty tissue as light green (M T.E Hopman, et al 2018)

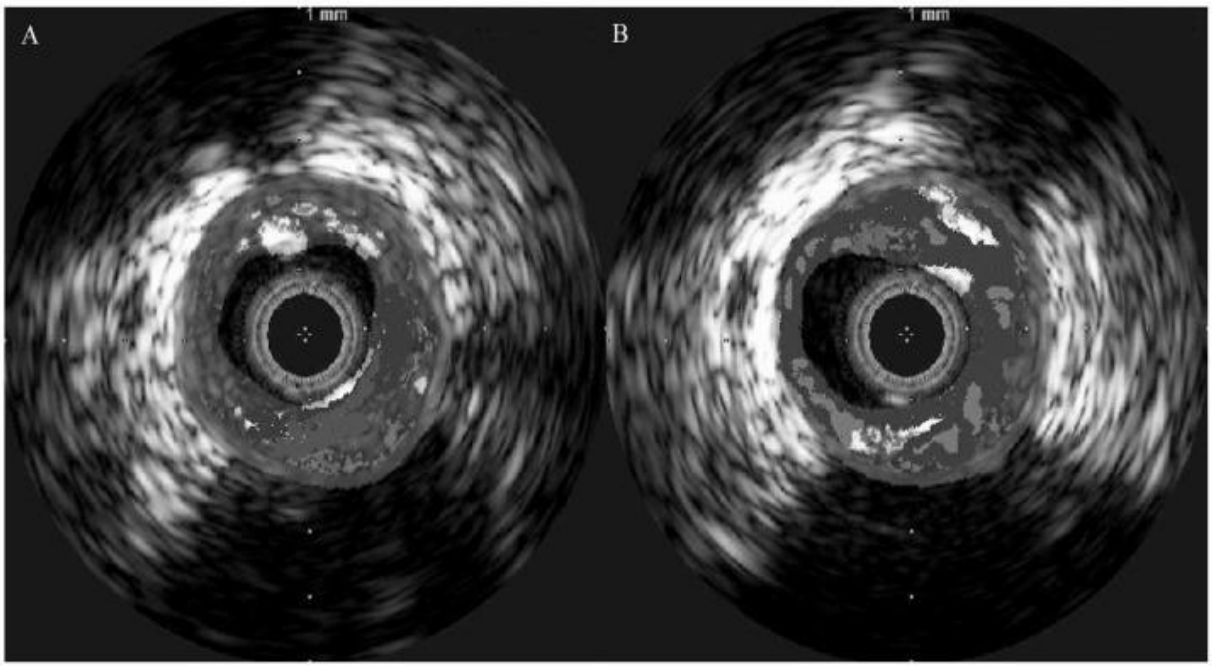

Figure 7 - Intravascular Ultrasound (IVUS) of 2 different plaques (A) Unstable plaque. (B) stable plaque . (Guo. S, et al. 2012)

1.7 Statins

HMG-CoA reductase inhibitors also known as statins are the most efficient hypolipidemic compounds know to significantly reduce the incidence of coronary events in both primary and secondary prevention. Consequently, they are vital as a means of decreasing the mortality rate in coronary patients. They are prescribed as a means for lowering the cholesterol levels to decrease plaque development and so reduce the risk of potential cardiovascular diseases. Statins work by interfering with one of the stages involved in cholesterol synthesis, they inhibit the enzyme HMG-CoA reductase preventing the production of mevalonic acid and thus inhibiting cholesterol production. Furthermore, since mevalonate is the precursor for other steroidal isoprenoid compounds interfering with its production can also lead to pleiotropic effects.

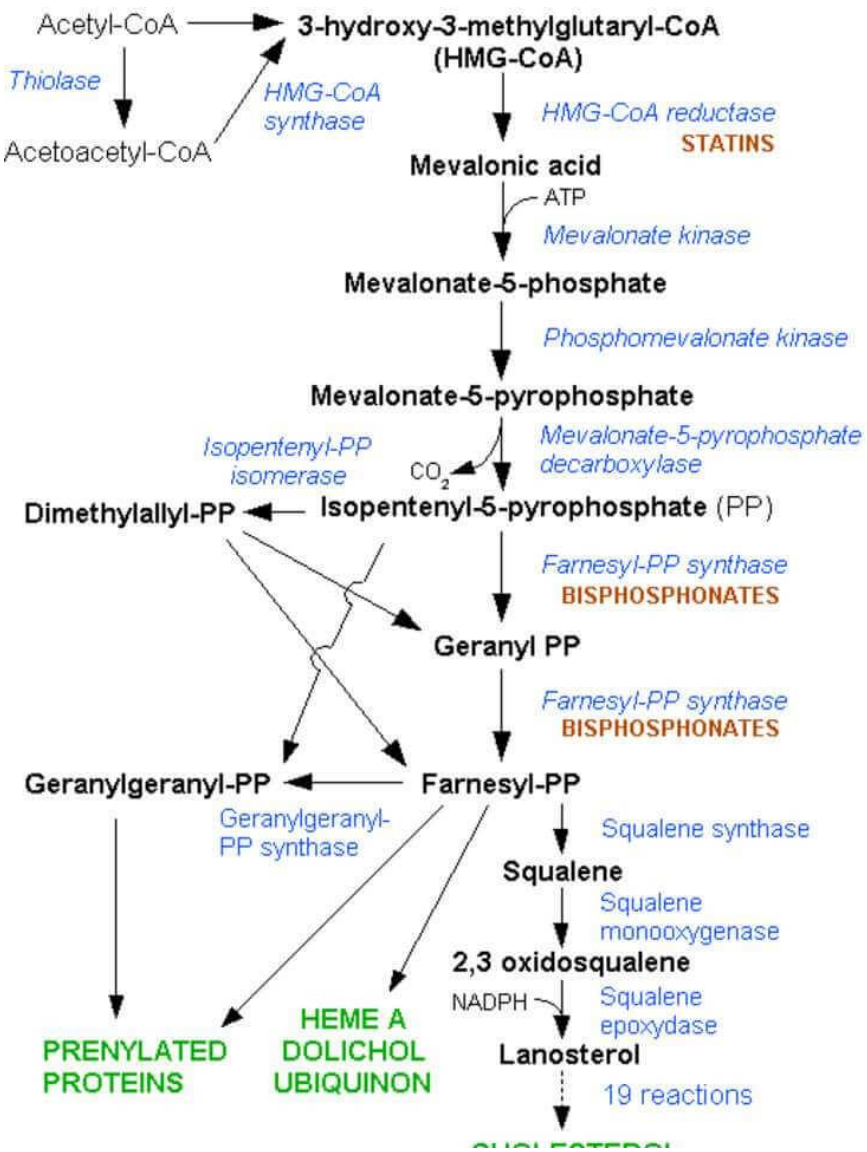

Figure 8 - Cholesterol synthesis pathway (EpoMedicine, 2020)

1.8 Aims and Hypothesis

There are many types of statins that are administered to patients with the objective to reduce and regress coronary plaque development. With each variant being better for administration depending on the patients' specific coronary conditions. Further research on these statins can help us gain a better understanding on the effects of these drugs and therefore provide improved treatment methods for patients. The studies aim is to identify the effects of statin treatments have on plaque regression and evaluate which statins are most effective and at what suggested doses. Statins are such a widely used drug therefore there are a lot of existing studies investigating their effects. To ensure they remain safe to for administration regular trials and reviews should be done to determine if there are any potential new side effects or applications for other areas in medicine.

2 Methods of Investigation – Inclusion/Exclusion Process

2.1 Search query and database

Prisma guidelines were followed for this systematic review, the search query is as displayed below:

("Coronary Atherosclerotic Plaque" OR "Coronary Heart Disease" AND (Statins OR "HMG-CoA reductase inhibitors)) NOT cancer [Title/Abstract] NOT Diabetes [Title/Abstract]

PubMed was the main database source for this review, with all papers to be reviewed were exclusively derived. Data collection started on October 12th, 2020 and finished on January 6th, 2021.

The key words within the search query were precisely selected to find papers related to statins and its association with coronary plaques. The use of medical subject heading terms (MeSH) such as "Coronary Plaque", "Atherosclerotic Plaque" and "Coronary Heart Disease" were vital in order to find a wider range of scientific publications without the requirement for multiple terms. It was necessary to use the term "Coronary Heart Disease" to ensure that papers that could include potentially significant information of coronary plaque were not ruled out. There were no specific date ranges for the articles.

The phrases "NOT Cancer" [Title/Abstract] and "Not Diabetes" [Title/Abstract] were included to avoid non-essential articles on cancers and diabetes. It was particularly important that the search engine excluded these papers due to their substantial article pool and relation to coronary heart diseases.

2.2 Exclusion Procedure

The articles displayed upon the initial raw search underwent a series of exclusion stages. These first stage papers were filtered out for: inaccessible text, duplicates, reviews, and foreign languages. Although most review papers were removed, exceptions were made for some due to their relevance in other studies.

Following this, a more precise exclusion stage was carried out to isolate the papers truly relevant to the study, in this case those reporting strictly on the association between statins and coronary plaque were selected. Articles on other diseases, organs and different treatments are irrelevant and therefore not included. Research articles that were written on carotid artery disease and associated cerebral strokes were excluded since this review does not focus on those aspects. Studies undertaken on animals were eliminated as any findings would not be representable for human diagnosis however, they have provided an alternative insight on statin effects.

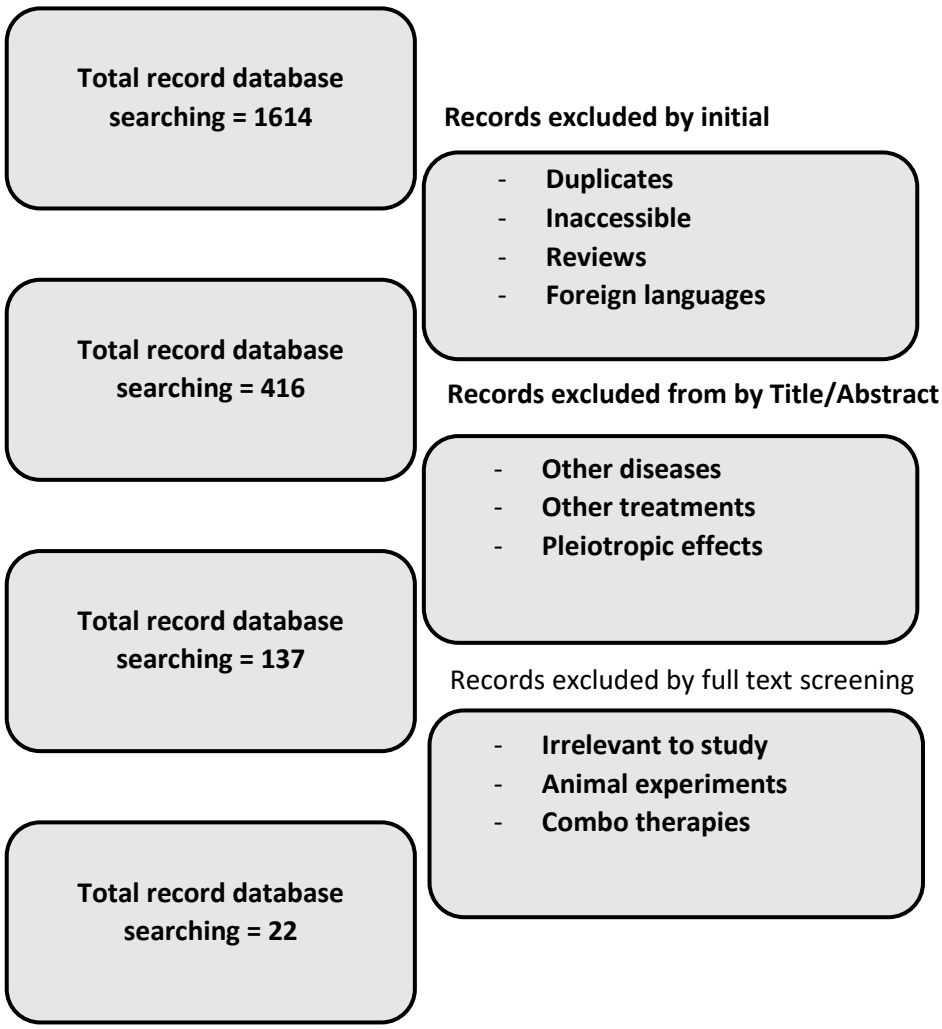

Figure 9 - A flowchart diagram representing the exclusion criteria for the articles sourced from PubMed

Note: A mistake leading to limitation occurred within the exclusion principal stage. There was an issue with the search phrases which could have potentially caused key studies to be excluded from data collection. Original search : (“Coronary/Atherosclerotic Plaque” AND (“Statins OR Coronary Heart Disease” OR “HMG-CoA reductase inhibitors)) NOT cancer [Title/Abstract] NOT Diabetes [Title/Abstract].

3 Information and Evaluation

3.1 Final Pool Summary

A total of five statin variants were studied across the entire final pool and the majority demonstrated successful changes in plaque volume after statin therapy so all variants can be deemed widely successful. The articles were examined for any significant changes in the plaque volume from baseline to follow up, while other key changes were also noted. However, some articles measured alternative mechanisms such as LDL cholesterol concentration which made it difficult to draw strict conclusions for the entire review. Some papers also had varying doses throughout the trial administering more after a certain past date some of these were accounted for. The papers were assorted according to the statins administered to the patients during the study. Note that all studies have different ranges for trial duration and dosage as well as the number of patients involved. The reported plaque volume changes were recorded, and the mean was calculated for each study which is displayed in Table 2 below.

Table 2 - Percentage change of plaque volumes reported by articles, according to statin type, duration, and number of patients

Articles (name/year)	Statin Type	Duration	Dosage (mg/day)	Number of Patients	Mean plaque volume % change
Guo, S.E. et al (2012)	Atorvastatin	3-6 months	80	39	-31.47%
Hirayama, A. et al (2009)	Atorvastatin	18 months	10-20	57	-17.8%
Hong, Y.J. et al (2010)	Atorvastatin & Rosuvastatin	11 months	Atorvastatin: 40 Rosuvastatin: 20	(A)Atorvastatin=63 (R)Rosuvastatin=65	-18.8% BUT, 15% of patients in group R showed plaque increase and 30% in group A
Inoue, K. et al (2010)	Fluvastatin	12 months	NA	24	-17.22%
Kodama, K. et al (2010)	Pitavastatin	12 months	2	90	N/A
Lee, S.W. et al (2012)	Atorvastatin	6 months	40	46	-4.28%

Makuuchi, H. et al (2005)	Pravastatin	60 months	NA	168	N/A BUT, decrease in LDL cholesterol is 19.6%
Miyauchi, K. et al (2006)	Atorvastatin & Pitavastatin	8-12 months	NA	NA	NA
Nasu, K. et al (2009)	Fluvastatin	12 months	NA	40	N/A BUT fibro fatty volume decreased by -59.4%
Nishiguchi, T. et al (2018)	Pitavastatin	1-8 months	4	53	N/A INSTEAD fibrous cap percentage increase by 8.3%
Noguchi, T, et al (2015)	Pitavastatin	12 months	10-20	48	-18.9%
Okada, K. et al (2012)	Atorvastatin	18 months		29	NA BUT LDL-C levels reduced by -44.47%
Otagiri, K et al (2011)	Rosuvastatin	6 months	40	20	-18.49% (plaque volume) -35.14% (lipid volume) -37.6% (LDL-C)
Park, S.J. et al (2016)	Rosuvastatin	12 months	40	312	-7.09%
Raber, L. et al (2019)	Rosuvastatin	13 months	40	103	N/A BUT LDL-C levels reduced by -40.16%
Raber, L. et al (2015)	Rosuvastatin	13 months	40	103	Atheroma volume reduced by -0.9% LDL-C reduced by -42.55%
Soeda, T. et al (2011)	Rosuvastatin	6 months		24	-17.09%

Solem, J. et al (2006)	**Atorvastatin**	**2 ½ months**	**80**	**22**	**No significant changes in plaque components BUT reduced T-cell content**
Takano, M. et al (2003)	**Atorvastatin**	**12 months**	**NA**	**15**	**NA BUT LDL-C decreased by 45%, plaque Yellow score decreased from 2.08 to 1.13**
Takashima. H. et al (2007)	**Pitavastatin**	**N/A**	**2**	**41**	**-10.6% LDL-C – 53.2%**
Takayama, et al (2009)	**Rosuvastatin**	**17 months**	**2.5-20**	**126**	**-5.1% LDL-C -38.6%**
Matsushita, K. et al (2016)	**Atorvastatin Pitavastatin Pravastatin Fluvastatin**	**10 months**	**Atorvastatin 20 Pitavastatin 4 Pravastatin 10 Fluvastatin 30**	**118**	**Atorvastatin: -11.1% Pitavastatin: -8.1% Pravastatin: -0.4% Fluvastatin: -3.1%**

3.2 Statin variants reviewed

Out of the five statin variants included in the studies Atorvastatin and Rosuvastatin were the most widely administered to patients. Globally these 2 statin variants are the most used worldwide and are regularly administer to patients with cardiovascular disease, so it makes sense as to why there are more studies done on them. Nine papers focus on atorvastatin and seven on rosuvastatin, six studies involved Pitavastatin, two studies on Fluvastatin, and on Pitavastatin. The remain articles do not mention the use of a specific statin. The majority of the studies concluded that the statins administered all had significant effects on either stabilising/regressing coronary plaques or reducing concentrations of plaque components such as LDL cholesterol and total lipid volume.

4. Discussion

4.1 Evaluation of Atorvastatin as a means for promoting coronary plaque regression

Focusing on the findings for each statin starting with atorvastatin, The data concluded that Atorvastatin was very successful in regressing plaque content and since results on Atorvastatin therapy was the most abundant with similar findings, we can agree that these are significant. It seems that this statin is more efficient when administered at higher dosages (Lee, S. W, et al 2012) especially at around 80mg/day. (Guo, S.E et al, 2012) Reasons for its significant effectivity could possibly be due to its association with adequate LDL cholesterol reduction reported to be around -44.47%. (Okada. K, et al 2012) Furthermore, it also contributes to reduced T-cell content in early treatments (Solem J. et al, 2006) as well as early loss off colour in plaques where it was found to decrease their yellow score significantly after 12 months. (Atsushi Hirayama et al, 2004 and Takano. M, et al 2003) On the other hand, one study by Young Joon Hong, et al (2010) found that out of 128 patients, 29 had shown an increased in plaque volume even after Atorvastatin treatment suggesting that there are possible factors that affect the degree of successful treatment for this statin. Perhaps differences in patient baseline plaque component levels, age, sex, and other factors could account for some treatments to be unsuccessful.

4.2 Evaluation of Fluvastatin as a means for promoting coronary plaque regression

The data found that Fluvastatin treatment was successful in decreasing plaque volume however due to the limited amount of data it is difficult to justify this as a representative for the majority of Fluvastatin treatments. Nonetheless, the results from the articles found that Fluvastatin therapy was associated with plaque and necrotic core volume regression. (Inoue K. et al, 2010). The other study by Nasu. K et al, (2009) found that after a year's treatment of Fluvastatin, patients showed significant fibrofatty volume reduction aswell as plaque volume, furthermore they discovered that the fibrous tissue volume also increased. Moreover, 4mg/day of Pitavastatin after three weeks was discovered to increase fibrous-cap thickness in plaques and even further after 36 weeks. (Nishiguchi et al, 2018)

4.3 Evaluation of Pitavastatin as a means for promoting coronary plaque regression

Compared to the other statins, Pitavastatin is generally administered in very low doses roughly around 2mg/day. One study found it to be effective in reducing the colour of yellow grade plaque, but it contributed no significant reduction to total plaque volume. (Kazahusi. et al, 2010) Although surprisingly, Okada. K, et al (2012) found that Pitavastatin treatment significantly reduced plaque volume by 18.9% and also reduced the plaque to myocardium signal intensity ratio of plaques suggesting the idea that it is associated with cell to cell signalling aswell. Lastly, aswell as its association with inducing coronary plaque regression it was also found to significantly reduce LDL cholesterol levels. (Takashima H. et al, 2007)

4.4 Evaluation of Pravastatin as a means for promoting coronary plaque regression

Since there was only one article reporting on the effects of Pravastatin treatment, analysing the results was difficult and evaluating this against other articles was simply not possible. Nonetheless, it was found to have decreased LDL cholesterol concentrations by -19.6%. From this study alone we can agree that it is a potentially good candidate drug for atherosclerosis stabilisation. (Haruo Makuuchi et al, 2005) On a different note, it has been reported that the administration of

pravastatin to heart transplant recipients was associated with a significant decrease in organ rejection cases and increased survival, independently of its action on blood cholesterol levels.

4.5 Evaluation of Rosuvastatin as a means for promoting coronary plaque regression

The majority of the studies on this statin concluded that it is most effective in moderate-high doses. (Takayama et al, 2009, Young Joon Hong et al, 2010, Soeda T. et al, 2011) Early intervention with Rosuvastatin in AES patients significantly reduces plaque volume via decreased lipid component concentration. It was found to cause a 18.49% decrease in total plaque volume, 35.14% decrease in lipid volume and a 37.6% decrease in LDL cholesterol levels. (Otagiri K. et al, 2011) Additionally, Rosuvastatin was found to increase fibrous cap tissue while reducing macrophage accumulation and promoting thin cap fibroatheroma regression. (Raber L. et al, 2019, Park S.J. et al, 2016) However, Soeda T. et al, discovered that the reduction in plaque volume was greater in patients with lower base level rations of LDL:HDL. So seemingly healthier patients may benefit more from this therapy than less healthier ones. Raber L. et al, 2015 also found that high intensity Rosuvastatin treatment after 13 months regresses atherosclerosis without changes in necrotic core volume. Furthermore, (found in the same study that discovered plaque volume increase in Atorvastatin (Young Joon Hong. et al, 2010) it was also discovered that 15% of patients who had received the alternative Rosuvastatin doses experienced plaque increase. This is potentially due to the same factors for Atorvastatin as previously mentioned above.

4.2 Overall evaluation and limitations

Overall, all statins analysed in this review were deemed effective in reducing plaque volume and inducing regression. However, due to the limited number of papers reviewable, it is agreeable to assume that Atorvastatin and Fluvastatin were the most effective by majority and representability. Not all studies reported plaque volume changes and instead other elements such as LDL cholesterol concentration and fibrous cap thickness, therefore we had to assume the differences in these are related to plaque volume. This is a fair assumption since LDL cholesterol is a component for coronary plaques, and high levels of this are associated with coronary artery disease. While fibrous cap thickness correlates with resitance to migrating macrophages to prevent further foam cell accumulation. Another note was that there was a wide range of differences in dosage and duration across all studies and so the effectivity of some statin treatments over others could be a result of longer exposure to medication and concentration of statins administered.

The study had a number of limitations which affected the overall quality of the discussion and evaluation. For example, some studies did not report findings for the difference between baseline and follow plaque volume, instead they reported results on changes in LDL cholesterol level and some even on fibrous cap percentage changes. This made it difficult to compare with other studies, and so these certain articles were analysed individually. On one such study (Miyauchi K. et al, 2006) no significant results were found, while three studies did not report the use of a specific statin just a general use, making it difficult to be evaluated with the others and so required individual assessment.

5 Conclusions

Despite the complications that came with analysing some studies and the awkward number of representative articles for each statin. We can conclude that all these statin variants contribute to reduced plaque growth and plaque stability. In order to achieve regressive effects slightly higher doses are required partnered with longer therapy duration. Further studies can look at the effects of administering statins as a combination therapy with other lipid-lowering molecules such as ezetimibe. Perhaps this combination of two different medications can provide a more effect treatment for patients but further trials are needed to investigate this. Furthermore, while statins alone are proven to be effective, medical professionals should always promote patients to engage in a healthy lifestyle, maintaining balanced diets and frequent exercising, all of which are factors that decrease the chances of developing atherosclerosis and other acute coronary syndromes.

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A study involving the comparison of rosuvastatin and atorvastatin on plaque regression in Korean patients. It found that moderate doses are associated with effective regression.

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Erling Falk, Renu Virmani, Fumiyuki Otsuka, Jacob Fog Bentzon. (2014 June). *Mechanisms of plaque formation and rupture.* doi:10.1161/CIRCRESAHA.114.302721

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A journal describing various techniques for the diagnosis of coronary heart disease.

Gillian Douglas, Keith M. Channon . (2014). *The Pathogenesis of Atherosclerosis - Pathogenesis, Risk Factors and Prevention, Medicine.* Retrieved from https://www.medicinejournal.co.uk/article/S1357-3039(14)00189-3/pdf

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A review on atherosclerosis

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Ruth Mcpherson, Anne Tybjaerg-Hansen. (2016 February). Genetics of Coronary Artery Disease. doi:https://doi.org/10.1161/CIRCRESAHA.115.306566

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A clinical study investigating the effects of rosuvastatin on reducing lipid core volume.

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A study with the aim to analyse the effect of statin treatment aswell as the relation of plasma lipids and lipoproteins to tissue composition in atherosclerotic plaques.

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A university of Michigan article explaining how smoking can increase likelihood of CAD development.

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A study evaluating the changes in coronary plaque colour and morphology after Atorvastatin therapy. Found that lipid lowering therapy induces plaque stabilisation.

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A study on the effects of Pitavastatin on coronary plaque regression associated with LDL-C levels. Found that the percentage change in PVI showed a significant positive correlation with the percentage change in LDL cholesterol levels.

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An article of CAD epidemiology.

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An brief review on the underlying genetic factors of coronary artery disease.

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This project was supervised under Dr Alessandro Siani. The projected started in October 2020 and ended in June 2021.

Appendices

Appendix 1

Analysing the Regressive Effects of Statins on Coronary Plaques – a systematic review

John Bonapos - Project Supervised by Dr Alessandro Siani, School of Biological Sciences Portsmouth

UNIVERSITY OF PORTSMOUTH

Introduction

Coronary artery disease (CAD/CHD) is a condition caused when the blood vessels supplying blood to the heart are severely damaged and narrowed as a result of atherosclerosis which causes the hardening and loss of elasticity of arteries as a result of plaque accumulation. Common symptoms include shortness of breath, pain and angina. In extreme events an artery may become completely blocked resulting in a heart attack[1].

Atheromatous plaque (atheroma's) are the main causes for this extensive hardening. Characterised as raised lesions protruding into the lumen consisting of a grumous cholesterol filled necrotic core covered by a fibrous cap[2]. Their accumulation results in the restriction of blood flow to areas in the heart.

Statins are 3-hydroxyl-3methylglutayl coenzyme A (HMG-CoA) reductase inhibitors predominantly prescribed for lowering cholesterol levels as a means for preventing cardiovascular disease[3].

The objective of this systematic review is to analyse how effective statin treatments are on coronary plaque regression.

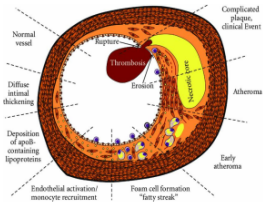

Figure 1 – diagram depicting stages of atherosclerotic plaque formation

Results & Conclusions

A more specific display of results from the systematic review is located within the main thesis. This will include the core data obtained from papers along with any necessary statistics.

A total of 4 statin variants were analysed within 22 studies. 2 studies reviewing the effect of general statin treatment, 8 studies involved in Atorvastatin, 3 in Pitavastatin, 2 in Fluvastatin and 8 in Rosuvastatin. Study 3 involved a joint observation of Atorvastatin and Rosuvastatin.

Conclusions: Statins regardless of type and dosage all have somewhat regressive effects on coronary plaque development. However, factors such as dosage, treatment duration and individual differences results in variations in effectivity. Seemingly, doses within the 40-60mg range (especially in atorvastatin) are the most efficient in the regression of plaque formation.

Statin	Studies involved	Conclusive comments
Atorvastatin	1,2,3,7,11,16,17,22	- Doses of 40 mg and 80mg worked best - Low to moderate could be most efficient level - Promotes early loss of yellow plaque
Fluvastatin	4,8	- Regressed volume in plaque necrotic core and fibro-fatty volume
Pitavastatin	5,9,18	- Early treatment stabilises plaque development - Associated with LDL-C reduction
Rosuvastatin	3,6,12,13,14,15,19,21	- Greatly reduces plaque volume and thin cap fibroatheroma rate - Not much difference between moderate and intense doses
General	10,20	- Statin treatment reduced high intensity plaque and CD40 expression on plaque T lymphocytes

Figure 3 – Table showing summarised conclusions for each statin

Methodology

All publications were sourced from PubMed using a concise search strategy: ((“Coronary Atherosclerotic Plaque” OR “Coronary Heart Disease” AND (Statins OR HMG-CoA reductase inhibitors)) NOT cancer [Title/Abstract] NOT Diabetes [Title/Abstract].
This systematic review follows the PRISMA guidelines for paper and data collation.

Coronary plaque characteristics such as lumen volume, cholesterol levels and plaque volume were recorded pre and post treatments and then quantified to analyse the effectiveness of statin treatment on plaque regression. This was done mainly thorough the use of descriptive statistics and some basic statistics. Treatment effects were pooled along with other associated factors such as duration, dosage, and combined treatments.

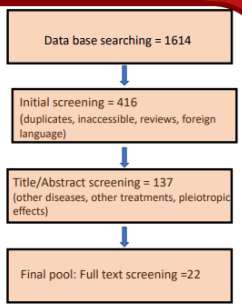

Figure 2 – Flow diagram presenting exclusion process

Discussion

- Changes in plaque lipid volume and plaque regression varies by statin and dosage but all can reduce cardiovascular events.
- Statins given in the dosage range between 40mg-60mg have the most significant effects in plaque reduction shown by follow up studies
- Moderate statin doses accompanied by ezetimibe can have greater regressive effects compared to intensive solo statin therapies
- Changes in HDL and LDL levels are potentially good indicators of coronary plaque status and likelihood of atherosclerosis development.
- Many factors could potentially contribute to a statins effectivity on plaque regression including treatment duration, age, ethnicity and sex.
- More research on the effects of statins on specific cardiac diseases is necessary in order for treatments to be better tailored to patients.

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DECLARATION

- I hereby declare that this dissertation is substantially my own work.
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