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Intitulé

Involvement of the *L55M* and *Q192R* polymorphism of the *Paraoxonase* gene in myocardial infarction: a meta-analysis

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Dedication

*I dedicate this **memoir** to:*

First and before all to my dear **parents**, my guards and my firewall since birth, I would like to thank them from the deep of my heart for all the trust, the strength they gave me since I was a child. This success is for you.

To my dear brother **Abd al Malek** for his support, trust and for standing by my side since the baccalaureate year, I would like to say you are such a great brother.

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Anfel

Dedication

This work is dedicated to

the most precious thing I have in the world, to **my dear mother**, **Boudaira Khadija**, to you all the credit, my sweetest queen, may God heal you and protect you for me, and also to **my dear father Hassan**, may God bless you for me, and to **my only brother Oussama**, I wish you success in your life.

Also, to **my dear and beautiful friends, Bouti, Itidal, Khawla and Rasha**, may you always be proud of me, my beloved ones, especially **Shaima and Itidal**, I will never forget your stances with me, I wish you all the best and happiness in your life.

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Maya

Abbreviations list

ACCU: Acute Cardiac Care Unit.

AMI: Acute Myocardial Infarction.

Apo A1: Apoliprotein A1.

Apo B: Apoliprotein B.

Apo D: Apoliprotein D.

Apo M: Apoliprotein M.

AVTs: Venous and Arterial Thrombosis.

BMI: Body Mass Index.

CABG: Coronary Artery bypass surgery.

CAD: Coronary Artery Disease.

CHD: Coronary Heart Disease

CI: Confidence Interval.

cTn: Cardiac Troponin.

CVA: Cerebral Vascular Accidents.

DM: Diabetes Mellitus.

ECG: Electrocardiogram.

HCTL: Homocysteine Thiolactone.

HDL: High-Density Lipoprotein.

HTA: Arterial Hypertension.

H1, H2, H3: Hinge 1, 2, 3.

HWE: Hardy-Weinberg Equilibrium**.**

KB: Kilo Base.

KDa: Kilo Dalton.

LDL: Low-Density Lipoprotein.

LDLc: Low-Density Lipoprotein cholesterol.

LP (a): Lipoprotein (a).

MI: Myocardial Infarction.

MPO: Myeloperoxidase.

NSTEMI: Non-ST-Elevation Myocardial Infarction.

OP: Organophosphorus.

PCI: Percutaneous Coronary Intervention.

PON 1: Paraoxonase 1.

PPARs: Peroxisome Proliferator-Activated Receptors.

ROS: Reactive Oxygen Species.

SNP: Single Nucleotide Polymorphisms.

SP-1: Specificity Protein-1.

SREBP-2: Sterol Regulatory Element Binding Protein-2.

STEMI: ST-Elevation Myocardial Infarction.

URL: Upper Range Limit.

VLDL: Very Low-Density Lipoprotein.

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Introduction

INTRODUCTION

Common chronic multifactorial diseases have the greatest need for healthcare services **(Sing *et al.*, 2003).** Coronary artery disease (CAD), including his most serious form: myocardial infarction (MI), is the leading cause of death in many countries **(Li, *et al.*, 2005).**

MI is a complex disease with multiple environmental and genetic factors **(Tobin *et al.*, 2004).** Commonly called a heart attack, it occurs when blood flow to one or more coronary arteries is suddenly blocked, cutting off blood supply to part of the heart muscle, causing it to die. If the blockage is severe, the heart may stop beating (cardiac arrest**) (Rathore *et al.*, 2018)**. It is responsible for over 15% of mortality each year. The prevalence of MI is higher among men in all age-specific groups than women. Although the incidence of MI is decreased in the industrialized nations partly because of improved health systems and implementation of effective public health strategies, nevertheless the rates are surging in the developing countries such as south Asia, pats of Latin America, and Eastern Europe **(Chadwich-Jayaraj *et al.*, 2017).**

A multiple reason has been included in MI risk, in varying proportions. MI risk factors can be classified into three general categories: non-modifiable risk factors (age, gender, and family history), modifiable risk factors (smoking, alcohol consumption, physical inactivity, poor diet, hypertension, diabetes, dyslipidemia, metabolic syndrome), and emerging risk factors (C-reactive protein (CRP), fibrinogen, coronary artery calcification (CAC), homocysteine, lipoprotein (a), and small, dense (LDL)) (**Boateng *et al.*, 2013).**

Paraoxonase, also known as aromatic esterase1 encoded by PON1 gene is a high-density lipoprotein linked enzyme that possesses antiatherogenic activity. It protects a low-density lipoprotein (LDL) from oxidation. Polymorphisms in PON1 genes, L55M and Q192R on exons 6 and 3 respectively are known to be risked in causing cardiovascular disease **(Aruljothi *et al.*, 2018).** Glutamine Q/Arginine R substitution at codon 192 results in different hydrolytic activities of the alleles towards various substrates. The leucine L/methionine M substitution at position 55 results in different plasma PON1 protein levels. The M allele is associated with low PON1 protein level **(Otocka-Kmiecik et Orlouska-Majdak, 2009).**

Numerous case-control studies have been conducted to determine whether the PON1 55M or 192R alleles are closely associated with MI; some of them have found an association between the polymorphism and the disease **(Aruljothi *et al.*, 2018)**, while others have not **(Ferre *et al.*, 2002).** In this study, we performed a meta-analysis which is a very useful tool to combine information from different sources, by pooling 14 case-control studies to comprehensively

determine the overall strength of associations between PON1 polymorphisms (L55M and Q192R) and the susceptibility to develop heart diseases.

For this we set the following goals:

- Updated bibliographic search for MI (Anatomy and Epidemiology and pathophysiology, risk factors, genetic factors, screening and treatment) and gene PON1 (Protein location, function, polymorphisms, and its relationship with the risk of MI)
- Carry out a genetic study of the type of meta-analysis with the aim of obtaining a highly accurate judgment of association of L55M and Q192R polymorphisms of PON1 genes and risk of MI.

Chapter 01

Myocardial infarction

1- Heart anatomy

The heart is a hollow muscular organ whose size is approximately that of a closed fist: 12 cm long, 8 cm wide and 6 cm thick (figure 1). It is located in the thorax in the middle between the sternum in front and the dorsal spine behind (figure 2) **(Brthet *et al*., 2006)**.

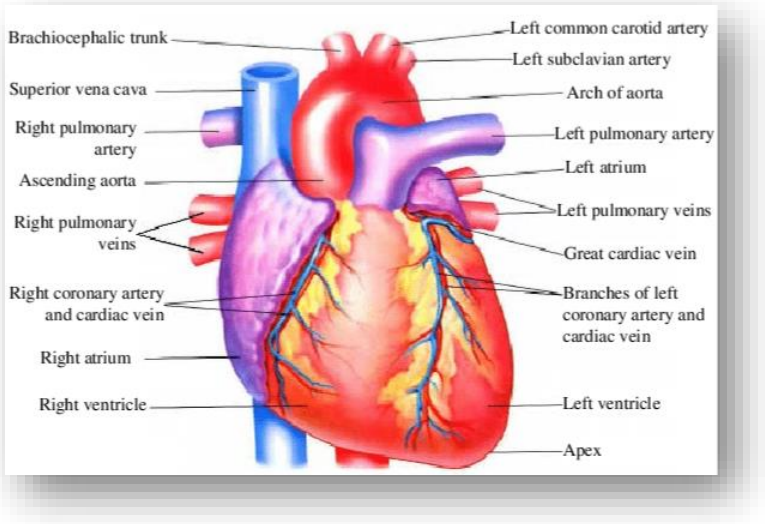


Figure 1: Heart anatomy (**Thibodeau et Patton, 2004**).

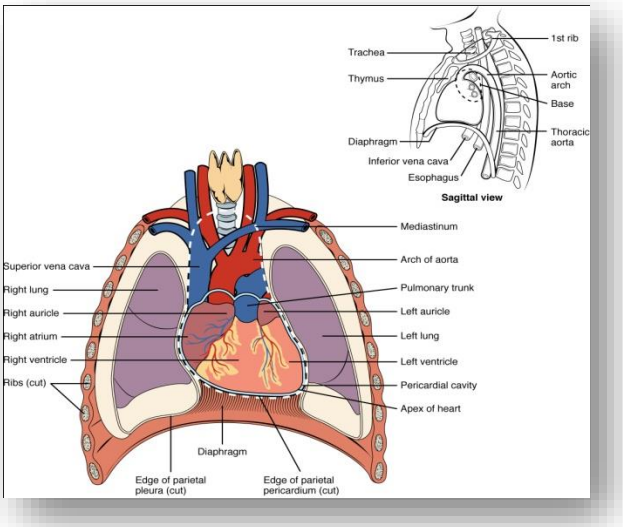


Figure 2: Position of the heart in the thorax (**Gordon *et al*., 2013**).

The heart is separated from the other mediastinal structures by a tough membrane known as the pericardium, or pericardial sac, and sits in its own space. It consists of four chambers: two upper (the artery) and two lower (the ventricles). It works like a pump that sends oxygenated blood to all parts of the body. There are two distinct but linked circuits in the

human circulation called the pulmonary and systemic circuits. Blood flows from the right atrium to the right ventricle, where it is pumped into the pulmonary circulation. Blood in the pulmonary artery branches is poor in oxygen and relatively rich in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen enters the blood and carbon dioxide exits), and blood high in oxygen and low in carbon dioxide is returned to the left atrium. From here, blood enters the left ventricle, which pumps it into the systemic circuit. Following exchange in the systemic capillaries (oxygen and nutriments out of the capillaries and carbon dioxide and wastes in), the blood returns to the right atrium and the cycle repeats (figure 3) **(Gordon *et al*., 2013)**.

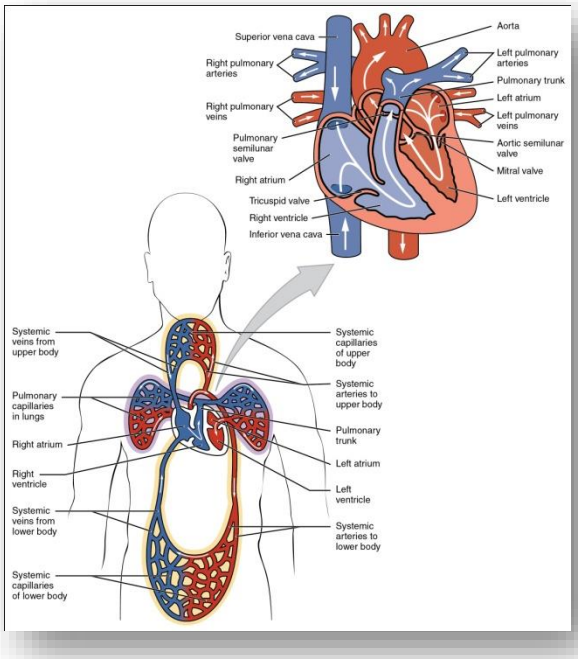


Figure 3: The human blood circulation (Gordon *et al*., 2013).

2- Vascularization of the heart

Blood circulates in the body through blood vessels. There are many types of blood vessels, classified by the type of blood they carry, their location and their function: the arteries, the veins and the capillaries **(Brahim, 2016)**.

2-1-The arteries

Coronary arteries are the arteries that supply the heart with nutrients and allow it to function. They emerge from the first part of the aorta just after the aortic valve and migrate to the surface of the heart, all small and medium-calibre arteries have three layers: (figure4)

-**The intima:** whose inner layer is formed by the endothelium which constitutes a real inter face with the blood and whose roles are very important:

Barrier (by allowing the exchange of nutrients with the internal environment, it acts as a molecular filter)
Control of blood coagulation (it inhibits this coagulation and its rupture promotes the aggregation of platelets and the formation of clots.
In vasomotor control (it can generate nitric oxide which causes muscle layer relaxation and vasodilatation **(Patrice, 2014)**.
-The media: depending on the size of the artery, the media changes the calibre of the artery by securing elasticity and causing muscle cells to contract (vasoconstriction) or relax (vasodilatation) **(Milutinovic` *et al.*, 2020)**.

-The adventitia: Provides the connection between the blood vessel and the tissue through which it passes. Small blood vessels (vasa vasorum) and through this layer **(Witter *et al.*, 2016)**.

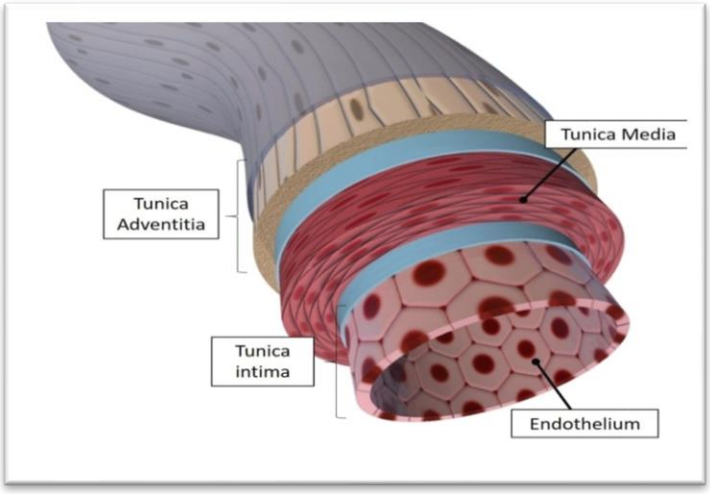


Figure 4: Cardiovascular tunics and endothelium (W1)

2-2-The veins

After leaving the capillaries, the blood which contains cellular waste. Follows the path of venules which are very small branches of veins. The blood eventually flows into the veins and is carried to the heart **(Stanley, 2021)**.

Veins are much higher on the body surface than arteries, and blood circulates more slowly and continuously than arteries. The walls of veins are much thinner than the walls of arteries and are shaped to prevent back flow of blood (valves) **(Brahim, 2016).** The main veins of the body are the superior vena cava and the inferior vena cava.

2-3-Capillaries

Capillaries connect your arteries to your veins. It is tiny blood vessel, 5 micrometres, which is less than a third of a hair's width. A capillary wall is only one cell in thickness and is made of endothelial cells, allows oxygen, nutriments, and waste to pass to and from tissue cells **(Nicola, 2021)**.

3- Cardiovascular diseases

They are represented by:Coronary heart disease (exertional angina, silent ischaemia, syndromes acute coronary, sudden death).Cerebral vascular accidents (CVA) (ischaemic or haemorrhagic, transitional or constituted). Peripheral vascular pathologies (obliterating arteriopathy of the lower limbs, aortic aneurysm, nephroangiosclerosis, carotid damage) **(Papon, 2014)**.

Cardiovascular diseases are famous for the first place they occupy in mortality statistics, and by the fact that they constitute a cause of premature death, especially among men **(Santos-Eggimann, 2006)**. They are the cause of many disabilities and complications. The triggering factor for these pathologies is atherosclerosis. This is due to the association between endothelial dysfunction and accumulation of low-density lipoprotein cholesterol (LDLc) in the intima. Vascular endothelium is affected by mechanical (arterial hypertension (HTA), biochemical (hypoxia, Tabacco free radicals, vasoactive substances, diabetes, axidationof LDLc), or infection factors (cytomegalo virus, chlamydia pneumoniae). These alterations will increase the permeability endothelial promoting the entry of LDLc into the intima, the inner layer of the arterial wall. It will be supported by monocytes which will transform into foam cells which will secrete substances that cause smooth muscle cells to produce collagen

and matrix extracellular which will form the fibrous cover of the atherosclerotic plaque **(Besse *et al*., 2005).**

4- Definition of Myocardial infarction

AMI is one of the most common diseases in developing countries **(Sathisha *et al*., 2011).** This is commonly known as a heart attack. It occurs when blood flow in one or more coronary arteries is suddenly cut off, cutting off the blood supply to part of the heart muscle and causing necrosis (massive cell death, permanent damage) (figure 5) **(Nagim, 2007)**. If the blockage is severe, the heart may stop beating (cardiac arrest). This is most commonly due to occlusion or blockage of a coronary artery following the rupture of a vulnerable atherosclerotic plaque which is an unstable collection of lipids and white blood cells (especially macrophages) in the wall of an artery **(naik, 2010; Rathor, 2017)**.

Myocardial infarction usually begins in the endocardium and spread towards the epicardium **(Bhagwat et Padmini, 2014)**. We distinguish between two types of MI on which clinical decision-making is based: ST-Elevation Myocardial Infarction (STEMI) and Non-ST-Elevation Myocardial Infarction (NSTEMI) **(Tibaut *et al*., 2016)**. Furthermore, MI is classified into five types based on an etiology and circumstances **(Sweis et Jivan, 2022)**.

Type 1: Spontaneous MI caused by ischaemia due to a primary coronary event (plaque rupture, erosion, or fissure, coronary artery dissection).
Type 2: Ischaemia due to increased oxygen demand (hypertension), or decreased supply (coronary artery spasm or embolism, arrhythmia, hypotension).
Type 3: Related to sudden unexpected cardiac death.
Type 4a: Associated with percutaneous coronary intervention (signs and symptoms of myocardial infarction with cardiac troponin (cTn) values> 5 * 99^{th} percentile upper range limit URL).
Type 4b: Associated with documented stent thrombosis.
Type 5: Associated with coronary artery bypass graft surgery (signs and symptoms of myocardial infarction with cTn>10 * 99^{th} percentile URL).

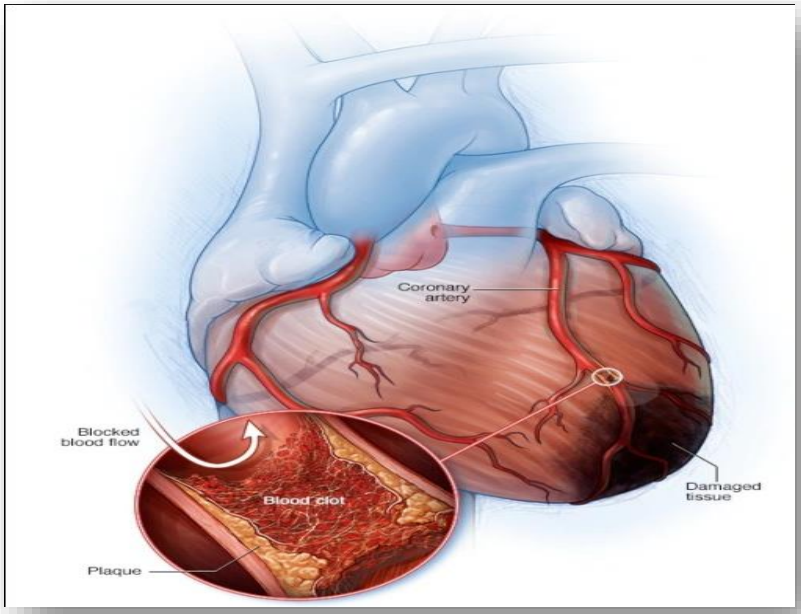


Figure 5: Myocardial infarction (W2)

5- Ethiology

The main cause of myocardial infarction is decreased coronary blood flow. The available oxygen supply fails to meet the oxygen demand, causing cardiac ischaemia. Decreased coronary blood flow is multifactorial. The atherosclerotic plaques classically rupture, causing thrombosis and share by reducing coronary blood flow. Other aetiologies of hypoxia/myocardial ischaemia include coronary embolism, which accounts for 2.9% of patients, cocaine, induced ischaemia, coronary dissection, and coronary vasospasm **(Oren *et al.*, 2022)**.

We speak of atherosclerosis when atherosclerotic plaques accompany arteriosclerosis: this is the most frequent case. Excess LDL cholesterol is responsible for the formation of atherosclerotic plaques. This process resembles that of lime clogging the ducts of a faucet. Over the years, these deposits gradually become impregnated with fibrinogen, platelets, blood cells, calcium and solidify **(Rossant-Lumbroso et Rossant, 2019)**.

It is possible to have a heart attack without an obstruction (block), but this is rare and accounts for only about 5% of all heart attacks, this kind of myocardial infarction can occur for the following reasons:

- Coronary artery spasm,
- Rare medical condition: an example of this would be any disease that causes unusual narrowing of blood vessels.
- Trauma: this includes tearing or rupturing a coronary artery.
- Obstruction that came from somewhere else in your body: a coronary artery.
- Electrolyte imbalance
- Eating disorders: These can damage the heart over time and eventually lead to a heart attack
- Takotsubo or stress cardiomyopathy
- Anomalous coronary arteries: a congenital heart defect in which the body's coronary arteries are in an unusual position **(Ojha et Dhamoon, 2022)**.

6- Pathophysiology

6-1- Formation of atherosclerotic plaque

Atherosclerosis, from its initiation to its growth to its complications (ex, myocardial infarction, stroke), is thought to be an inflammatory response. A lesion of the endothelium would play an important role in triggering or aggravating the disease **(Bui *et al*., 2009).**

It is known that nonlaminar or turbulent blood flow (e.g., at arterial branching points) induces endothelial dysfunction and inhibits its endothelial production of nitric oxide, a potent anti-inflammatory and vasodilator molecule **(Wilensky et Hamamdzic, 2007).**

Inflammatory cells are also recruited and bind to such blood flow when endothelial cells produce adhesion molecules **(Wilensky et Hamamdzic, 2007).**

It has been found that factors associated with atherosclerosis, such as oxidative stress (e.g. superoxide radicals), angiotensin II, inflammation, and systemic infection, inhibit the production of nitric oxide, and stimulate it, as well as adhesion molecules, pro-inflammatory cytokines **(Bui *et al*., 2009).**

However, its exact mechanism remains unknown. As a result, monocytes and T lymphocytes are bound to the endothelium, migrate to the subendothelial spaces, and initiate and maintain local vascular inflammation **(Thanassoulis *et* Aziz, 2022).**

In the subendothelial space, monocytes become macrophages **(figure7**) **(Bobryshev 2006; Moore *et al.*, 2013).**

LDL cholesterol and VLDL cholesterol bind to endothelial cells and are oxidized within the sub endothelial space **(Thanassoulis *et* Aziz, 2022).**

As a result of oxidized lipids being taken up by macrophages and macrophages becoming foam cells, fatty streaks are characteristic early atherosclerotic lesions **(Rosenfeld *et al*., 2000).**

The atherosclerotic plaques may also contain lipids from the degradation of erythrocyte membranes caused by vasa vasorum rupture and intraplaque hemorrhages **(Thanassoulis *et* Aziz, 2022).** Pro-inflammatory cytokines produced by macrophages attract and stimulate medial smooth muscle cells. Extracellular matrix production and smooth muscle cell replication are both promoted by several factors. Smooth intimal muscle cells surrounded by connective tissue and intra- and extracellular lipids form a sub endothelial fibrous plaque covered by a fibrous cap. Plaque forms calcification similar to bone formation **(Rohwedder *et al*.,2012).**

The relationship between infection and atherosclerosis has been demonstrated, in particular the association between serological markers of certain infections (e.g. Chlamydia pneumonia, cytomegalovirus) and coronary artery disease. Chronic systemic inflammation, autoantibodies, and infectious pathogens causing inflammatory effects on arterial walls are thought to be the mechanisms. As a result, the evidence for such a link is conflicting, and infection may play only a minor role in atherosclerosis **(Thanassoulis *et* Aziz, 2022).**

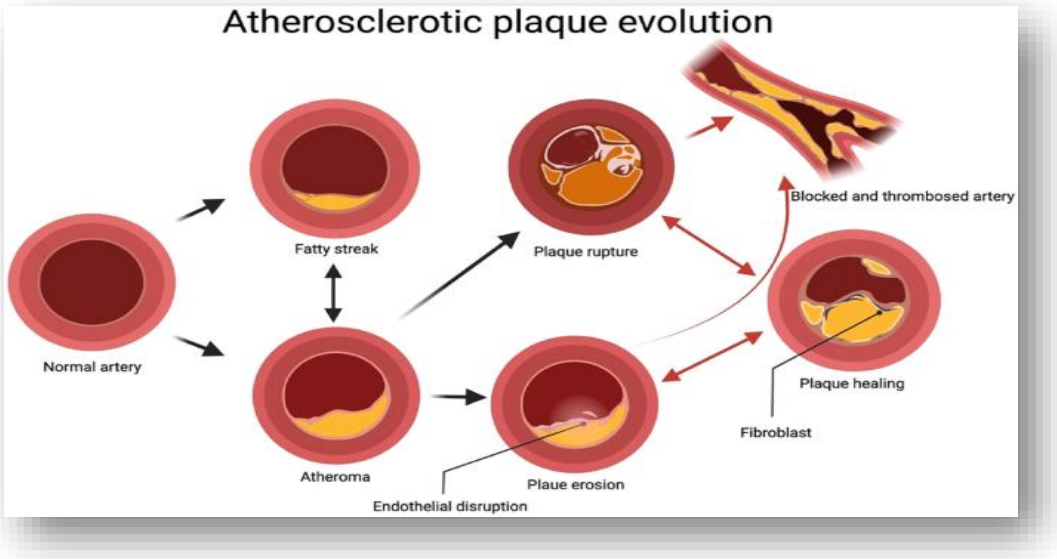


Figure 6: **evolution of atherosclerotic plaque (W3)**

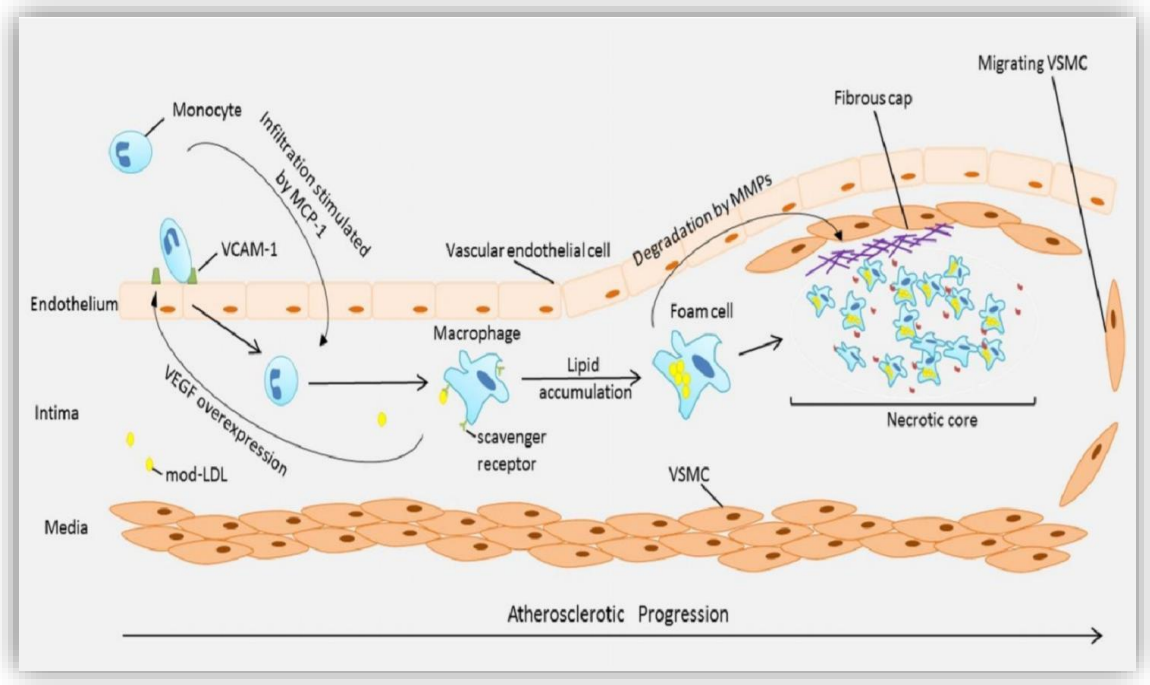


Figure 7: The pivotal role of macrophages in atherogenesis (Ward, 2019).

6-2- Stability and rupture of atherosclerotic plaque

The atherosclerotic plaques can be stable or unstable**.**

Plaques that are stable regress stabilize or evolve slowly over several decades before they become stenotic or blocked **(Min Htun, 2017).**

Plaques that are unstable are prone to spontaneous erosion, fissures and ruptures, which can be accompanied by acute thrombosis, occlusions, infarctions and long before there becomes hemodynamically significant stenosis. Most clinical events result from unstable plaques, which are often not hemodynamically significant on angiography; thus, plaque stabilization may be a way to reduce morbidity and mortality **(Shah, 2002).**

Fibrous caps and their resistance to rupture depend on collagen synthesis and degradation. Active macrophages in plaque secrete metalloproteinases, cathepsins, and collagenases to disrupt plaque **(Wissing *et al*., 2022)**.

Enzymes digest fibrous caps, particularly their edges, causing them to thin and eventually break. T cells in the plaque contribute to the process by secreting cytokines **(Hansson *et al*., 2015).**

As a result of cytokines, smooth muscle cells are unable to synthesize and deposit collagen, a substance that is normally responsible for strengthening plaque (**Hansson *et al*., 2015).**

There are two important factors which facilitate thrombosis; the rupture of a plaque exposes its contents to circulating blood, thus leading to the formation of a thrombus; the macrophages are also factors which facilitate thrombosis because they contain tissue factor that causes thrombin to be formed in vivo. It could happen in one of these 5 ways:

- Thrombosis can form into plaques that grow rapidly and change shape.
- A thrombus can cause an ischemic attack by blocking the vascular lumen.
- The thrombus can migrate.
- An artery can be blocked by a plaque filled with blood and swelling.
- A plaque's contents (rather than thrombus) may migrate, occluding downstream vessels **(Thanassoulis et Aziz, 2022).**

A plate's stability is determined by a variety of factors, including its composition (relative proportion of lipids, inflammatory cells, smooth muscle cells, connective tissues, and thrombus) (**Badimon et Vilahur, 2014)**, the amount of stress placed on its wall, its location and size, as well as its configuration in relation to blood flow. Intraplaque hemorrhage can cause plaques to become unstable by contributing to the rapid plaque growth and lipid deposition **(Thanassoulis et Aziz, 2022).**

There's a high macrophage content in unstable coronary artery plaques, a thick lipid core, and a thin fibrous cap (**Badimon et Vilahur, 2014).**

They reduce vessel lumen by 50% and tend to rupture randomly. A stable carotid plaque has the same composition, but usually causes problems through severe stenosis and occlusion or platelet thrombus deposits, which embolize rather than rupture. The fibrous cap on low-risk plates is thicker and contains fewer lipids; they often decrease vessel lumen by more than 50% and produce stable exertional angina **(Thanassoulis et Aziz, 2022).**

Plaque rupture may have clinical implications not only based on its location and anatomy, but also on the blood's procoagulant or anticoagulant activity and the myocardium's vulnerability to arrhythmia **(Thanassoulis et Aziz, 2022).**

6-3-Thrombosis

Plaque cells, particularly macrophages produce the tissue factor, which plays a key role in thrombosis (**Badimon et Vilahur, 2014)**.

One can therefore imagine that a rupture bringing the blood with an area rich in tissue factor will progress more frequently to an accident acute thrombotic than a rupture in an area where the amount of tissue factor is small. The amount of tissue factor in plaques causing acute coronary syndrome was higher than in plaques causing stable angina, for example. By increasing prothrombogenic factors such as fibrinogen, in the case of rupture**,** inflammation can also increase the risk of thrombosis by increasing certain prothrombogenic factors such as fibrinogen**. (Ardissino, 1997).**

In most cases, localized, usually occlusive thrombus formation is the result of plaque rupture and superficial erosion. This occurs in the coronary artery, downstream ischemia and MI are the consequence **(Palasubramaniam, 2019).**

In the end, determining whether thrombosis contributes to infarction depends on the evidence that one precedes the other. Space and time factors bear on this point, but in order to consider evidence properly, it is essential to recognize that thrombi and infarcts are neither static nor deterministic. Both require time to develop and evolve. Since the estimation of the age of either an infarct or a thrombus in histologic material is at best crude, comparison of the age of one with the other is made doubly hazardous. Infarct and thrombi usually have easier spatial relations **(Chandler, 1974).**

7- Epidemiology

7-1- In the world

In 2020, about 22,200 people suffered from MI, conforming to around 290 people per 100,000 inhabitants. Since 2019 the incidence was decreased with 9%, which could be an effect of fewer people seeking care during the COVID-19 pandemic **(The National Board of Health and Welfare, 2021).**

In the same year, about 4,800 people died from MI with an average of 60 deceased per 100,000 inhabitants. By 2020, the age-standardized incidence and the age-standardized mortality rate was around twice as high for men as for women **(The National Board of Health and Welfare, 2021).**

7-2- Middle East and North Africa

IHD alone is responsible for more than 8,931,000 deaths in 2017; an increase of 26.5% over the 1990 significant is recorded in the Middle East and North Africa **(James, 2018; Roth, 2018).**

In Algeria: 3420 patients were registered in Setif, with the prevalence of 28.54% for men and 11.65% for women; the hospital mortality rate is of 5%. **(Boussouf *et al.*, 2019)**

8- Risk factors

Risk factors are something that increases a person's chances of developing a disease **(Conrad, 2021)**. The concept of risk factors is now very central in clinical practice, especially in disease prevention and the possibility of modifying it to prevent disease, in addition to emphasizing modification of individual risk factors **(Vaz *et al.*, 2005)**. Finally, the potential risk factors involved in the development of MI have been categorized divided in to two groups: constitutional risk factors non-modifiable (cannot be changed) and modifiable (treatable, environmental risk) in addition to other factors:

8-1- Non-modifiable risk factors (constitutional)

8-1-1 Increasing Age

Older people are more likely to die from AMI **(Yoshida *et al.*, 2006).** The mechanisms by which aging contributes to mortality so dramatically are unknown **(Guo *et al.*, 2009)**. Approximately 80% of deaths from heart disease occur in people over the age of 65 years **(Huma *et al.*, 2012)**.

8-1-2 Gender (sex)

Men tend to have heart attacks earlier in life than women, women's rate of heart attack increases after menopause but does not equal men's rate. Even so, heart disease is the leading cause of death for both men and women **(Huma *et al.*, 2012)**.

8-1-3 Heredity/Family history

First-degree relatives are at increased risk if they develop coronary artery disease or stroke before age 55 for male relatives and 65 for female relatives **(Braunwald *et al.*, 2001)**.

8-2- Modifiable risk factors (Environmental)

8-2-1 Smoking

Smoking is considered a major risk factor for MI, premature atherosclerosis, and sudden cardiac death **(Zhang *et al*., 2010).** It raises blood levels of LDL cholesterol and triglyceride levels and reduces serum HDL cholesterol, and cigarette smoke promotes free radical damage to LDL, leading to accumulation elevation of oxidized LDL cholesterol within the arterial wall. Smoking appears to contribute vascular inflammation characteristic of atherosclerosis, as reflected by higher serum c-reactive protein levels in smokers than is nonsmokers **(Yusuf *et al*., 2004)**.

8-2-2 Obesity/Body mass index (BMI)

Incidence of myocardial infarction is directly related to the increased BMI. Recognized risk factor for MI is obesity by which infarction is greatly enhanced. Overweight and obesity may affect health, and to prevent MI it is necessary to control one's BMI **(Zhu *et al*., 2014)**.

8-2-3 Hypertension

The risk of myocardial infarction because of both systolic and diastolic hypertension and the higher the pressure, the greater the risk. Atherosclerosis in coronary blood vessels due to the higher systolic and diastolic pressure result in heart attack or myocardial infarction. In old age, hypertension is responsible for at least 70% of heart disease and even worse to the heart **(Kannel, 2000).** Strict compliance of proper medication and adoption of lifestyle modifications may control hypertension and reduce the risk of myocardial infarction significantly **(Khan *et al*., 2016).**

8-2-4 Diabetes mellitus (DM)

Diabetes is defined as a fasting blood glucose level above or equals 1.26 g/L (7 mmol/L) on at least two occasions. When the blood sugar level is greater than or equal to 1.10 g/L (6.1 mmol/L), counter glucose intolerance, which is a risk factor for diabetes. Hyperglycemia promotes atherogenesis and thrombosis by several mechanisms: increased in LDL oxidation, chronic inflammation increased Very Low-Density Lipoprotein (VLDL) production, endothelial dysfunction and activation of coagulation **(Bongard et Ferriéres, 2006).** Type 2 diabetes mellitus significantly increase the cardiovascular risk, coronary artery disease is more severe in presence of diabetes (higher post-infarction mortality, lesions more severe, more frequent heart failure) **(Cui *et al*., 2021)**.

8-2-5 Dyslipidemia

The dyslipidemia is associated with total cholesterol, LDL, triglycerides, Apo B, or Lp (a) levels above the 90 the percentile, or HDL and apo A level below common norms **(Rathore *et al.*, 2018)**. High triglyceride levels and a high density of small LDL particles as predisposing risk factors for MI. Non-fasting triglyceride levels appear to be a strong and independent predictor of future AMI risk, especially if total cholesterol is also elevated. This is because it causes metabolic disturbances with consequent adverse effects **(Hedayatnia *et al.*, 2020)**.

8-2-6 Stress

The risk of heart attack and stroke is increased by chronic life stress, social isolation and anxiety **(Alemu *et al.*, 2011).** Acute psychological stress is also associated with increased risk for coronary heart disease, and it has been reported that intense grief in the days after the death of a significant person may trigger the onset of myocardial infarction **(Mostofsky *et al.*, 2012).**

8-3 Other factors

8-3-1 Genetic factor

MI is a complex multifactorial disorder caused by the interaction of environmental and genetic factors. In the context of CAD and MI, as for other disorders with complex inheritance patterns, it is also important to consider epigenetic mechanisms that regulate the expression of these genes, and interactions between multiple genes and between these genes and environmental factors, as well as isolated genetic factors **(Nikpay *et al.*, 2015)**.

The strongest genetic effect on the risk of myocardial infarction is that of a segment on chromosome 9p21 **(Schunkert *et al.*, 2008)**. This risk locus for heart attack has now been replicated in more than 45,000 cases and 85,000 controls. Interestingly, this chromosome region does not contain any gene coding for a protein. The underling pathogenetic mechanism remains unclear **(Erdmann *et al.*, 2010)**.

The presence of family history of premature CAD as a risk factor highlights the genetic contribution to the pathogenesis of CAD and MI **(Msheik et Mahfouz, 2017).** Familial genetic defects with an autosomal dominant form resulted in MI in humans (figure 8) **(Chen *et al.*, 2021).** In these families, a genetic factor must be at work that elevates the risk of myocardial infarction so massively that nearly every individual possessing the risk-

conferring gene, every other child of an affected person, actually goes on to have a myocardial infarction **(Erdmann *et al.*, 2010).**

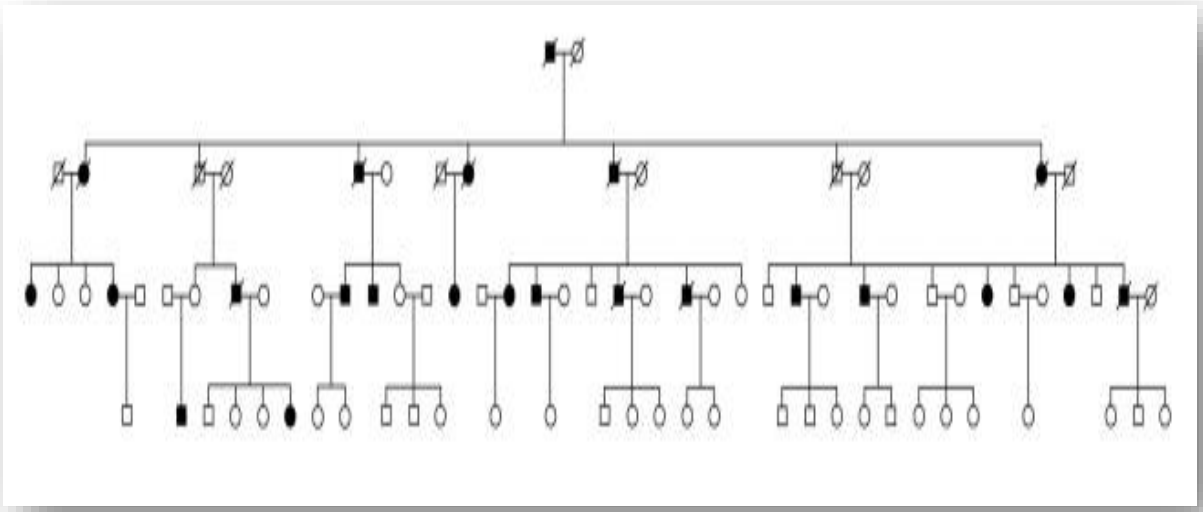


Figure 8: A family tree from the German Myocardial Infarction families study with an autosomal dominant form (Erdmann *et al.*, 2010).

8-4 Less important factors

8-4-1 Consumption of cocaine

MI is increasingly recognized as a complication of cocaine abuse. A significant number of people who suffer cocaine-related MI do not have significant coronary atherosclerosis, and the mechanism of infarction in these patients remains unclear **(Huma *et al.*, 2012)**.

8-4-2 Alcohol Consumption

Alcohol is usually associated with a sharply increased risk of MI in the subsequent hour among people who do not drink alcohol on a regular basis. There is consistent evidence that moderate and habitual alcohol consumption is associated with a reduced risk of cardiovascular events in the following months and years **(Ronksley *et al.*, 2011)**.

9- Clinical description

Symptoms of a heart attack are chest pain, pain in the left shoulder or left arm may up into the neck or along the jaw line, or high blood pressure, tightness of the chest, squeezing, burning sensations, aching, heaviness in the chest for more than 10 min. Also, it can cause a shortness of breath, profuse sweating and dizziness and other symptoms **(lu *et al.*, 2015).**

However, it can be a silence heart attack wish doesn't have any symptoms heartbeat (diabetics, elderly, postoperative, or female) **(Boateng *et al*., 2013).**

10- Diagnosis

If we think there is a possibility of a heart attack, we should go immediately to the hospital. And we will be admitted to an acute cardiac care unit (ACCU), or directly to the cardiac catheterization unit, to confirm the diagnosis. The patient's history, physical examination, and blood pressure are determined when the patient gets to the hospital **(Danchin *et al*., 2007).**

Electrocardiogram (ECG)

It's a very important test wish should be done within 10 minutes of being admitted to hospital. ECG is the first test should do, by making a 12-lead recording. Results allow prioritizing the degree of medical emergency **(Roffi *et al*., 2015).**

ECG checks the presence or absence of ST elevation, which requires the implementation of immediate reperfusion treatment by thrombolysis or angioplasty **(Anderson *et al*.,2017).**

A blood test should also be taken to analyze proteins level and fats in the blood stream wish could damage the heart muscles **(Lu *et al*., 2015).**

cTn isoforms I and T are the preferred diagnostic biomarkers, because they are highly sensitive and specificity for myocardial injury, detectable within 2-3 h, and peak within 24-28 h **(Reed *et al*., 2017).** This test has led to a 20% increase in the diagnosis of non-ST elevation myocardial infarction (NSTEMI). Although available in Europe, but it has yet to be approved in the USA **(Reed *et al*., 2017).**

11- Treatment and screening

If the heart attack is individual, in this case it's necessary to call emergency service or go to the hospital in time emergency medical providers can do the following treatment.

11-1- Medications

Aspirin: Can help break up blood clotting. Keeps blood moving through a narrowed artery **(Boersma *et al*., 2003).**

Clot busters (thrombolytic or fibrinolytic): Streptokinase or Urokinase these drugs help break up any blood clots that are blocking blood flow to the heart. It is given after a heart attack (3h) **(Nahrendorf, 2012).**

Other blood-thinning medications. A medicine called heparin may be given an injection. Heparin makes the blood less sticky and less likely to form clots **(Hirsh *et al*., 2001).**

Painkillers: such as morphine**,** this medicine is given to relieve chest pain, 2–4 mg IV push over 5 min every 5–15 min as needed for pain **(Boateng *et al*., 2013).**

Beta blockers and ACE inhibitors: slow the heartbeat and decrease blood pressure. Beta blockers can limit the amount of heart muscle damage and prevent future heart attacks **(Anderson *et al*.,2017).**

Statins: These drugs help lower unhealthy cholesterol levels. Too much bad (low-density lipoprotein, or LDL) cholesterol can clog arteries **(Boersma *et al*., 2003).**

Dopamine or dobutamine: increase the blood flow to the heart and strengthen the heart beat **(lu *et al*., 2015).**

11-2- Surgical and other procedures

Surgery help to open a blocked artery, it treats a heart attack include:

Coronary angioplasty and stenting: It may also be called percutaneous coronary intervention (PCI), done during a procedure to find blockages and it helps to open a blocked artery **(Torpy *et al*., 2004)**

During angioplasty, a cardiologist guides a thin, flexible tube (catheter) to the narrowed part of the heart artery. A tiny balloon is inflated to help widen the blocked artery and improve blood flow. A small wire mesh tube (stent) may be placed in the artery during angioplasty, it helps keep the artery open. It lowers the risk of the artery narrowing again **(Torpy *et al*., 2004)**

Coronary artery bypass surgery (CABG): a healthy blood vessel will be taken from another part of the body by the surge on to create a new path for blood in the heart **(The National Heart, Lung, and Blood Institute., 2022).** Then the blood goes around the

blocked or narrowed coronary artery. CABG may be done as an emergency surgery at the time of a heart attack. Sometimes it's done a few days later, after the heart has recovered a bit **(The National Heart, Lung, and Blood Institute., 2022).**

11-3- Cardiac rehabilitation

It is a personalized practice, and education program that inform ways to improve heart health after heart surgery. It focuses on exercise, a heart-healthy diet, stress management and a gradual return to usual activities. The program typically continues for a few weeks or months after you return home **(Wenger; 2008).**

Rakhshan et al. studied the potential complications of heart rhythm device malfunction after eight weeks of cardiac rehabilitation, but the study revealed a decrease in physical complications in patients who received cardiac rehabilitation versus a control group **(Rakhshan *et al*., 2017).**

Chapter 02

Paraoxonase 1 (PON1)

CHAPTER 2
PARAOXONASE 1 (PON1)

1- Paraoxonase protein

Paraoxonase protein **(**PON1) is a glycoprotein composed of 354 amino acids with a molecular weight of 43 kDa. Structural analysis by X-ray crystallography reveals the six bladed B-propeller structure of PON 1 (figure1), with a central tunnel that houses two calcium ions **(Blaha-Nelson *et al*., 2017)**. Each calcium ion plays an important role in the activity of PON 1, depending on its position within the enzyme **(Harel *et al*., 2007)**.

Calcium ions deep in the tunnel play an important structural role in the conformational stability of PON 1. Other calcium located at the bottom of the active site cavity has a catalytic role and is important for substrate positioning and ester bond activation. Above the active site of PON 1 are three helices H1, H2 and H3, with H1 and H2 functioning for PON 1-HDL interaction **(Blaha-Nelson *et al*., 2017)**.

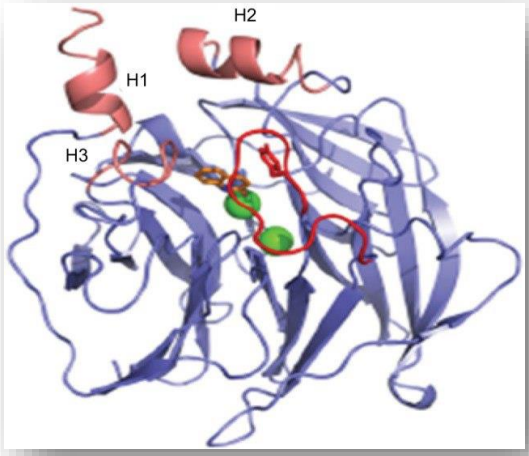


Figure 9: Structure of PON1 (W7)

2- Function of PON 1

PON 1 is mainly synthesized in the liver and partly secreted into the plasma **(Lucio, 2015).** After being synthesized in the liver, PON 1 is released into the circulation and is found primarily in HDL, but also to a lesser extent in very low-density lipoproteins (VLDL) and chylomicrons **(Deakin *et al*., 2002).** Moreover, a specific interaction of myeloperoxidase (MPO)-apoA1-PON1 on HDL surface that seems to be germane to atherogenesis. MPO specifically inhibits PON1 and PON1 mitigates MPO effects. Surprisingly, very little is

known about the routes by which PON1 gets integrated in the intravascular space **(Gugliucci et Menini, 2015).** Free PON 1 has lower enzymatic activity than HDL-bound PON1.

PON1 is transported from the liver to various tissues (figure 9) **(Marsillach *et al.*, 2008)** where it binds to cell membranes and protects lipids from peroxidation **(Deakin *et al.*, 2002).** In addition, PON1 prevents low-density lipoprotein (LDL) oxidation and attenuates inflammatory responses **(Shekhanawar *et al.*, 2013).**

A second important role of PON1 is protection against specific exposures to organophosphates (Ops). Studies in knockout mice (PON1 -/-) have shown that PON1 is a key safeguard against exposure to the Ops chlorpyrifos Oxon and diazoxone, but not to paraxon **(Mahrouz *et al.*, 2019).** Furthermore, neonates express only one third of the levels of PON1 that adults express, and it takes up to two years to reach adult PON1 level, suggesting an increased susceptibility of infants to Ops exposure (**Marsillach *et al.*, 2016).** Therefore, construction of more catalytically efficient variants of PON1 is needed to treat OP poisoning.

Another protective function of PON1 is the hydrolysis of homocysteine thiolactone (HCTL). HCTLs are toxic metabolites that interact with lysine to modify proteins, leading to protein inactivation and dysfunctions. Elevated blood levels of HCTLs are associated with an increased risk of developing cardiovascular, neurological, autoimmune, and cancer **(Vos, 2008; Bacchetti *et al.*, 2019).** However, the physiological relevance of PON1 for HCTL is questionable due to its very low specific enzymatic activity **(Billeks *et al.*, 2000).**

The enzymatic activities of PON1 include lactonase, thiolactonase, arylesterase, and aryldialkylphosphatase activities. Lactonase is the only one enzymatic activity affected by the presence of the apolipoprotein apoA-1. The letter is commonly known as paraoxonase, phosphodiesterase or organophosphatase activities. Activity-related functions of PON1 include clearance of previously mentioned OPs (such as insecticides and nerve agents) **(Himbergen *et al.*, 2006; Lapierre, 2020; Petriç *et al.*, 2021)**, involvement in drug metabolism (both activating and inactivating drugs) **(Biggadike *et al.*, 2000),** and a protective role in atherosclerosis by reacting with proinflammatory oxidized lipids that are present in LDL **(Otocka-kmiecik et Orlowska-Majdak, 2009).**

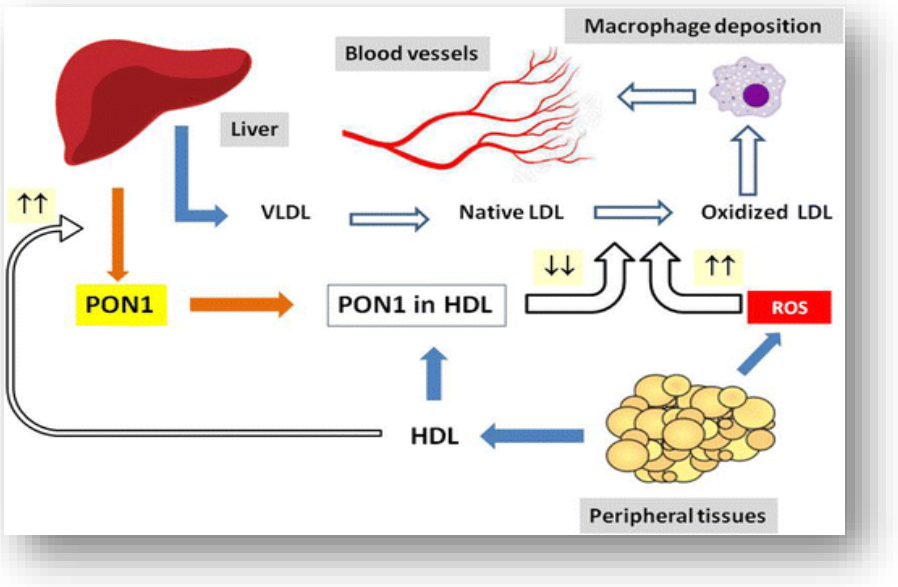


Figure 10: Role of PON1 in the lipoprotein turnover (W8)

HDL mediate reverse cholesterol transport and stimulate hepatic secretion of PON1. The enzyme is then incorporated into HDL particles and confers them the ability to inhibit the oxidation of LDL by reactive oxygen species (ROS), an event that is a prerequisite for the sub endothelial deposition by macrophages, leading to atherosclerosis.

3- PON 1 gene

PON1 was the first discovered member of the paraoxonase (PON) multigene family, which includes three members, PON1, PON2, and PON3, whose genes are arranged side by side **(Shunmoogam *et al.*, 2018)**.

The PON1 gene is located on chromosome 7 q21-q22 in humans (figure 11) (proximal region of chromosome 6 in mice). The PON1 gene comprises approximately 26 KB. The coding sequence contains 9 exons with splice donor and acceptor sites typical of mammalian genes **(Vavlukis *et al.*, 2022).**

The promoter region of the PON1 gene contains binding sites for sterol regulatory binding protein 2 (SREBP2) and specificity protein1 (SP-1), which are putative to upregulate PON1 in the presence of statins. Aryl hydrocarbon receptors and peroxisome proliferator-activated receptors (PPARS) have also been reported to regulate the PON1 gene, but their binding sites remain elusive **(Mackness B et Mackness M, 2015).**

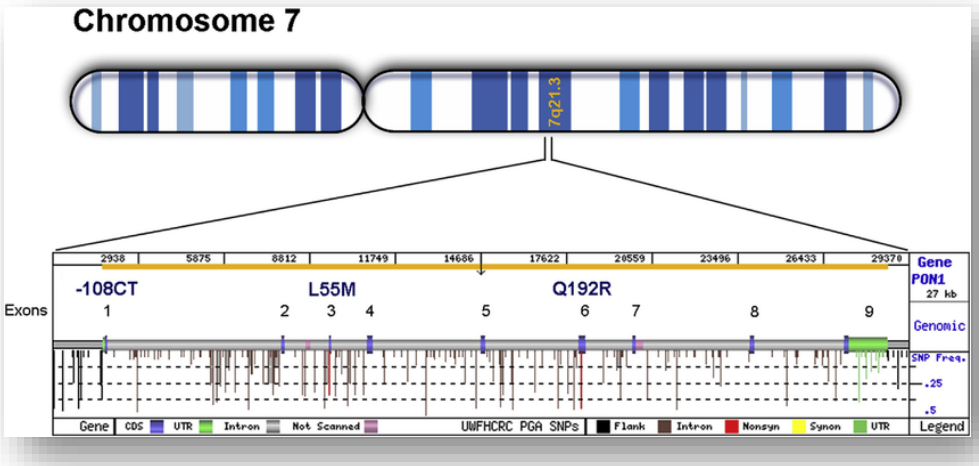


Figure 11: Gene structure of the human PON1 (judit-Masillach et Lucio, 2016).

4- PON1 polymorphisms

The PON1 gene has nearly 200 SNPs (single nucleotide polymorphisms) **(Darneya *et al.*,2020).** Two of them are:

4-1- L55M

It results from leucine (L)/methionine (M) substitution in position 55 in exon 3 rs854560 (c.163A> T) **(AruIJothi; 2018).**

It has a much smaller, but significant, effect on PON1 activity than the QR192 polymorphism **(AruIJothi; 2018).**

4-2- Q192R

It results from glutamine (Q)/arginine (R) substitution in codon 192 in exon 6 located in the coding region **(AruIJothi *et al.*, 2018).**

PON1 Q192R polymorphism affects PON1 catalytic efficiency for some of its substrates **(Gupta *et al.*; 2011).**

As opposed to the polymorphisms in the coding region, mutations of the regulatory region, such as rs705379 (− 108C/T), rs854572 (− 909G/C) and rs705381 (− 162A/G), seem to increase serum PON1 levels **(Grzegorzewska *et al.*, 2021).**

5- Association between PON1 and myocardial infarction

Human serum paraoxonase-1 prevents oxidation of low-density lipoprotein cholesterol (LDL-C) and hydrolyses the oxidized form, therefore preventing the development of atherosclerosis and the coronary artery disease (CAD) **(Navab *et al.*, 2004).** Some clues suggest that PON1 Involved in atherogenesis due to its ability to attenuate Oxidative modification of lipoprotein particles **(Carey *et al.*, 2005).**

PON1 activity has been shown to be lower after acute myocardial infarction or in patients with familial hypercholesterolemia and diabetes mellitus, who are more prone to CAD. As a result, they think that the lower the PON1 activity is, the higher will be the accumulation of oxidized LDL and risk of CAD **(Gupta *et al.*; 2011).**

Due to this, there's been a debate about whether the qualitative or quantitative aspect of PON1 is more correlated with CVD risk. In order to grasp this clearly, we can say that every factor that influences the serum levels of PON1 will certainly influence the anti-oxidative properties of HDL, therefore being associated with atherosclerosis **(Vavlukis *et al.*, 2022).**

There are several studies demonstrating an association between Q192R and L55M polymorphisms and susceptibility to CAD **(Najafi *et al.*, 2009).** Also, there are a few studies that have also looked at association between -108 C/T polymorphism and risk of CAD **(Najafi *et al.*, 2009).**

Few studies show that the R allele of Q192R is an independent risk factor for CVD **(Gupta *et al.*; 2011).**

According to **Sikora *et al.* 2020** genetic PON1 level depletion caused proatherogenic plasma proteome shifts. As a result of the PON1-Q192R polymorphism, APOM and APOD were upregulated in subjects carrying the PON1-192QR genotype, apolipoproteins that inhibit lipid oxidation was downregulated by APOC1 and APOA1, apolipoproteins that regulate cholesterol transport, and APOB, an apolipoprotein that stimulates cholesterol retention, were upregulated. Both findings suggest a proatherogenic proteomic shift by reducing PON1 levels. PON1-192QQ genotype is associated with downregulation of F13B and SERPINA1, both involved in the coagulation process, increasing the risk of atherothrombosis **(Sikora *et al.*, 2020).**

CHAPTER 2
PARAOXONASE 1 (PON1)

A study of **Van Himbergen *et al*., 2008** shows that paraoxonase activity was a risk factor for AMI only and not for CHD in general.

When comparing the highest tertile of paraoxonase activity in current smokers with the lowest tertile of paraoxonase activity in never smokers, the combined effect of paraoxonase activity and smoking status resulted in heart 19-fold greater risk of seizures hypothesized **(Himbergen *et al*., 2008)**.

Practical part

Material and methods

1- Principle of meta-analysis

Meta-analysis did not appear regularly in the medical literature until the late **1970**s, but growing exponentially overtime (figure 12). Moreover, meta-analysis has been shown to be the most cited form of clinical research.

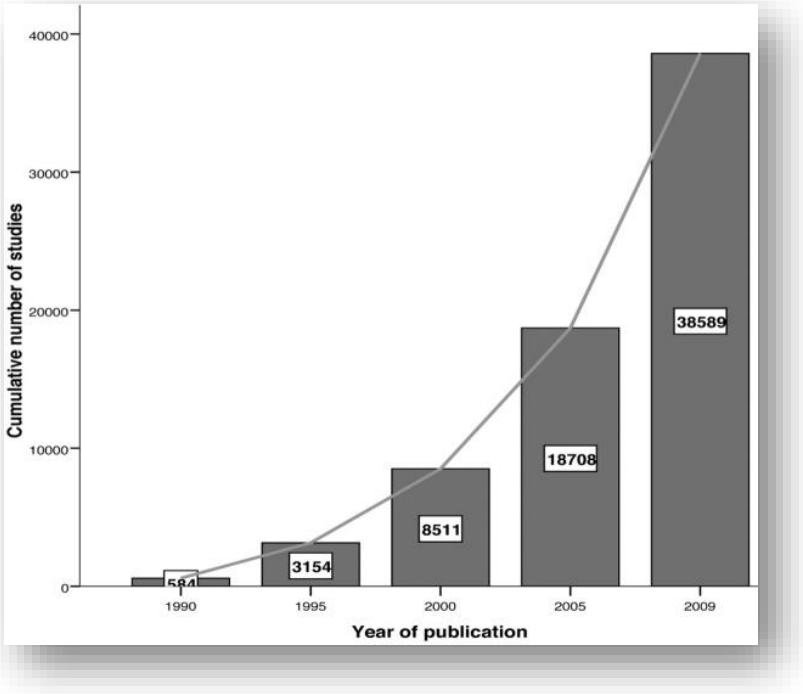


Figure 12: Cumulative of publication about meta-analysis over time, until 17 December 2009

The first statistical meta-analysis was performed in **1904** by **Karl Pearson** in an attempt to overcome the problem of reduced statistical power in studies of small sample sizes.

A meta-analysis is a quantitative formal epidemiological study design used to systematically evaluate the results of previous studies in order to draw a conclusion about this study group. Usually, but not always, research is based on randomized controlled clinical trials. Meta-analysis results may provide more accurate estimates of treatment effects, disease risk factors, or other outcomes than the individual studies contributing to the pooled analysis **(Haiditch, 2010)**.

The results of meta-analysis can improve precision of estimates of effect, answer questions not posed by the individual studies, settle controversies arising from apparently conflicting studies, and generate new hypotheses. In particular, the examination of heterogeneity is vital to the development of new hypotheses.

MATERIAL AND METHOD

Before data are combined in a quantitative way, certain requirements must be met, without which the estimate of the combined effect will be biased, rendering the conclusions drawn inaccurate. The most common biases are

- Publication bias: When results are statistically insignificant, they tend not to be published.
- Selection bias: the selection conditions are not fulfilled.
- Detection bias: the search for studies and conducted incompletely.
- Estimation bias: not all studies performed are published.

The realization of a meta-analysis goes through several steps which are as follows:

-Define the objective of meta-analysis by specifying the disease, the endpoints envisaged and the type of patients.

- Based on the objective and a priori, establish the list of criteria that the trials to be included in the meta-analysis must meet.
- Search for all published and unpublished trials that may match the trials you are looking for.
- Eliminate the studies found whose methodological quality does not sufficiently guarantee the absence of bias, these potentially biased studies risk in turn biasing the result of the meta-analysis.
- Select the trials by applying the pre-established criteria and justifying the exclusions.
- Collect and summarize in tables the characteristics of the tests. Call on the investigators to obtain the missing data and confirm the data retained for the meta-analysis.
- Estimate effects using appropriate statistical techniques when possible (sufficient and available data).
- Compare the different options by sensitivity analyses. If necessary, look for the causes of heterogeneity.

The critical reading of a meta-analysis must verify that these different steps have been followed and correctly carried out.

2- Methodology

2-1 Research strategy

2-1-1 Literature search

It is important in systematic reviews and meta-analyses that the literature search be approached systematically in an effort to exhaust both published and unpublished research. According to Lipsey and Wilson (2001), the exclusion of searching and including will likely to lead to an upward bias in effect sizes. An exhaustive search for studies and research were searched using a combination of the keywords “PON1”, “Q192R”, “L55M”, “myocardial infarction”.

2-1-2 Electronic Databases

In order to conduct a meta-analysis, it is important to do search for studies that have addressed the same research question, using electronic databases such as Google Scholar, PubMed and Science Direct. Our study took the results of various studies related to the association between PON1 polymorphism and MI.

2-2 Study selection

The studies thus found on the databases were selected on the following criteria:

2-2-1 Inclusion criteria

-Studies on the association of the PON1 polymorphism and the risk of developing MI

- A case-control type study established according to defined criteria: construction of two independent groups; patients and controls.

- There should be information available in the publication regarding the size of the two cohorts (patients and controls) and the genotype frequencies of the three genotypes (homozygous wild, heterozygous and homozygous mutated) and/or allelic (wild-type allele and mutated alleles) allowing the calculation of Odds Ratio (OR) and p-value.

2-2-2 Exclusion criteria

- Studies on MI prospecting the effect of polymorphism other than that of our study.

- Studies investigating the effect of the Q192R and L55M polymorphism of the PON 1 gene in the response to a particular treatment for MI.

-Studies that have worked on this polymorphism, but it is associated with other diseases

-Studies without a control population

- Articles only with an abstract.

2-3 Data extraction

As part of our meta-analysis, we collected the following information from each study that was included: author(s), year of publication, country, ethnicity of the study population, size of both the patient and control populations, genotypic and allelic distributions of the patients and controls.

3- Statistical analysis

This is a statistical study based on the calculation of the confidence interval (CI), odds ratio (OR) and the p-value to determine if there is a significant association between the studied polymorphisms and MI.

3-1 Calculation of the Odds ratio

The OR is frequently used to demonstrate the strength of an association between risk factors and clinical outcomes **(Norton *et al*., 2018).** The odds ratio is a ratio of two sets of odds: the odds of the event occurring in an exposed group versus the odds of the event occurring in a non-exposed group, the larger the odds ratio, the higher odds that the event will occur with exposure **(Tenny et Hoffman, 2022)**. To calculate the OR we established following contingency table:

Table I: Cross-contingency table for a case-control study.

	Case (M+)	**Witness (M-)**
Exposed (E+)	A	C
Unexposed (E-)	B	D
Total	A+B	C+D

Where

A = Number of exposed cases

B = Number of exposed non-cases

C = Number of unexposed cases

D = Number of unexposed non-cases

OR= **The probability of being exposed (ill)** / **The probability of not being exposed (healthy)**

«Case exposure probability»: (case E+/case E-) / **«Probability of exposing witnesses»: (witnesses E+/witnesses E-)**

Either: **OR = A/B/C/D = (A*D/B*C)**

3-2 Confidence interval

The 95% confidence interval (CI) is used to estimate the precision of the OR. A large CI indicates a low level of precision of the OR whereas a small CI indicates a higher precision of the OR. It is important to note, however, that unlike the p-value, the 95% CI does not report a measure's statistical significance **(Szumilas, 2010).**

Statisticians use confidence intervals to measure the uncertainty in a sample variable. The confidence is in the method, not in a particular CI. Approximately 95% of the intervals constructed would capture the true population mean if the sampling method was repeated many times **(Hayes, 2023).**

3-3 p-value

P-value is the probability of rejection or noncompliance reject the null hypothesis (H0) **(Boos; Stefanski, 2011).** H0 is the hypothesis that there is no difference between two groups for a specific variable **(Thiese *et al*., 2016).**

P-value is calculated as the probability that the observed effect equator greater than when H0 is true. The P-value measures the strength of evidence for H0. The smaller the p-value, the stronger the evidence against H0 **(O'Brien *et al*., 2015).**

To conclude statistical significance, reject H0, and show differences between groups, the P value should be compared to a predetermined alpha (α) value. The most commonly used α level is 0.05 **(Thiese *et al.*, 2016).**

3-4 *Z* value

Z-value is a statistical measure that describes the relationship between a value and the group of a set of values **(Nevil,2023)**

The z-scores are measured using standard deviations from the mean. When the z-score is 0, it means that the score of the data point is the same as the mean score. A z-score of 1.0 indicates that the value is one standard deviation away from the mean. Z-scores can be positive or negative, with a positive value indicating a score above the average and a negative value indicating a score below the average **(Curtis et al.,2016).**

Z-scores are calculated as follows:

$$Z = \frac{(\chi - \mu)}{\delta}$$

where χ = the observed measurement, μ = the expected measurement (population mean), and σ = the population standard deviation

3-5 Hardy-Weinberg equilibrium

Hardy-Weinberg equilibrium (HWE) is the state in which the genotype frequencies of the two alleles of an autosomal gene locus are discretely generated after random mating in an infinitely large population **(Mayo.,2008)**

Since alleles of diploid loci are randomly reassorted at each new conception, it follows that for allele frequencies p and q (where p+q=1) for biallelic loci, the frequencies of genotypes are expressed by the expansion (p þ q)2 **(Rodriguez *et al.*, 2008)**

So**:** $$HWE = p\,2 + 2\,pq + q\,2$$

Results and discussion

1- Characteristics of the included studies

We identified a total of 200 studies which examined the association of L55M and Q192R polymorphisms of the PON1 gene and cardiovascular disease. According to the inclusion and exclusion criteria, 26 articles identified as potentially relevant studies. These articles have documented the association between the both studied polymorphisms and the risk of MI. 12 articles were excluded according to our exclusion criteria already cited. 14 studies were finally included in the analysis (table II).

Table II: List of studies published on PubMed, Google Scholar and Science direct carried out on the impact of the Q192R and L55M polymorphisms of the PON1 gene.

L55M and Q192R polymorphisms of the PON1 gene and the association with cardiovascular disease.	**200**
L55M and Q192R polymorphisms of the PON1 gene and myocardial infarction.	26
Number of studies selected.	14

The main characteristics of the selected studies are presented in the table below (Table III). The studies were carried out in China, India, Pakistan, Germany, Spain, UK, Italy, Mexico, Brazil, Tunisia, Egypt and they were published from 2000 to 2018. In total, 9882 individuals divided to 4509 cases and 5373 controls were included in this meta-analysis. Case-control studies come either from the hospital setting or from the general population. All control samples of the included studies were in HWE.

Table III: Characteristics of the selected studies.

Author	Year	Country	Ethnicity	Cases	Controls	polymorphism	HWE		Source of cohorts	Average age		Genotyping method
							Cases	controls		Cases	Witnesses	
Aubo et al.	2000	Spain	Caucasian	156	310	Q192R	1	1	Population	57.1	55.4	PCR-RFLP
Senbanergee el al.	2000	Mexico	American	492	518	Q192R	1	1	Hospital environment	57	56.5	PCR-RFLP
						L55M	1	1				
Gardemann et al.	2000	Germany	Caucasian	1059	1190	Q192R	1	1	Hospital environment	62.2	61.4	PCR-RFLP
						L55M	1	1				
Senti et al.	2001	Spain	Caucasian	280	396	Q192R	1	1	Hospital environment	57.7	53.7	PCR-RFLP
Arca et al.	2002	Italy	Caucasian	163	178	L55M	1	1	Hospital environment	60.5	60.7	PCR-RFLP
Ferre et al.	2002	Spain	Caucasian	215	215	Q192R	1	1	Hospital environment	60.6	62.1	PCR-RFLP
						L55M	1	1				

Tobin et al.	2004	UK	Caucasian	547	505	Q192R	0.98	0.98	Hospital environment	61.9	58.6	PCR-RFLP
						L55M	1	0,9				
Li et al.	2005	China	Asian	154	154	Q192R	0.98	0.98	Hospital environment	56.2	56.3	PCR-RFLP
Baum et al.	2006	China	Asian	234	336	Q192R	0.96	0.82	Hospital environment	85.3	71.0	PCR-RFLP
Saeed et al.	2007	Pakistan	Asian	211	370	Q192R	0.92	0.86	Hospital environment	54	49.7	PCR-RFLP
						L55M	0.27	0.81				
Izar et al.	2009	Brazil	American	386	604	Q192R	1	1	Hospital environment	62	59	PCR-RFLP
Kallel et al.	2010	Tunisia	Arab	310	375	Q192R	1	1	Hospital environment	53.9	50.9	PCR-RFLP
						L55M	1	1				
Abdel Rahman et al.	2015	Egypt	Arab	102	72	Q192R	1	1	Hospital environment	45	37	PCR-RFLP
Aruijothi et al.	2018	India	Asian	200	150	Q192R	1	1	Hospital environment	54.8	51.7	PCR-RFLP
						L55M	1	1				
Total				**4509**	**5373**					**54.5**	**48**	

2- Distribution of genotypic and allelic frequencies in studies of the meta-analysis

Table IV and V show the distribution of genotypic frequencies (QQ, RR and QR) (LL, MM and LM) and allelic frequencies (Q and R) (L and M) of the PON1 gene of the fourteen studies: Thirteen studies about the Q192R polymorphism and eight about the L55M polymorphism retained for our meta-analysis.

Table IV: Genotypic and allelic frequencies of the Q192R polymorphism of the PON1 gene in cases and controls.

Author/Year	Case genotypes			Genotypes of controls			Alleles for case		Alleles for controls	
	QQ	QR	RR	QQ	QR	RR	Q	R	Q	R
Aubo *et al.* 2000	84	60	12	154	123	33	288 (0.73)	84 (0.26)	431 (0.69)	189 (0.30)
Senbanergee *et al*. 2000	230	257	5	279	226	13	717 (0.72)	267 (0.27)	784 (0.76)	252 (0.24)
Gardemann *et al*. 2000	533	442	84	608	498	84	1508 (0.71)	610 (0.29)	1714 (0.72)	666 (0.28)
Senti *et al*. 2001	139	109	32	193	165	38	387 (0.69)	173 (0.30)	551 (0.69)	214 (0.30)
Ferre *et al*. 2002	105	87	23	106	93	16	297 (0.69)	133 (0.31)	297 (0,69)	125 (0.29)
Tobin *et al*.2004	291	206	50	261	211	33	788 (0.72)	306 (0.27)	733 (0.72)	277 (0.27)
Li *et al.* 2005	27	66	61	31	73	50	120 (0.38)	188 (0.61)	135 (0.43)	173 (0.56)
Baum *et al.* 2006	38	91	102	65	135	110	167 (0.35)	295 (0.63)	265 (0.39)	355 (0.52)
Saeed *et al.* 2007	75	102	26	166	137	46	252 (0.60)	154 (0.36)	469 (0.63)	229 (0.30)
Izar *et al.* 2009	120	217	47	181	335	81	457 (0.59)	311 (0.4)	697 (0.58)	497 (0.42)
Kallel *et al.* 2010	129	127	54	191	143	41	385 (0.62)	235 (0.38)	525 (0.70)	225 (0.30)
Abdel Rahman *et al.* 2015	39	50	13	18	6	48	128 (0.63)	76 (0.37)	42 (0.29)	102 (0.70)
AruIJothi *et al.* 2018	60	101	39	75	60	15	221 (0.55)	178 (0.45)	210 (0.7)	90 (0.3)
Total 13	**1870**	**1915**	**548**	**2328**	**2205**	**608**	**5715**	**3010**	**6853**	**3394**

Table V: Genotypic and allelic frequencies of the L55M polymorphism of the PON1 gene in cases and controls.

L55M										
Author/Year	**Case genotypes**			**Genotypes of controls**			**Alleles for case**		**Alleles for controls**	
	LL	**LM**	**MM**	**LL**	**LM**	**MM**	**L**	**M**	**L**	**M**
Senbanergee et al., 2000	30	195	267	42	188	288	255 (0.26)	534(0.74)	272 (0.26)	764 (0.74)
Gardemann et al.,2000	472	454	133	459	555	176	1398(0.62)	720(0.32)	1473(0.65)	907(0.4)
Arca et al.,2002	59	84	20	76	81	21	202(0.61)	124(0.38)	233(0.65)	123(0.34)
Ferre et al., 2002	78	107	30	86	91	38	263 (0.61)	167 (0.38)	263 (0.61)	167 (0.38)
Tobin et al., 2004	86	240	221	66	235	204	412 (0.39)	682 (0.64)	367 (0.34)	643 (0,61)
Saeed et al.,2007	127	68	6	209	130	11	322 (0.76)	80(0.18)	548 (0.74)	152 (0.20)
Kallel et al., 2010	139	135	36	147	178	50	413 (0.66)	207 (0.33)	472 (0.62)	278 (0.37)
Aruljothi et al.,2018	83	97	20	90	45	15	263 (0.65)	137 (0.34)	225 (0.75)	75 (0.25)
Total 8	**1074**	**1380**	**733**	**1175**	**1503**	**803**	**3528**	**2651**	**3853**	**3109**

Differences in the expression of the three genotypic forms in patients and witnesses were observed in the studies included in the meta-analysis. In all meta-analysis case-control studies, witnesses and case cohorts have higher genotypic frequencies for both QQ and QR genotypes compared to the RR genotype. We also observe that the frequencies of the wild Q allele are higher compared to the mutated R allele in both populations cases and witnesses in all studies except for the studies by **Li *et al.*, 2005** and **Baum *et al.*, 2006** (table IV) where the results are reversed.

In table V, all case-control studies included in our meta-analysis, cases and controls cohorts have higher genotypic frequencies for both LL and LM genotypes compared to the MM genotype. We also observe that the frequencies of the wild L allele are higher compared in both populations' cases and witnesses in all studies except for the study by **Senbanergee *et al.*, 2000** and **Tobin *et al.*, 2004** where the results are reversed i.e. there is a predominance of the M allele rather than the L allele.

3- Effect of L55M and Q192R polymorphisms of PON1 gene in MI

Table VI was generated to assess the impact of the mutated genotype RR and the mutated allele R of the Q192R polymorphism on the risk of developing MI in each study included in our meta-analysis.

Table VI: Effect of the RR genotype and R allele of the PON1 gene in the occurrence of MI.

Study name	RR vs. QQ				R vs. Q			
	OR	95% CI	*Z*-value	*p*-value	OR	95% CI	*Z*-value	*p*-value
Aubo et al.2000	0.667	0.327 -1,359	-1.116	0.264	0.665	0.494 -0.895	-2,690	**0.007***
Senbanergee et al.2000	0.467	0.164 -1.328	-1.428	0.153	1.159	0.949 -1.415	1.444	0.149
Gardemann et al.2000	1.141	0.825 -1.577	0.796	0.426	1.041	0.914 -1.185	0.607	0.544
Senti et al.2001	1.169	0.696 -1.963	0.591	0.554	1.151	0.906 -1.462	1.154	0.249
Ferre et al.2002	1.451	0.726 -2.901	1.054	0.292	1.064	0.794 -1.425	0.416	0.678
Tobin et al.2004	1.359	0.849 -2.175	1.278	0.201	1.028	0.849 -1.244	0.279	0.780
Li et al.2005	1.401	0.741 -2.649	1.037	0.300	1.223	0.887 -1.685	1.226	0.220
Baum at al.2006	1.586	0.979 -2.570	1.874	0.061	1.836	1.421 -2.372	4.649	**0.000***
Saeed at al.2007	1.251	0.720 -2.174	0.794	0.427	1.252	0.970 -1.616	1.723	0.085
Izar et al.2009	0.875	0.571-1.341	-0.612	0.541	0.954	0.794-1.148	-0.49	0.620
Kallel et al.2010	1.950	1.227-3.100	2.825	**0.005***	1.424	1.137-1.224	3.078	**0.002***
Abdel Rahman et al.2015	0.125	0.055-0.286	-4.916	**0.000***	0.244	0.135-0.386	-6.029	**0.000***

Aruijothi et al.2018	3.250	1.638-6.450	3.370	**0.001***	1.879	1.370-2.578	3.912	**0.000***
Total	**1.122**	**0.985-1.278**	**1,730**	**0.084**	**1.027**	**0.966-1.093**	**0.859**	**0.390**

*p <0.05

Table VII was generated to assess the impact of the mutated genotype MM and the mutated allele M of the L55M polymorphism on the risk of developing MI in each study included in our meta-analysis.

Table VII: Effect of the MM genotype and M allele of the PON1 gene in the occurrence of MI.

Study name	MM vs LL				M vs L			
	OR	**95% CI**	***z*-value**	***p*-value**	**OR**	**95% CI**	***z*-value**	***p*-value**
Senbanergee et al,2000	1.298	0.789-2.134	1.028	0.304	0.746	0.608-0.914	-2.828	**0.005***
Gardemann et al,2000	0.735	0.567-0.952	-2.329	**0.020***	0.836	0.740-0.945	-2.866	**0.004***
Arca et al,2002	1.227	0.609-2.472	0.572	0.567	1.163	0.851-1.590	0.946	0.344
Ferre et al, 2002	0.870	0.493-1.537	-0.478	0,632	1 000	0.760-1.316	0.000	1 000
Tobin et al, 2004	0.831	0.573-1.207	-0.970	0,332	0,945	0.791-1.128	-0.628	0,530
Saeed et al,2007	0.898	0.324-2.487	-0.208	0.835	0.869	0.661-1.214	-0.711	0.477
Kallel et al,2010	0.761	0.468-1.239	-1.097	0.273	0.851	0.681-1.064	-1.417	0.156
Aruljothi,2018	1.446	0.695-3.009	0.986	0.324	1,563	1.120-2.180	2.627	**0.009***
Total	0.868	0.738-1.020	-1.722	0.085	0.900	0.836-0.968	-2.832	**0.005***

*p <0.05

According to table VI, heterogeneity was observed among the selected studies. Results of Five of the thirteen case-control studies included in our meta-analysis showed an existence association between the Q192R polymorphism of the PON1 gene and risk of heart attack. Indeed, the calculation of odds ratios and 95% CI note a statistical difference between cases and witnesses (*p*-value are less than 0.05). The study conducted by **Aubo *et al.*, 2000, Baum *et al.*, 2006, Kallel *et al.*, 2010, Abdel Rahman et al., 2015 and Aruljothi *et al.*, 2018** shows that the R allele is statistically associated with MI susceptibility with a value of p value less than 0.05.

According to table VII, there is no significant association of the MM genotype of the PON1 gene and risk of MI. Results of three of the eight case-control research blanketed in our meta-analysis notice a statistical difference of the M frequencies between cases and witnesses. *P*-value less than 0.05 in studies by **Senbanergee *et al*., 2000, Gardemann *et al*., 2000 and Aruljothi *et al*., 2018** shows that the M allele is statistically associated with MI.

4- Result of the meta-analysis

Some previous studies have reported conflicting results related to the risk of MI, which is why we have grouped the fourteen studies under five genetic model subgroups analyses by origin ethnicity to assess the potential source of heterogeneity between studies.

4-1- Association of Q192R polymorphism and the risk of MI

Table VIII: Results of the association of the Q192R polymorphism of the PON1 gene and MI.

Genetic model		Statistics for each study			
		OR	**Z-Value**	***P*-Value**	**95 % CI**
Total	**R vs Q**	1.027	0.859	0.390	0.966-1.093
	RR vs QQ	1.122	1.730	0.084	0.985-1.278
	QR vs QQ	1.081	1.772	0.076	0.992-1.179
	QR+RR vs QQ	1.090	2.075	**0.038***	1.005-1.182
	RR vs QQ + QR	1.079	1.216	0.224	0.954-1.221
Caucasian	**R vs Q**	1.012	0.271	0.786	0.927-1.105
	RR vs QQ	1.131	1.145	0.252	0.916-1.395
	QR vs QQ	0.952	-0.819	0.413	0.845-1.071
	QR+RR vs QQ	0.980	-0.352	0.725	0.876-1.097
	RR vs QQ + QR	1.156	1.396	0.163	0.943-1.417
Asian	**R vs Q**	1.549	6.311	**0.000***	1.352-1.774
	RR vs QQ	1.738	4.256	**0.000***	1.348-2.242

	QR vs QQ	1.498	3.514	**0.000***	1.196-1.876
	QR+RR vs QQ	1.583	4.326	**0.000***	1.285-1.949
	RR vs QQ + QR	1.367	2.848	**0.004***	1.102-1.695
Arab	**R vs Q**	1.048	0.467	0.640	0.861-1.275
	RR vs QQ	0.937	-0.341	0.733	0.643-1.365
	QR vs QQ	1.478	2.570	**0.010***	1.097-1.991
	QR+RR vs QQ	1.275	1.763	0.078	0.973-1.671
	RR vs QQ + QR	0.781	-1,384	0.166	0.551-1.108
American	**R vs Q**	0.973	-0.396	0.692	0.852-1.112
	RR vs QQ	0.727	-1.706	0.088	0.504-1.049
	QR vs QQ	1,110	1.109	0.267	0.923-1.336
	QR+RR vs QQ	1,055	0.587	0.557	0.881-1.264
	RR vs QQ + QR	0.685	-2.109	**0.035***	0.483-0.974

*p <0.05

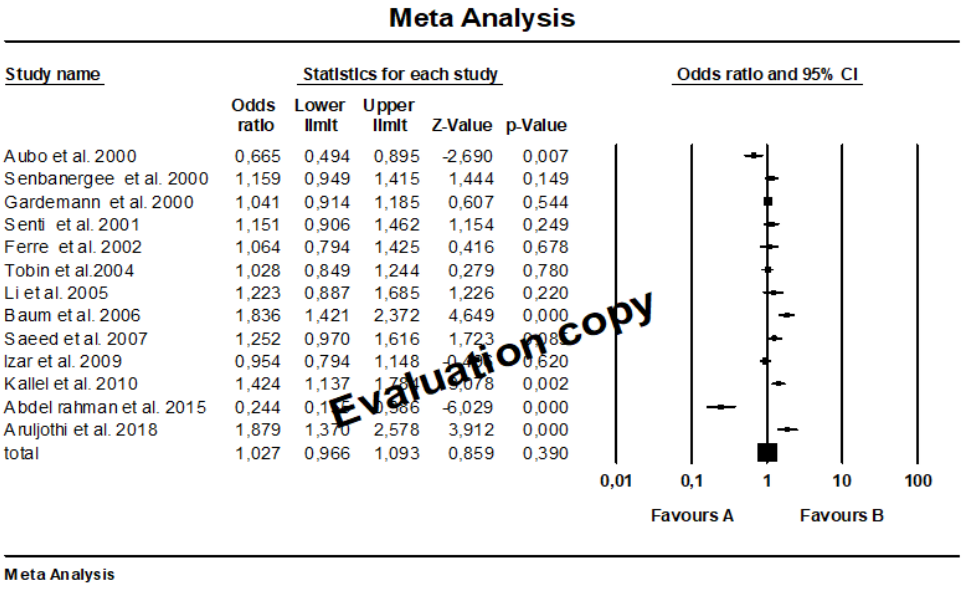


Figure 13: forest plot on the association of the Q192R polymorphism of the PON1 gene and the risk of MI

A total of 13 studies with 4333 patients and 5141 controls were eligible for the pooled analysis of Q192R polymorphism. Overall, no significant association was found between the PON1 gene Q192R polymorphism and MI. The main results of meta-analysis are shown in Table VIII. However, in the stratification analysis by type, a significantly decreased risk of MI in recessive model (OR 1,027, 95% CI 0.966-1.093) was identified.

In a stratified analysis by specific ethnicity, the Q192R polymorphism had a significant effect under all genetic models in Asians (allelic model: OR 1,549 , 95%CI 1.352-1.774.; homozygote model: OR 1.738, 95%CI 1.348-2.242; heterozygote model: OR 1.498, 95%CI 1.196-1.876; dominant model: OR 1.583, 95%CI 1.285-1.949; and recessive model: OR 1.367, 95%CI 1.102-1.695) and Arab populations under dominant models (OR 1.275, 95%CI 0.973-1.671) and Americans under recessive model (OR 0.685, 95%CI 0.483-0.974).No significant association between the Q192R polymorphism and MI risk were detected in Caucasian, American and Arab populations in other genetic models (Table VIII).

Figure 13 presents a forest plot that allows comparison of the impact of the Q192R polymorphism on PON1 and the results of different studies dealing with MI selected in the meta-analysis. According to this graph, the intervals of confidence of 13 studies cross the absence of effect, so they are not significant, the same is true for the result of the meta-analysis, like our result that shows no association between the polymorphism and MI.

4-2-Association of L55M polymorphism and the risk of MI

Table IX: Results of the association of the L55M polymorphism of the PON1 gene and MI.

Genetic model		Statistics for each study			
		OR	***Z*- Value**	***P*- Value**	**95 % CI**
Total	**M vs L**	0.930	- 2.049	**0.040***	0.868-0.997
	MM vs LL	0.999	-0.020	0.983	0.877-1.137
	ML vs LL	1,005	0.080	0.936	0.900-1.122
	MM+ML vs LL	1.002	0.048	0.962	0.906-1.110
	MM vs LL+ML	0.996	-0.066	0.947	0.889-1.117
Caucasian	**M vs L**	0.945	-1.270	0.204	0.865-1.031
	MM vs LL	0.910	-1.082	0.279	0.766-1.080
	ML vs LL	0.909	-1.335	0.182	0.791-1.045
	MM +ML vs LL	0.965	-0.523	0.601	0.844-1.103
	MM vs LL+ML	0.960	-0.521	0.602	0.825-1.118

Asian	**M vs L**	1.247	2.016	**0.044***	1.006-1.545
	MM vs LL	1.424	1.212	0.226	0.804-2.522
	ML vs LL	1.342	2.089	**0.037***	1.018-1.770
	MM +ML vs LL	1.353	2.234	**0.026***	1.038-1.764
	MM vs LL+ML	1.264	0.820	0.412	0.722-2.213
Arab	**M vs L**	0.851	-1.417	0.156	0.681-1.064
	MM vs LL	0.761	-1.097	0.273	0.468-1.239
	ML vs LL	0.802	-1.342	0.180	0.581-1.107
	MM +ML vs LL	0.793	-1.489	0.137	0.585-1.076
	MM vs LL+ML	0.854	-0.676	0.499	0.540-1.350
American	**M vs L**	0.746	-2.828	**0.005***	0.608-0.914
	MM vs LL	1.298	1.028	0.304	0.789-2.134
	ML vs LL	1.452	1.435	0.151	0.872-2.417
	MM+ML vs LL	1.359	1.237	0.216	0.836-2.208
	MM vs LL+ML	0.948	-0.425	0.671	0.740-1.214

*p <0.05

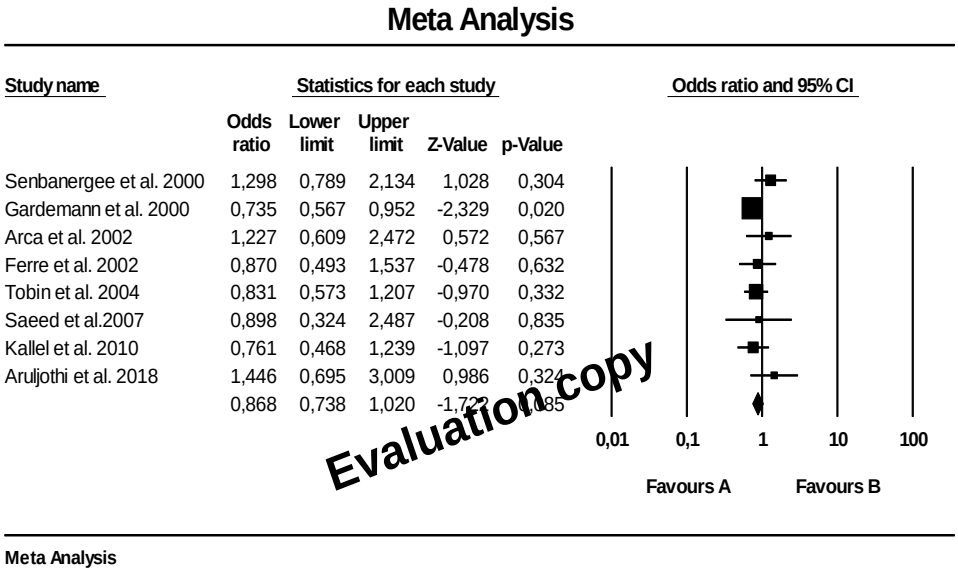


Figure 14: Forest plot on the association of the L55M polymorphism of the PON1 gene and the risk of MI

The association between L55M polymorphism and the risk to MI was analyzed in 8 studies; there was no statistical evidence of the association between the L55M polymorphism and an overall risk of MI (Table IX). In the subgroup analysis, no association among this polymorphism and MI was observed in all genetic models except the allelic one where the mutated allele M was associated with the risk of MI (p = 0.040). When performing a meta-

analysis by ethnicity, higher risk was detected in Asian populations (allelic model: OR 1,247 ,95 % CI 1.006-1.545; heterozygote model: OR 1,342, 95%CI 1.018-1.770; and recessive model: OR 1,353, 95%CI 1.038-1.764), but not in Caucasian, Arab and American populations except in the allelic model in the American population (p = 0.005) (Table IX).As the first polymorphism Q192R, results of the subgroup analysis for the second polymorphism L55M showed that ethnicity could be a cause of heterogeneity.

Figure 14 presents a forest diagram that allows comparison of the impact of the L55M polymorphism on PON1 and the results of different studies dealing with MI selected in the meta-analysis. According to this graph, the intervals of confidence of 8 studies cross the absence of effect, so they are not significant, the same is true for the result of the meta-analysis, in this case it crosses the line of absence of effect and proves a significant association, on the other hand, the meta-analysis itself did not find a significant effect of the variable studied.

5- Discussion

Although the multifactorial nature of MI is well known, genetic factors are considered to be strong determinants of this disease. Thus encouraging researchers to search for the responsible genes. PON1 genes are known to determine strongly the activity of serum paraoxonase against exogenous substances. Thus, many association studies have reported on PON1 -L55M and Q192R polymorphisms and CHD **(Mackness *et al*., 2001).** These studies have yielded apparently conflicting results, perhaps partly because of small sample sizes, racial or regional differences. Therefore, we performed this meta-analysis to assess the relationship between PON1 polymorphisms and MI risk.

The present meta-analysis suggests that the Q192R polymorphism of the PON1 gene is not statistically associated with the risk of developing MI. This agrees with the results of the meta-analyses by **Li et al., (2005)**, who were unable to demonstrate the existence of the association between the R allele of the PON1 gene and susceptibility to MI. However, our results are inconsistent with those of some meta-analyses that confirmed an association between the Q192R polymorphism of the PON1 gene and MI. we take for example the case of **Guxens et al., (2007)** who suggests that QQ genotype is associated with greater susceptibility to MI. In addition to **Hernández-Díaz et al., (2016)** The 192R allele significantly decreased the risk of MI (OR 0.75, 95%CI 0.57–0.99) and CAD (OR 0.91,

95%CI 0.84–0.98); however, individuals with 192Q allele had a markedly increased risk of coronary artery disease development (OR 1.38, 95%CI 1.22–1.56). The Q allele is a risk allele for the development of coronary artery disease. It can be argued that the Q allele can lead to HDL deficiency and thus reduced PON1 activity due to coexisting oxidative stress. In addition, HDL deficiency is known to increase the risk of heart attack. In a meta-analysis done by **Wang *et al.*, (2018)**, an association was found between the Q192R variant and CHD risk both under the dominant model (pooled OR: 1,26, 95 % CI: 1.04-1.54, P = 0.021) and recessive model (pooled OR: 1,20, 95 % CI: 1.03-1.40, P= 0.021),

The results of the present meta-analysis showed no significant associations of the L55M polymorphism and MI In the overall and subgroup analyses by geographic areas, among all analysis models except in the Asian population. The findings were consistent with the previous meta-analyses. **Zhang et *al.*, (2019)**, a total of 46 studies, involving 15,554 cases and 18,137 controls, were included in his meta-analysis. Overall analysis showed an insignificant association between PON1 L55M polymorphism and CAD and MI under all genetic models. However, subgroup analyses showed a significant association in Asians like our results. Also, **Zhang *et al.*, (2022)** have examined by meta-analysis the association between PON1-L55M polymorphism and risk of CHD in the Chinese population. The results showed no significant associations with CHD among all analysis models. Another meta-analysis on the Chinese population that of **Wang *et al.*, (2018)** did not show any association of L55M variant with the susceptibility to either CHD or IS. However, our results do not agree with those of **Hernández-Díaz *et al.*, (2016)** who found that the L55M polymorphism showed a significant association with heart diseases in Europeans (OR 1.44, 95%CI 1.33–1.56) and Asians (OR 1.18, 95%CI 1.03–1.35).

This difference in the results of different meta-analyses may be related to several factors, such as sample size, ethnicity, control sources (hospital or population), genotyping method, participant's lifestyle, diet, and setting in different countries.

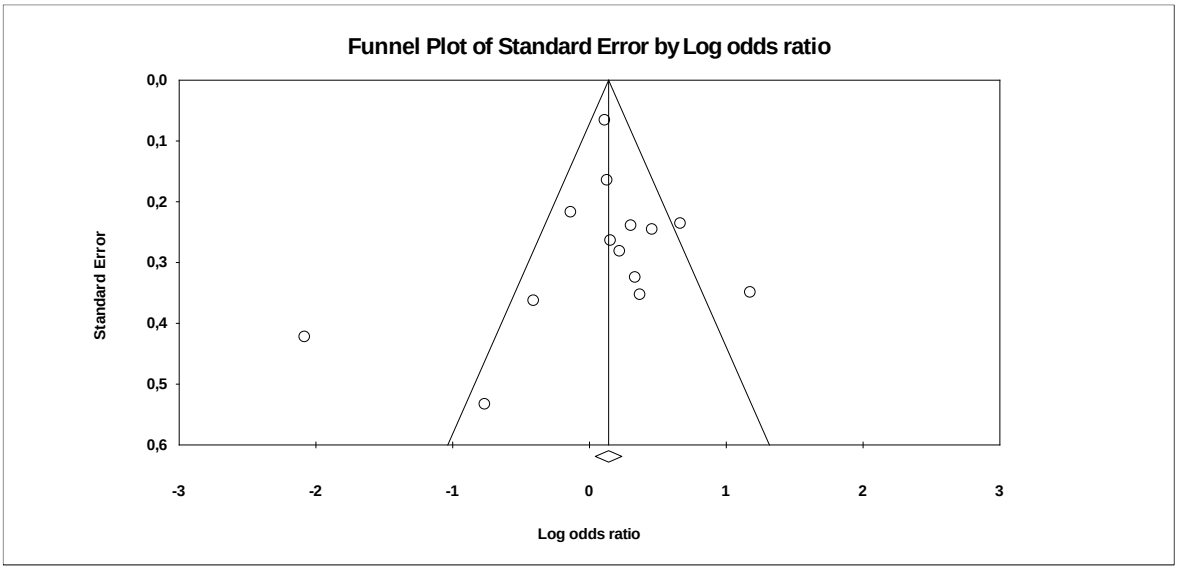
Our meta-analysis had some limitations that need to be described and considered when interpreting the results. The small number of studies and the relatively small sample size of the referenced studies may reduce statistical power and weaken the results of the overall meta-analysis. Our meta-analysis didn’t include a lot of populations, and we found no studies of other races such as Africans, Latinos, or mixed races. Publication bias may be present as only published studies were included. Finally, the effects of gene-gene and gene-

environment interactions that might influence the L55M and Q192R polymorphisms in the PON1 gene have not been studied.

Publication Bias

Begg's funnel plot was used to assess the publication bias of the selected literature. The shape of the funnel plot for Q192R variants and the susceptibility of MI appears to be symmetrical. Subsequently, Egger's test was used for the statistical assessment of funnel plot symmetry. Results showed that there was significant publication bias in **Abdel Rahman *et al.*, 2015**'s study (figure 15).

Results of Begg's funnel plot for L55M variants and the susceptibility of MI showed that there was no significant publication bias in any of the pooled studies (figure 16).



. **Figure 15: Funnel plot for the association between the Q192R polymorphism of the PON1 gene and the risk of MI.**

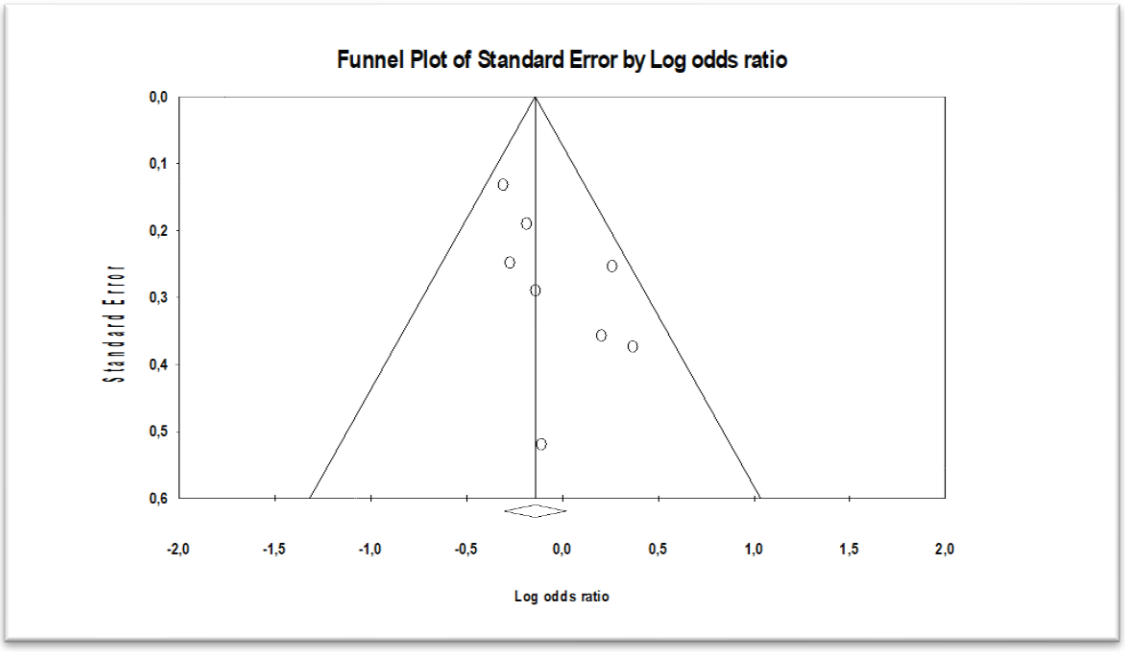


Figure 16: Funnel plot for the association between the L55M polymorphism of the PON1 gene and the risk of MI.

Conclusion and perspectives

CONCLUSION AND PERSPECTIVES

The burden of cardiovascular disease is substantial and increasing worldwide, with the majority of those affected living in developing countries. Cardiovascular disease is now the second-leading cause of death after infectious diseases in most African countries, accounting for 11% of all deaths **(Jamison *et al*., 2006).**

This meta-analysis aims to assess the effect of the L55M and Q192R polymorphisms of the PON1 gene and the risk of MI. For this, we have grouped together all the case-control studies dating from 2000 to 2018 which have dealt with this association. Fourteen relevant studies were selected.

Our results showed no significant association between L55M polymorphisms and MI. However, subgroup analysis, performed by ethnicity, showed this association was significant in the Asian population under four genetic models (M vs L: OR=1,247; 95%CI=1.006-1.545 MM vs LL: OR=1,424, 95%CI=0.804-2.522; ML vs LL: OR=1.005, 95%CI=0.900-1.122, MM+ML vs LL: OR=1.002, 95%CI=0.906-1.110, MM vs LL+ML: OR=0.996, 95%CI=0.889-1.117). However, the association was still insignificant among Caucasians, Arabs and Americans indicating that ethnicity differences had a significant impact on the polymorphism effects and that Asians are more susceptible toPON1 polymorphisms in occurrence of MI.

For the Q192R polymorphism, our meta-analysis demonstrated that Q192R polymorphism may not be associated with MI risk. However, in the stratification analysis by type, a significantly decreased risk of MI in recessive model (OR 1,079, 95% CI 0.954-1.221) was identified. Also in a stratified analysis by specific ethnicity, the Q192R polymorphism had a significant effect under all genetic models in Asians (allelic model: OR 1,549, 95%CI 1.352-1.774; homozygote model: OR 1.738, 95%CI 1.348-2.242; heterozygote model: OR 1.498, 95%CI 1.196-1.876; dominant model: OR 1.583, 95%CI 1.285-1.949 ; and recessive model: OR 1.367, 95%CI 1.102-1.695) and Arab populations under dominant models (OR 1.275, 95%CI 0.973-1.671) and Americans under recessive model (OR 0.685, 95%CI 0.483-0.974).No significant association between the Q192R polymorphism and MI risk were detected in Caucasian, American and Arab populations in other genetic models.

In conclusion, this meta-analysis demonstrated that the PON1 L55M and Q192R polymorphisms may not be associated with the MI risk. For future association studies, strict selection of patients and controls, larger studies of different ethnic populations will be required to clarify the findings.

CONCLUSION AND PERSPECTIVES

Nevertheless, our meta-analysis has certain limits, the relatively small size of the cohorts used for these studies does not make it possible to highlight the real effect of this polymorphism on the ethnic origin of this pathology

As a result of this work, we consider the following perspectives:

- Include studies with larger sample sizes to increase statistical power.
- Include large studies that include different ethnicities such as African, Latino and mixed to better understand this possible association.
- Study the gene-gene and gene-environment interactions between this polymorphism and the risk of MI.

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Webography

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summary

ملخص

فحصت العديد من الدراسات العلاقة بين تعدد الأشكال باروكسوناز 1 L55M-و Q192Rوخطر الإصابة باحتشاء عضلة القلب، لكن النتائج ظلت غير متسقة. لذلك نهدف إلى معالجة هذا الارتباط من خلال إجراء تحليل وصفي محدث.

تم تضمين مجموعه 14 دراسة حالة وشواهد ذات صلة نُشرت من 2000 إلى 2018 في التحليل الوصفي (4509 حالة و5373 مجموعة تحكم). تم تحليل البيانات المستخرجة إحصائياً، واستخدمت نسب الأرجحية بفواصل ثقة 95٪ لتقدير قوة الارتباط.

تظهر نتائج دراستنا ارتباطًا غير مهم بين تعدد الأشكال المدروس و RR و MM في النماذج تقريبًا باستثناء حالة العرق الآسيوي M) مقابل L: OR = 0.930 ؛ 95٪ CI = 0.868-0.997 ، MMمقابل OR = 0.999 :LL ، 95٪ CI = 0.877-1.137 =؛ ML مقابل OR = 1.005 :LL ، 95٪ CI = 0.900-1.122 ، MM + MLمقابل OR :LL = 1.002 ، 95٪ CI = 0.906-1.110 ، MMمقابل OR = 0.996 :LL + ML ، 95٪ (CI = 0.889-1.117 ، Rمقابل OR: 1.027 :Q ، 95٪ CI: 0.966-1.093 ، RRمقابل OR = 1.122 95٪ CI = 0.985-1.278 ، QQ: OR = 1.081 ، 95٪ CI = 0.992-1.179 ، QQ: OR = 1.090 ، QR + RRمقابل QR ، 95٪ CI = 1.005-1.182 =، RRمقابل .(QQ + QR: OR = 1.079 95٪ CI = 0.954-1.221 وبالمثل، لم يُظهر تحليل المجموعات الفرعية المصنفة حسب العرق أي ارتباط مهم في كل نموذج وراثي في السكان الأمريكيين أو العرب أو القوقازيين.

في الختام، لا ترتبط تعدد الأشكال L55M و Q192Rفي جينات PON1 بقابلية الإصابة بـ .MI ومع ذلك، كان الارتباط مهمًا في السكان الآسيويين. يجب إجراء المزيد من الدراسات عالية الجودة للتحقق من صحة الاستنتاجات الحالية.

الكلمات الأساسية: جينPON1 ، احتشاء القلب، التحليل الوصفي، تعدد الأشكال Q192R و.L55M

Résumé

De nombreuses études ont examiné l'association entre les polymorphismes paraoxonase1 L55M et Q192R et le risque d'infarctus du myocarde, mais les résultats sont restés incohérents. Nous avons donc cherché à traiter cette association en effectuant un méta analyse mise à jour.

Au total, 14 études cas-témoins pertinentes publiées de 2000 à 2018 ont été incluses dans notre méta-analyse (4509 cas et 5373 témoins). Les données extraites ont été analysées statistiquement et des rapports de cotes avec des intervalles de confiance à 95 % ont été utilisés pour estimer la force de l'association.

Les résultats de notre étude montrent une association non significative entre le polymorphisme étudié et RR et MM dans presque les modèles sauf dans le cas de l'ethnicité asiatique (M vs L : OR=0,930 ; 95%CI=0,868-0,997, MM vs LL : OR = 0,999, IC à 95 % = 0,877-1,137 ; ML vs LL : OR = 1,005, IC à 95 % = 0,900-1,122, MM+ML vs LL : OR =1,002, IC à 95 % = 0,906-1,110, MM vs LL+ ML : OR = 0,996, IC à 95 % = 0,889-1,117) (R vs Q : OR : 1,027, IC à 95 % : 0,966-1,093, RR vs QQ : OR = 1,122 IC à 95 % = 0,985-1,278, QR vs QQ: OR = 1,081, IC à 95 % = 0,992-1,179, QR+RR vs QQ : OR = 1,090, IC à 95 % = 1,005-1,182, RR vs QQ + QR : OR = 1,079 IC à 95 % = 0,954-1,221). De même, l'analyse de sous-groupes stratifiée par origine ethnique n'a montré aucune association significative dans chaque modèle génétique dans les populations américaines, arabes ou caucasiennes.

En conclusion, les polymorphismes L55M et Q192R dans les gènes PON1 ne sont pas associés à la susceptibilité à l'IM. Cependant, l'association était significative dans les populations asiatiques. Davantage d'études de haute qualité devraient être menées pour valider les conclusions actuelles.

Mots clés : gène PON1, MI, méta-analyse, polymorphisme Q192R et L55M.

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Involvement of the *Q192R* and *L55M* polymorphism of the *Paraoxonase* gene in myocardial infarction: a meta-analysis

Memoir for obtaining the Master's degree in Genetics

Summary

Many studies have examined the association between paraoxonase1-L55M and Q192R polymorphisms and risk myocardial infarction, but the results remained inconsistent. We therefore aimed to address this association by performing an
updated meta-analysis.

A total of 14 relevant case-control studies published from 2000 to 2018 were included in our meta-analysis (**4509** cases and **5373** controls). The extracted data were statistically analyzed, and odds ratios with 95% confidence intervals were used to estimate the strength of the association.

The results of our study show a non-significant association between the studied polymorphism and RR and MM in almost models except in the case of Asian ethnicity (M vs L: OR=0.930; 95%CI=0.868-0.997, MM vs LL: OR=0.999, 95%CI=0.877-1.137; ML vs LL : OR=1.005, 95%CI=0.900-1.122, MM+ML vs LL: OR=1.002, 95%CI=0.906-1.110, MM vs LL+ML: OR=0.996, 95%CI=0.889-1.117) (R vs Q: OR:1.027, 95%CI:0.966-1.093, RR vs QQ: OR=1.122 95%CI= 0.985-1.278, QR vs QQ: OR=1.081, 95%CI=0.992-1.179, QR+RR vs QQ: OR=1.090, 95%CI=1.005-1.182, RR vs QQ + QR: OR=1.079 95%CI= 0.954-1.221). Similarly, subgroup analysis stratified by ethnicity showed no significant association in each genetic model in American, Arab or Caucasian populations.

In conclusion, L55M and Q192R polymorphisms in PON1 genes are not associated with susceptibility to MI. However, the association was significant in Asian populations. More high-quality studies should be carried out to validate present conclusions.

Key words: PON1 gene, MI, meta-analysis, Q192R and L55M polymorphism.

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