Carla Susana Mendes Ferreira

Marcadores de prognóstico em 980 doentes com SCA internados no CHBV

Prognostic markers in 980 patients with ACS hospitalized in CHBV

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Molecular, realizada sob a orientação científica do Doutor José Adelino Mesquita Bastos, Professo Adjunto da Escola Superior de Saúde da Universidade de Aveiro

Dedico este trabalho aos meus pais

o júri

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palavras-chave aterosclerose, síndrome coronário agudo, fatores de risco, biomarcadores, prognóstico

resumo

O síndrome coronário agudo consiste num estado de sintomas físicos compatíveis com isquemia miocárdica aguda, podendo resultar de várias doenças arteriais coronárias: angina instável, enfarte agudo do miocárdio sem elevação do segmento-ST e enfarte agudo do miocárdio com elevação do segmento-ST. Esta doença ocorre normalmente devido a aterosclerose, através da rutura de uma placa aterosclerótica instável ou através de erosão endotelial. Eventualmente a ativação da cascata de coagulação e a adesão, ativação e agregação de plaquetas levam a trombose aguda.

A estratificação do risco em pacientes com síndrome coronário agudo é muito importante na determinação da estratégia terapêutica adequada. Várias características clínicas estão associadas com um risco aumentado de um prognóstico adverso aquando de um síndrome coronário agudo, sendo tidos em conta em várias tabelas de previsão de risco. O principal objetivo deste trabalho é a determinação de características clínicas associadas com pior um prognóstico num grupo de doentes com síndrome coronário agudo internados na unidade de cuidados intensivos cardíacos do Hospital Infante D. Pedro, no Centro Hospitalar do Baixo Vouga, de forma a identificar potenciais marcadores de prognóstico nestes doentes, e a determinação da sua associação com outras características clínicas, de forma a determinar a sua influência na fisiologia de doentes com síndrome coronário agudo.

Levou-se a cabo um estudo prospetivo observacional em 980 doentes com síndrome coronário agudo internados na unidade de cuidados intensivos cardíacos do Hospital Infante D. Pedro, no Centro Hospitalar do Baixo Vouga, entre Janeiro de 2008 e Junho de 2012. A informação recolhida foi analisada usando Student's T-test, One-way Anova, Kruskal-Wallis test, Pearson's X^2 test, Fisher's Exact test, Cox Proportional Hazards Model e Kaplan-Meyer estimate, e incluiu informação clínica geral e informação sobre fatores de risco cardíacos, análise sanguínea geral, marcadores cardíacos séricos, fração de ejeção ventricular esquerda, terapia de revascularização e eventos cardíacos prévios e posteriores.

Os resultados obtidos indicam que sexo feminino, idade avançada, baixa fração de ejeção ventricular esquerda, a presença de um evento prévio, hipertensão, dislipidémia e obesidade estão associados com um prognóstico adverso em pacientes com síndrome coronário agudo.

keywords atherosclerosis; acute coronary syndrome, risk factors, biomarkers, prognosis

abstract

Acute coronary syndrome consists in a state of clinical symptoms compatible with acute myocardial ischaemia that may result from various thrombotic coronary artery diseases: unstable angina, non–ST-segment elevation acute myocardial infarction and ST-segment elevation myocardial infarction. This disease normally occurs due to atherosclerosis, through the rupture of an unstable atherosclerotic plaque or through superficial endothelial erosion. Eventually the activation of the coagulation cascade and platelet adhesion, activation and aggregation ends up leading to acute thrombosis.

Risk stratification in patients with acute coronary syndrome is very important in the determination of the proper treatment strategy. Various clinical features are known to be associated with an increased risk of a worse outcome in the event of an acute coronary syndrome and are taken into account in various risk scores. The main aim of this work is the determination of clinical characteristics that are associated with a worse outcome in a group of patients with acute coronary syndrome admitted to the Cardiac Intensive Care Unit of Hospital Infante D. Pedro, in Centro Hospitalar do Baixo Vouga, in order to identify potential prognostic markers in these patients, and the assessment of the association of these markers with other clinical characteristics, in order to determine their influence in the physiology of patients with acute coronary syndrome.

A prospective observational study was conducted in 980 patients with acute coronary syndrome admitted to the cardiac intensive care unit of Hospital Infante D. Pedro, in Centro Hospitalar do Baixo Vouga, between January 2008 and June 2012. Data collected was analysed using Student's T-test, One-way Anova, Kruskal-Wallis test, Pearson's X^2 test, Fisher's Exact test, Cox Proportional Hazards Model e Kaplan-Meyer estimate, and included general clinical information and information regarding cardiac risk factors, general blood test, serum cardiac markers, left ventricular ejection fraction, provided revascularization therapy and previous and posterior cardiac events

The results obtained indicate that female gender, advanced age, anemia, low left ventricular ejection fraction, the presence of a previous event, hypertension, dyslipidemia and obesity are associated with a poorer prognosis in patients with acute coronary syndrome.

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ABBREVIATIONS

Item	Definition
ACS	Acute Coronary Syndrome
Ang II	Angiotensin II
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CHBV	Centro Hospitalar do Baixo Vouga
CK	Creatine Kinase
CRP	C-Reactive Protein
CRUSADE	Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guideline
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
ECG	Electrocardiogram
EDRF-NO	Endothelium-Derived Relaxing Factor-Nitric Oxide
ERKs	Extracellular signal-Regulated protein Kinases
GFR	Glomerular Filtration Rate
GRACE	Global Registry of Acute Coronary Events
HDL	High-Density Lipoprotein
ICAM-1	Intercellular Adhesion Molecule-1
IL	Interleukine
IMA	Ischaemia Modified Albumin
JAK	Janus Kinase
JNKs	c-Jun N-terminal Kinases
LDL	Low-Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction

Item	Definition
MAPK	Mitogen-***A***ctivated Protein Kinase
MCP-1	Monocyte Chemoattractant Protein 1
M-CSF	Macrophage Colony-Stimulating Factor
MMPs	Matrix Metaloproteinases
NF-κB	Nuclear Factor-κB
NO	Nitric Oxide
NSTEMI	Non–ST-segment Elevation Acute Myocardial Infarction
oxLDL	Oxidadated Low-Density Lipoprotein
PAI-1	Plasminogen Activating Inhibitor-1
PPARγ	Peroxisome Proliferator Activated Receptor γ
PCI	Percutaneous Coronary Intervention
PCT	Procalcitonin
PDGF	Platelet-Derivered Growth Factor
PlGF	Placental Growth Factor
Pro-BNP	Pro-Brain Natriuretic Peptide
PTCA	Percutaneous Transluminal Coronary Angioplasty
PURSUIT	Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy
RAS	Renin-Angiotensin System
ROS	Reactive Oxygen Species
sCD-40L	soluble CD40 Ligand
STEMI	ST-segment Elevation Myocardial Infarction
TIMI	Thrombolysis In Myocardial Infarction
TNF-α	Tumor Necrosis Factor-α
TNF-β	Tumor Necrosis Factor-β
t-PA	tissue Plasminogen Activator
UA	Unstable Angina
VCAM-1	Vascular Cell Adhesion Molecule-1
VLDL	Very Low-density Lipoprotein
vWf	von Willebrand Factor
WHO	World Health Organizati

1 – INTRODUCTION

1.1 – Atherosclerosis

Atherosclerosis is a multifactorial disease, in which both genetic and environmental factors play a role, characterized by narrowing of blood vessels due to the formation of an atheromatous plaque. This is a disease that may lead to severe complications like ischaemic cardiac disease and stroke, which constitute a major cause of death and morbidity worldwide. [1]–[3]

Atherosclerosis may be considered a persistent state of chronic inflammation, due to the interaction of diverse factors, such as modified lipoproteins, monocyte-derived macrophages, T cells, and the normal cellular elements of the arterial wall. [4]

1.1.1 – Overview of the atherosclerotic process

Endothelial dysfunction, resulting from various factors, triggers an inflammatory process and induces an increase in the permeability of the arterial wall. This increase in the permeability of the arterial wall allows the passage of low-density lipoprotein (LDL) and inflammatory cells from the blood to the arterial wall, where LDL suffers oxidation and uptake into macrophages and vascular smooth muscle cells, leading to the formation of foam cells and to the development of an atherosclerotic lesion. [5]

The initial and most simple atherosclerotic lesions are called fatty streaks, and are characterized by the accumulation of foam cells (macrophages and vascular smooth muscle cells that contain droplets of lipids) in the intima layer of the artery. These lesions normally develop in areas where endothelial dysfunction causes a sufficient increase in permeability that allows the passage of LDL and inflammatory cells into the arterial wall. [4]–[6]

The recruitment of vascular smooth muscle cells from the subendothelium and the media induces the formation of a fibrotic cap, composed of vascular smooth muscle cells

embedded in connective tissue. This leads to the formation of a stable atherosclerotic plaque, the fibrotic lesion. [5], [7]

Eventually various factors, such as vascular smooth muscle cell apoptosis and macrophage production of matrix metaloproteinases (MMPs), end up resulting in a thinning of the fibrotic cap, making the plaque unstable and prone to rupture, originating a complicated atherosclerotic lesion. [5], [7]

1.1.2 – Pathogenesis of atherosclerosis

Endothelial lesion

There isn't a clear understanding of the events leading to the development of an atheromatous plaque, although the most accepted hypothesis to explain this phenomenon is the Modified Response-to-Injury Hypothesis, which considers that endothelial dysfunction, resulted from injury, due to, for instance, elevated LDL, free radicals, hypertension, diabetes mellitus (DM), cigarette smoking, increase of plasma homocystein, and infectious microorganisms, such as herpes virus, is the first step in development of atherosclerosis. [5], [8], [9]

The endothelial surface that covers the lumen of arteries is prone to change in response to various types of stimuli. Endothelial cells have several physiologic functions that are important in the protection of arteries and in preventing the development of atherosclerotic plaques. These functions include, for example, forming a barrier that prevents the efflux of large molecules such as LDL, into the subendothelial spaces, providing the artery with a nontrombogenic surface and releasing PGI2, heparan sulfate and endothelium-derived relaxing factor-nitric oxide (EDRF-NO), which relax smooth muscle, increasing the diameter of the lumen, and inhibit smooth muscle cell migration and proliferation. [8] Endothelium is also important for nutrient delivery and waste removal, and is involved in the secretion of various substances that participate in the processes of regulation of vascular tone, inflammation and thrombosis, such as nitric oxide (NO), prostaglandins, endothelin, and angiotensin II (Ang II). Thus, a functional endothelium is fundamental for the maintenance of an equilibrium between

vasodilation/vasoconstriction and thrombosis/anticoagulation. [10]

With injury, endothelial cells may become dysfunctional. These dysfunctional cells are morphologically different from normal endothelial cells and present increased permeability and a reduction of the secretion of PGI2 and EDRF-NO, causing these cells to have procoagulant instead of anticoagulant properties. [5], [8] Furthermore, endothelial dysfunction may also cause a decrease in NO and an increase in oxidative stress. [9] Endothelial lesion also triggers an inflammatory response that may turn chronic if the causing agent is not eliminated. The functional differences between normal and injured endothelium are described in table 1. [8]

Recent studies have focused on endothelial function, which has been shown to be an important indicator in the determination of the presence of coronary artery disease (CAD). [11]

TABLE 1 – Functions of vascular endothelium in normal and injured states

Function	Normal Endothelium	Injured Endothelium
Permeability	Tight junctions prevent the passage of large molecules into subendothelium.	Loss of tight junctions increases penetration of large molecules
Thrombogenicity	Platelets are repelled by the negative surface charge of endothelial cells. Inhibition of platelet aggregation and promotion of thrombolysis	Function is converted from antithrombotic to prothrombotic.
Vasomotor tone	Promotion of vasodilatation	Promotion of vasoconstriction
Smooth muscle migration and proliferation	Inhibition of smooth muscle cell migration and proliferation	Promotion of smooth muscle proliferation
Inflammation	Inflammatory cells fail to adhere to normal endothelium.	Leukocytes are recruited to sites of injury

Note. Adapted from *Consigny* [5]

Inflammation

The continuous inflammatory state verified in atherosclerosis, particularly in regions of disturbed laminar flow, such as branch points, leads to migration, from the blood, of macrophages and lymphocytes that accumulate and multiply in the lesion. [7], [12] This inflammatory process may be triggered by endothelial dysfunction, structural alterations in the luminal elastin layer and exposure of proteoglycans. [12] T-lymphocytes are found in various stages of atherosclerotic lesions, along with a prominent presence of macrophages, which constitutes an indicator of the presence of a nonspecific inflammatory response. [7]

Dysfunctional endothelium expresses adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), P-selectins and E-selectins. VCAM-1 appears to be regulated by inflammatory stimuli, is highly expressed in endothelial cells within lesion areas, and a deletion of the genes responsible for the codification of E-selectins, P-selectins and ICAM results in a significant reduction in monocyte recruitment and atherosclerotic lesions. [4], [6], [10] These molecules adhere to circulating monocytes that then migrate to the vascular wall, in a process mediated by chemoattractants such as monocyte chemoattractant protein 1 (MCP-1) and in which the connective tissue matrix is degraded by enzymes such as MMPs. [4], [6], [10] Monocyte migration into the cell wall may also be stimulated by oxidated LDL (oxLDL), that may both directly attract monocytes and stimulate the secretion, by endothelial cells, of adhesion molecules.[4]

Leukocyte recruitment induces the secretion of various proinflammatory molecules, like interleukines (IL), chemokynes, cytokines and growth factors, such as IL-1, IL-6, IL-18, tumor necrosis factor-α (TNF-α), tumor necrosis factor-β (TNF-β), macrophage colony-stimulating factor (M-CSF), MCP-1, and soluble CD40 ligand (sCD-40L), that stimulate smooth muscle cells and endothelial cells and are associated with the development of the atherosclerotic plaque. [6], [10] Platelet-derivered growth factor (PDGF) is secreted by platelets, considered key cell types in the development of atherosclerosis, and also by macrophages and endothelial cells and is involved in the migration of smooth muscle cells to the intimal region of arteries and in smooth muscle proliferation. [7] M-CSF, responsible

for the differentiation and proliferation of monocytes, is also found in atherosclerotic lesions, as well as sCD-40L, expressed by macrophages, lymphocytes, endothelial cells and smooth muscle cells, important for leukocyte adhesion, matrix degeneration and cytokine-induced inflammation. [7], [10]

Lipid metabolism

Triglycerides and lipoproteins have an important role in the development of the atherosclerotic lesion, with high levels of triglycerides and LDL and low levels of high density lipoprotein (HDL) being associated with a higher risk of development of atherosclerosis and an increase in blood thrombogenicity. [1], [2] Lipids were once considered initiating agents of the atherosclerotic process, but now it is believed that lipid accumulation, characteristic of atherosclerosis and fundamental in the development of the atheromatous plaque, occurs in response to changes in endothelial function. [6] Triglyceride concentration is usually high in DM specially in the insulin resistent type, and excess insulin promotes glycation of the lipoproteins, which has a predominant role in the formation of atheroma. [2]

Lipid accumulation most probably results from the passage of LDL from the blood to the vessel wall. Once in the medial region, LDL may be oxidated, as a result of free radicals and the action leukocytes, and suffer uptake by macrophages and monocytes. The high atherogenic capacity of oxLDL results from the fact that macrophages and monocytes may only bind to oxLDL, as the scavenger receptors, through which they bind to oxLDL, only recognize LDL after it suffers oxidation. [6] The oxLDL uptake by macrophages results in alterations in these cells, that become foam cells, less mobile, which causes the accumulation of these cells in the intima. Furthermore, oxLDL constitutes a cause of endothelial lesion and stimulates the expression of proinflammatory molecules. The proatherogenic effects of oxLDL are described in table 2. [6], [9], [13]

Very low-density lipoprotein (VLDL) is also known to play a role in atherogenesis and is associated with inflammatory effects, inducing the expression of ICAM-1, VCAM-1, nuclear factor-κB (NF-κB), and other proinflammatory molecules, such as TNF- α. [9]

Table 2 – Mechanisms of the proatherogenic effects of oxLDL components

oxLDL Components(s)	Effect	Mechanism
Lyso phosphatidyl choline; oxidized phospholipids	Increased monocyte adhesion	Expression of adhesion molecules on endothelial cells
Lyso phosphatidyl choline; oxidized phospholipids	Increased monocyte and T cell chemotaxis	Stimulation of chemokine production
9-hydroxyeicosatetraenoic acid	Increased CD 36 expression	Activation of PPARγ
Modified apo B and oxidized phospholipids	Increased foam cell formation	Enhanced uptake of oxLDL
Lyso; phosphatidyl choline, oxidized phospholipids	Induction of proinflammatory genes	Activation of NF-kB, AP-1, and cAMP
Oxidized lipids and apo B adducts	Cellular and humoral immune response	Neoepitope formation
lyso phosphatidyl choline, cholesterol, oxysterols	Increased apoptosis and necrosis	Activation of programmed cell death. Loss of membrane integrity
Oxidized lipids	Enhanced procoagulant activity	Induction of tissue factor, increased platelet aggregation

Note. PPARγ: Peroxisome proliferator activated receptor γ; oxLDL: oxidated LDL; NF-kB: nuclear factor-κB; AP-1: activator protein 1; cAMP: Cyclic adenosine monophosphate

Adapted from *Glass et al.* [4]

Smooth muscle cell proliferation

Accumulation and proliferation of vascular smooth muscle cells in the arterial intima is also a key feature of atherosclerosis. [14], [15] In the early development of the atheromatous plaque, vascular smooth muscle cells play an important role in the production of pro-inflammatory mediators such as MCP-1 and VCAM-1. In a later state, these cells contribute to the formation of a fibrous cap and stabilization of the plaque. [15]

During vascular formation, there is a reduction in the secretion of extracellular matrix proteins and an increase in the production of intracellular myofilament, and cells go through a phenotypic change. Cells undergo a transition from an active synthetic state, in which they express genes for a number of growth-regulatory molecules and cytokines, to a quiescent contractile state, that allows the cells to contract and dilate in response to agents that cause vasoconstriction or vasodilation, such as catecholamines, leukotrienes

and NO, regulating the diameter of blood vessels and blood pressure. [13], [16]

In atherosclerosis injured vascular smooth muscle cells are stimulated, for instance, by growth factors and chemokines, produced by various cell types, such as endothelial cells, platelets and inflammatory cells. [10], [13] This results in phenotypic modifications in vascular smooth muscle cells, that suffer again a change into an active synthetic state, migrate to the intima, proliferate and segregate matrix proteins and enzymes. [10], [13]

Vascular smooth muscle cells are important in the secretion of various components of the extracellular matrix of the atherosclerotic plaque, such as glycosaminoglycans, proteoglycans, collagen, elastin, fibronectin, laminin, vitronectin, and thrombospondin, inducing the formation of a mature fibrofatty atheroma. [10], [13]

Ultimately, smooth muscle is also involved in plaque rupture. Vascular smooth muscle cells present in atherosclerotic plaques are more sensitive to apoptosis, leading to a thinning of the plaque's fibrous cap and, eventually, plaque rupture. [13]

Renin-angiotensin system and oxidative stress

Renin-angiotensin system (RAS) plays an important role in the atherosclerotic process, mainly through AngII and reactive oxygen species (ROS). Furthermore, RAS is associated with the development and proliferation of bone marrow derived cells, that are thought to have a contribution in the pathogenesis of atherosclerosis. [17]

AngII has vasoconstrictive properties, due to the stimulation, in vascular smooth muscle cells, of the activity of phospholipase C, resulting in an increase in the intracellular levels of calcium and in smooth muscle contraction and hypertrophy. AngII also plays a major role in atherosclerosis, with its inhibition being associated with a decrease in the progression of atherosclerosis and in the number of cardiovascular events. [8], [18]

AngII is associated with the up-regulation of various adhesion molecules, chemokines and cytokines such as VCAM-1, ICAM-1 and MCP-1, known to be involved in the atherosclerotic process, inducing endothelial dysfunction and the uptake and oxidation of LDL. [17], [19] The increase in the expression of adhesion molecules promoted by AngII

makes the endothelium more prone to infiltration by inflammatory cells and facilitates the characteristic chronic inflammatory process. [19] AngII also promotes platelet aggregation through a decrease in the anticoagulant effect of NO and an increase in the expression of plasminogen activating inhibitor-1 (PAI-1). In advanced lesions AngII stimulates the expression of MMPs, leading to the destabilization of the plaque and may also alter vascular smooth muscle cell function, as it is capable of inducing cellular hypertrophy and extracellular matrix production. [2], [9], [17]

Furthermore, AngII promotes the formation of ROS, which is also a major factor in the development of atherosclerosis, in macrophages, endothelial cells and vascular smooth muscle cells, both as a result of the stimulation of the expression of cytokines such as TNF-α, IL-1, IL-6 and PDGF, that induces extracellular production of ROS, and by the direct stimulation of the activity of the membrane-bound NADH/NADPH oxidase, responsible for the intracellular production of ROS. [2]

ROS is involved in the modulation of vascular tonus and activation of various molecules in neutrophils and polymorphonuclear leukocytes, such as NF-κB, p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinases (JNKs) Akt kinases, janus kinase (JAK) and extracellular signal-regulated protein kinases (ERKs), inducing the activation of signaling pathways important in the events that result in the development of atherosclerosis. ERKs, for instance, are mediators of cell proliferation, Akt kinases are associated antiapoptotic signaling, JNKs and p38 MAPK are important in the process of apoptosis and p38 MAPK is thought to lead to the upregulation of ICAM-1 and endothelial dysfunction. [2], [19]

ROS is also responsible for interfering in the growth, apoptosis and survival of endothelial and vascular smooth muscle cells, influencing the extent of the response of these cell types to stimulation by growth factors [2]

Plaque rupture and thrombosis

Plaque rupture is a major concern in atherosclerosis, as it induces platelet activation and thrombosis. This results in an impairment of the blood supply to the heart that may have serious consequences, with plaque rupture being associated to as much as 50 % of the cases of acute coronary syndrome (ACS). [8]

Vulnerable plaques, more prone to rupture, often present a large lipid core and a thin fibrous cap, as a result of the action of MMPs and other substances secreted by macrophages stimulated by activated T cells, that degrade collagen and extracellular matrix.[8], [10]

The apoptosis of vascular smooth muscle cells is also a prominent factor in the events leading to plaque rupture, as these cells are responsible for the secretion of important components of the fibrous cap. [13], [15] In the normal artery there are low level of mitotic and apoptotic activity. In atherosclerosis, however, various factors seem to modify the existent equilibrium, making vascular smooth muscle cells more sensitive to proapoptotic stimuli. This could explain why rupture occurs particularly at the plaque shoulders, which often exhibit apoptotic vascular smooth muscle cells and a more prominent presence of inflammatory cells.[13]

With plaque rupture subendothelial collagen, the lipid core and procoagulants become in contact with the circulating blood. This induces the activation of the coagulation cascade and the adhesion of platelets to the vessel wall, that begin to accumulate and recruit additional platelets, inducing the formation of a thrombus and, eventually, occlusion of the vase. [8], [10]

1.2 – Acute coronary syndrome

ACS may be defined as a state of clinical symptoms compatible with acute myocardial ischaemia and results from various thrombotic coronary artery diseases, that occur normally due to atherosclerotic plaque rupture or superficial endothelial erosion: unstable angina (UA), non–ST-segment elevation acute myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), with UA and NSTEMI normally resulting from a partially occluded artery and STEMI from a fully occluded artery. [20]–[23]

1.2.1 – Epidemiology

Cardiovascular disease (CVD) in one of leading causes of mortality and morbidity in the world and ACS is one of the most common initial manifestations of CVD, having reached pandemic levels in developed countries. [23]–[25]

In the last couple of years there has been a reduction in the mortality rate due to ischaemic heart disease, specially in developed countries, but, nonetheless, this disease is still responsible for approximately one third of all deaths in persons older than 35 years of age. It is also estimated that CVD causes approximately 4 million deaths in Europe every year, representing 47% of all deaths, that ACS has an annual incidence between 1/80 and 1/170 of the population in Europe per year and that each year in the US approximately 1,360,000 patients are admitted due to ACS. [26]–[28]

1.2.2 – Pathophysiology

The most common cause of ACS is atherosclerosis, normally through the rupture of an unstable atherosclerotic lesion or through superficial endothelial erosion. This causes the activation of the coagulation cascade and platelet adhesion, activation and aggregation, causing, eventually, acute thrombosis. [22], [27]

The thrombotic lesion may develop through two processes. One of them is endothelial erosion, a process in which endothelial denudation in the plaque, probably due to endothelial cell death and apoptosis, due tho the action of macrophages, exposes larges areas of the subendothelial connective tissue. The other is plaque disruption, in which the rupture of the plaque's fibrotic cap exposes the underlying subendothelial matrix, rich in tissue factor, collagen and crystalline surfaces, thrombogenic elements that accelerate coagulation. [29], [30]

The thrombus normally develops in stages. Initially the thrombus starts developing within the lipid core and is essentially composed of platelets. The thrombus then begins to protrude to the lumen and acquires a more prominent fibrotic content and may eventually continue to grow until it occludes the artery. [29]

The complete occlusion of a coronary artery leads, eventually, to myocardial infarction, as a result of severe ischaemia, due to a reduction of myocardial oxygen supply. Ischaemia progresses normally from the subendocardium to the subepicardium and the extent of the infarction will depend on the location, severity, and duration of the ischaemic event and on the presence, or not, of collateral circulation. [27], [30]

Collateral circulation plays a very important role in preventing myocardial infarction. In UA, for instance, it is very common for patients to present a completely occluded artery but, due to the presence of collateral circulation, these patients end up not developing myocardial infarction. In STEMI, on the other hand, patients normally also present a completely occluded artery, but with no collateral circulation. [27]

1.2.3 – Clinical presentation

In the case of UA, chest pain, often described by the patients as a burning sensation is the most common symptom and may also be felt in the arm, neck, jaw, inferior teeth, back or epigastrum. [21], [27], [31] Stable angina in normally characterized as as deep chest or arm pain that is exacerbated by activity or emotional stress and relieved by rest or nitroglycerin, whereas UA is characterized by pain that occurs at rest and lasts typically less than 20 minutes. [20], [22], [27] In certain situations, patients present atypical

symptoms, more common in diabetic patients (10%), women and elderly patients, that normally lead to a delayed diagnosis. These include, for instance, dyspnea, fatigue, lethargy, diaphoresis, indigestion and anxiety. Normally, in UA, blood levels of specific myocardial biomarkers are not elevated. [20]–[22], [31], [32]

In acute myocardial infarction chest discomfort that lasts more than 20 minutes is the most common symptom, being normally described as “pressure”, “dull”, “squeezing” or “aching”. More commonly the discomfort is in the center of the chest and may also be felt in the left arm, neck, right arm, epigastrium, jaw, teeth or back. In NSTEMI pain is normally more intense and lasts for a longer period of time and in STEMI pain is more waning and waxing. Associated symptoms include dyspnea, nausea, palpitations and a sense of impending doom. Normally, in acute mycardial infarction, blood levels of specific myocardial biomarkers are elevated and for the dyagnosis of acute myocardial infarction at least two of three features must be present: pain, electrocardiographic alterations and positive myocardial biomarkers. [31]

Finally, ischaemia may also occur without any specific signs or symptoms. This phenomenon is called silent ischaemia and is more common in patients with DM, women, older adults, and those with a history of congestive heart failure (CHF). [20]

1.2.4 – Diagnosis

Physical examination

In patients with chest pain and other symptoms suggestive of ACS physical examination should include chest examination, auscultation and measure of heart rate and blood pressure. This evaluation is important to exclude possible non cardiac causes of chest pain and non ischaemic cardiac disorders, such as pericarditis or valvular disease and to determine the potential existence of haemodynamic instability or ventricular dysfunction. [27], [30]

Occasionally patients do not present any abnormalities at physical examination. However, when the area of ischaemia is larger and, consequently, the prognosis is worse, patients

may present cyanosis, respiratory distress and diaphoresis. [21], [22]

Heart rate should be evaluated for the detection of arrhythmia, heart block or sinus tachycardia, what is crucial before the administration of β-blockers. Blood pressure may also be normal, elevated due to, for instance, hypertension, sympathetic stimulation, or anxiety, or decreased, due to, for instance, pump failure or inadequate preload, with extremes of blood pressure being associated with poor diagnosis. The assessment of blood pressure is very important, as severe hypertension is a contraindication to fibrinolytic treatment and should be treated emergently.

Cardiac auscultation should target the detection of complications of ACS and the presence of comorbidities. The first and second heart sounds are often reducted due to poor myocardial contractility and patients may also present a third or fourth heart sound, in the case of heart failure due to large infarctions. The presence of a pericardial friction rub may indicate established infarction that has happened days earlier. Signs of left heart failure and pulmonary hypertension should be sought at physical examination. [22], [24]

Electrocardiogram

A patient presenting with chest pain and other symptoms compatible with ACS should do a 12-lead electrocardiogram (ECG) as soon as possible, as this exam is the fastest way of objectively diagnosing acute myocardial infarction and it may help in the differentiation between myocardial ischaemia, injury, and infarction and locate the affected area. Furthermore, the ECG may also be very helpful in risk stratification. [20], [22], [25]

It is, however, fundamental to have in consideration that a normal ECG does not completely rule out the possibility of ACS, that the traditional 12-lead ECG does not directly capture right-sided or posterior regions of the heart, and that it is important to compare the results with the results of previous ECGs, as changes in the ECG seem to be related with an increased possibility of complications. [22], [25]

ECG findings are very helpful in the diagnosis of ACS and certain findings may even lead to a suspicion of a lesion of a specific blood vessel, as described in table 3. Some possible findings in the ECG suggestive of UA and NSTEMI are, for instance, ST-segment

depression, transient ST-segment elevation, T-wave inversion, or some combination of these factors. These alterations normally resolve when ischaemia has resolved, although T-wave inversion may persist. On the other hand, ST elevation on a 12-lead ECG in two contiguous leads is indicative of STEMI, where T-wave inversion may also be present. ST-segment deviation is an important and specific measure of ischaemia and T-wave inversion is sensitive for ischaemia but is less specific, unless it is marked. [20], [22], [33]

Table 3 – ECG findings in the diagnosis of ACS

ECG findings	Lesion	Sensitivity (%)	Specificity (%)
ST elevation greater in lead III than in lead II. ST depression in lead I, lead aVL or both.	Right coronary artery	90	71
ST elevation in leads I, aVL, V5, and V6. ST depression in leads V1, V2, and V3.	Left circumflex coronary artery	83	96
ST elevation in leads V1, V2 and V. ST-elevation of > 2.5 mm in lead V 1, right bundle branch block with Q wave, or both.	Proximal LAD coronary artery	12	100
ST elevation in leads V1, V2 and V. ST depression > 1mm in leads II, III and aVF.	Proximal LAD coronary artery	34	98
ST elevation in leads V1, V2 and V. ST depression ≤ 1mm or ST elevation in leads II, III, and aVF	Distal LAD coronary artery	66	73

Note. ECG: electrocardiogram; LAD: left anterior descending

Adapted from *Achar et al.* [21]

Serum cardiac markers

Serum cardiac markers are vital for the diagnosis and prognosis of acute myocardial infarction and should be measured in all patients with chest pain or other symptoms suggestive of ACS. These markers are also especially important in the distinction between UA and myocardial infarction, as markers of myocardial necrosis and ischaemia are normally elevated in myocardial infarction but not in UA. [22], [25]

The measurement of cardiac-specific troponins T and I constitutes a highly accurate, sensitive, and specific determination of myocardial injury and has replaced CK-MB as the preferred marker for the detection of myocardial necrosis. Troponins have, however, some inconveniences: they usually do not increase until at least 6 hours after the onset of

symptoms and remain elevated for a prolonged period after myocardial necrosis, what decreases their usefulness in detecting recurrent myocardial damage. [22]

Another promising marker being studied is copeptin, the c-terminal of the vasopressin hormone precursor. It is associated with states of acute stress and may be useful in combination with a marker of myocardial injury. [24]

Other biochemical markers, such as C-reactive protein CRP and fibrinogen are also normally elevated in patients with ischaemic chest pain and are indicative of pour prognosis CRP is a marker of inflammation and the presence of fibrinogen indicates the activation of the coagulation cascade. [33]

Table 4 presents a compendium of the various features that have been discussed and that are important in the diagnosis of ACS.

Table 4 – Likelihood that signs and symptoms indicate an ACS secondary to CAD

Feature	High likelihood	Intermediate likelihood	Low likelihood
History	Chest or left arm pain/discomfort Previously documented angina Known history of CAD, including MI	Chest or left arm pain/discomfort Age ≥70 and male sex DM	Probable ischaemic symptoms in absence of any intermediate likelihood characteristics
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST deviation or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression of 0.5-1.0 mm or T-wave inversion >1.0 mm	T-wave flattening or inversion <1 mm Normal ECG tracing
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

Note. ACS: acute coronary syndrome; CAD: coronary artery disease; CK-MB: muscle and brain fraction of creatine kinase; ECG: electrocardiogram; MI: myocardial infarction; MR: mitral regurgitation; TnI: troponin I; TnT: troponin T.

Adapted from Kumar et al. [22]

1.2.5 – Risk stratification

Clinical risk stratification

Certain clinical features are know to indicate an increased risk of a bad outcome, such as an advanced age, DM, high glucose concentration, low left ventricular ejection fraction (LVEF), extracardiac vascular disease, rest pain, haemodynamic instability, pulmonary congestion and evidence of CHF as, for instance, a Killip class II or higher, mitral regurgitant murmur or a third heart sound. [22], [34]

Electrocardiographic risk stratification

The electrocardiographic examination is also useful in the determination of the risk of an adverse outcome. ST-segment depression or transient ST segment elevation, for instance, are indicative of a higher risk of adverse outcome and are predictive of three vessel or left main stem coronary disease. On the other hand, T wave inversion without ST segment shift implies a modest increased risk or no increased risk at all and no abnormal findings on the electrocardiographic examination are indicative of a favorable prognosis. The number of leads demonstrating ST elevation is also an important risk marker in patients with STEMI. [22], [34]

Biochemical risk stratification

Biochemical markers are also important in risk stratification. A troponin increase, for instance, even if minor, is associated with an adverse prognosis and predictive of reinfarction, with the level of risk being proportional to the degree of increase. This is also important for the selection of the treatment that the patient should undergo, as it appears that patients that present a troponin elevation seem to be more responsive to treatment with low molecular weight heparins and platelet glycoprotein IIb/IIIa receptor inhibitors. [22], [34] Recent studies indicate that other biochemical markers, such as brain natriuretic peptide (BNP) fibrinogen, CRP and sCD-40L are indicators of increased risk and may be important in the prediction of recurrent events in troponin negative patients. [34]

The assessment of multiple biochemical marker is, though, very important in the improvement of risk stratification and patient outcomes. [22]

Echocardiographic risk stratification

Left ventricular systolic function is very important in risk assessment, as well as hypokinesia or akinesia in segments of the left ventricle wall. Left ventricular dysfunction or other underlying conditions such as aortic stenosis or hypertrophic cardiomyopathy are associated with increased risk.

Angiographic risk stratifiction

Angiography is helpful both in risk stratification and in patient management. This examination allows the determination of the presence of coronary artery disease, the assessment of its severity and whether the patient is in need of revascularization or not.

In addiction, this examination is also important in risk stratification, as multiple-vessel disease, complex, long, heavily calcified lesions or filling defects indicating coronary thrombus are associated with a higher risk of serious cardiac events.

Table 5 presents a compendium of the various features important for the risk assessment of patients with ACS.

Table 5 – Short-term risk of death or nonfatal MI in patients with UA/NSTEMI

Feature	High Risk	Intermediate Risk	Low Risk
History	Accelerating ischemic symptoms in preceding 48 h	Previous MI, peripheral or cerebrovascular disease, or CABG	
Character of pain	Prolonged ongoing resting pain	Prolonged resolved rest angina Rest angina relieved with rest or nitroglycerin Nocturnal angina New-onset or progressive CCS class III or IV angina in the past 2 weeks without prolonged rest pain	Increased angina frequency, severity, or duration Angina provoked at a lower threshold New-onset angina with onset of 2 wk to 2 mo
Examination	Pulmonary edema New or worsening MR murmur Hypotension Bradycardia, Tachycardia Age ≥75	Age ≥70	
ECG	Angina at rest with transient ST-segment changes Bundle branch block Sustained ventricular tachycardia	T-wave changes Pathologic Q waves or resting ST-depression in multiple lead groups	Normal or unchanged findings
Cardiac markers	Elevated cardiac TnT, TnI, CK-MB	Slightly elevated cardiac TnT, TnI, or CK-MB	Normal

Note: CABG: coronary artery bypass graft; CCS: Canadian Cardiovascular Society; CK-MB: muscle and brain fraction of creatine kinase; ECG = electrocardiogram; MI: myocardial infarction; MR: mitral regurgitation; NSTEMI: non–ST-elevation myocardial infarction; TnI: troponin I; TnT: troponin T; UA: unstable angina

Adapted from *Kumar et al.* [22]

1.2.6 – Risk scores

Risk assessment uses quantitative or qualitative measures to determine the level of risk associated with a specific hazard. A quantitative risk assessment may be done using algorithms or mathematical formulas. Risk scores, that rank-order individuals according to the likelihood of developing a specific outcome are more complicated to use, but are also more precise than the simple qualitative risk assessment. [35] There are different scores, based on initial clinical history, ECG, and laboratory tests, including Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), Thrombolysis In Myocardial Infarction (TIMI), Global Registry of Acute Coronary Events

(GRACE) and Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guideline (CRUSADE) [35]–[37]

PURSUIT

The PURSUIT is a risk score, developed in 2000, that predicts 30-day risk and ranges from 0 to 18. This score is based on age, sex, worst Canadian Cardiovascular Society (CCS) angina class in the previous six weeks, heart rate, signs of heart failure and ST depression, as described in table 6. In this score age is the most significant predictor. The original trial score presented a c-statistic of 0.84 for death alone and 0.67 for the composite endpoint of death/miocardial infarction. [37], [38]

Table 6 – PURSUIT risk score

Characteristic		**Score**
Age	50 60 70 80	8 9 11 12
Sex	Male Female	1 0
Worst CCS class past 6 weeks	No angina/ CCS I/II CCS III/IV	0 2
Signs of heart faillure		2
ST depression on ECG		1

Note: CCS: canadian cardiovascular society

Adapted from Backus et al. [37]

TIMI

The TIMI risk score, developed in 2000, analyzes various independent prognostic variables and uses logistic regression, assigning the value of 1 if the variable is present and the value of 0 if the variable is absent. The variables utilized are age of 65 years or older, at least three risk factors for CAD, prior coronary stenosis of 50% or more, ST-segment deviation on ECG at presentation, at least two anginal events in the previous 24h, use of

acetylsalicylic acid in the previous seven days and elevated serum cardiac markers. The TIMI score predicts the risk of all cause mortality, miocardial infarction and severe recurrent ischaemia requiring urgent revascularization within 14 days after admission and had, in the original trial, a c-statistic of 0.65. [37], [38]

GRACE

The GRACE score was developed in 2003 and analyzed 8 independent risk factors: Killip class, systolic blood pressure, heart rate, age, creatinine level, cardiac arrest at admission, ST segment deviation on ECG and elevated cardiac enzyme levels, as described in table 7. Each one of these elements has its own scoring, resulting in a possible score ranging from 1 to 372. The GRACE score had, in the original trial, a c-statistic of 0.83. [37]

Table 7 – GRACE risk score

Killip Class	Score	Sistolic b. presure	Score	Heart Rate	Score	Age	Score	Creatinine Level	Score	Other	Score
I	0	<80	58	<50	0	<30	0	0-0.39	1	Cardiac	
II	20	80-99	53	50-69	3	30-03	8	0.40-0.79	4	arrest at	39
III	39	100-119	43	70-89	9	40-49	25	0.80-1.19	7	admission	
IV	59	120-139	34	90-109	15	50-59	41	1.20-1.59	10		
		140-159	24	110-	24	60-69	58	1.60-1.99	13	ST	28
		160-199	10	149	28	70-79	75	2.00-3.99	21	deviation	
		>200	0	150-	46	80-89	91	>4	28		
				199		>90	100			Elevated	
				>200						cardiac	14
										markers	

Note: Adapted from *Backus et al.* [37]

CRUSADE

The CRUSADE risk score estimates baseline risk of in-hospital major bleeding in patients with NSTEMI and takes into account baseline hematocrit, creatinine clearance, heart rate, gender, signs of CHF at presentation, prior vascular disease, DM, and systolic blood pressure. [39]

1.2.7 – Therapy

Oxygen

The routine usage of oxygen therapy in patients with uncomplicated ACS without signs of hypoxia or heart failure is not recommended. There is not enough evidence to suggest a benefit in patients with normal oxygen saturation levels, with some trials even indicating the possibility of harm and, although oxygen therapy has been linked with a reduction in the extent of ischaemic lesion in animal models and with an improvement in ST-segment changes, it seems to not influence the mortality rate. [24], [40], [41]

Oxygen administration is normally recommended only when patients with ACS present breathlessness, signs of heart failure, shock, or an arterial oxyhemoglobin saturation of less than 90% and, in that case, oxygen should be administered at 2 to 4 L/min by nasal cannula. [20], [28], [40], [41]

Anti-ischaemic agents

Various anti-ischaemic agents are used in the treatment of ACS, such as β-blockers, nitrates, calcium channel blockers and potassium channel activators.

β-blocking agents seem to have a beneficial action in patients presenting with ACS without ST-elevation. These agents competitively inhibit the effects of circulating catecholamines and seem to exert their beneficial function in the management of ACS through their action on beta-1 receptors, that results in a decrease in myocardial oxygen consumption. [30] Studies suggest that the use of β-blockers in the treatment of UA is associated with a 13% relative reduction in risk of progression to acute miocardial infarction and that these agents are associated with a reduction in mortality and in the size of the ischaemic lesion in patients with acute myocardial infarction. However, it seems to be associated with an increase in the number of cases of cardiogenic shock. [30], [41], [42] There are some contraindications in the use of β-blockers, such as left ventricular failure, pulmonary edema, bradycardia, hypotension and poor peripheral perfusion. [40], [43]

Nitrates and similar drug classes exert their beneficial therapeutic effects in patients with ACS through their action on the peripheral and coronary circulation, as they have vasodilator properties that cause a decrease in myocardial preload and left ventricular diastolic volume, leading to a decrease in myocardial oxygen demand. Furthermore nitrates have also a role in improving coronary collateral flow and inhibiting platelet aggregation. [22], [30] There aren't, however, trials that confirm their benefits in relieving symptoms, in reducing major adverse cardiac events or in increasing survival in younger patients, although in the elderly their use is associated with a reduction in mortality, heart failure, and left ventricular dysfunction. Therefore, when symptoms are controlled, intravenous nitrates should be replaced by alternatives such as sydnonimines or potassium channel activators. [30], [42] Some contraindications in the use of nitrates include, for instance, bradycardia or tachycardia in the absence of heart failure, or the use of a phosphodiesterase inhibitor for erectile dysfunction within 24 or 48 hours, depending on the therapeutic agent used. [22], [24]

Calcium channel blockers have vasodilating properties and also exert a direct effect on atrioventricular conduction and heart rate, inhibiting the contraction of both myocardium and vascular smooth muscle. [22], [30] This therapeutic class may be divided in 3 subclasses with distinct pharmacological effects that cause similar levels of coronary vasodilatation: dihydropyridines, benzothiazepines, and phenylalkylamines. [30] Calcium channel blockers seem to have an efficiency in the relieve of ACS symptoms similar to that of β-blockers and seem to provide symptom relief in patients already receiving nitrates and β-blockers. Thereby, their use is recommended in patients that present persistent or recurrent symptoms even after treatment with nitrates and β-blockers, although β-blockers should always be the first choice, if they are not contraindicated, as they have been used more broadly and have a safer profile. [22], [30], [41] Calcium channel blockers, however, do not seem to prevent the development of acute myocardial infarction or reduce mortality and should not be administered to patients presenting with severe left ventricular dysfunction or pulmonary edema. [22], [30]

Potassium channel activators exhibit both arterial and venous dilating properties, although they do not exhibit the same tolerance as seen with nitrates. [27], [30] The use

of such therapeutic agents in patients with stable angina is associated with a reduction of cardiovascular death, non-fatal myocardial infarction and unplanned hospitalization due to angina, although there seems to be no significant alteration in coronary heart disease mortality and non-fatal myocardial infarction and no specific data in the case of acute coronary syndromes.[30]

Antithrombotic therapy

Antithrombotic therapy plays a major role in the management of ACS, as thrombosis is a major factor in ACS. Anti-thrombotic agents include agents that inhibit thrombin, such as unfractionated heparin or low-molecular-weight heparin, and antiplatelet agents such as aspirin, clopidogrel, ticagrelor and GPIIb/IIIa receptor blockers. [30]

Unfractionated heparin has the inconvenience of having variable anticoagulant effects and limited effectiveness against platelet-rich and clot-bound thrombin but, in the absence of aspirin, its use is associated with a lower frequency of refractory angina/ myocardial infarction and death, although its use with aspirin does not seem to increase the protective effect of aspirin alone. However, this initial protective effect is lost with the discontinuation of therapy. [22], [30] It should be paid close attention to the complete blood cell count, as autoimmune heparin-induced thrombocytopenia in association with thrombosis, although rare, may happen with treatment with unfractionated heparin. If this complication occurs heparin therapy should be immediately discontinued. [22]

Low-molecular-weight heparins seem to have an enhanced anti-Xa activity in relation to anti-IIa activity and seem to be associated with a decrease in sensitivity to platelet factor 4, having a more predictable anticoagulant effect and lower rates of thrombocytopenia. Low-molecular-weight heparins do not seem to be associated with an increased beneficial effect, in relation to placebo, when administrated in the presence of aspirin and there also does not seem to exist a significant difference in the efficacy of low-molecular-weight heparins in relation to unfractionated heparin. Furthermore, although low-molecular-weight heparins offer some practical advantages, such as simplicity of administration, more consistent antithrombin effects and lack of need of monitoring, they seem to be

associated with a significantly increased risk of major bleeding. [30]

Acetylsalicylic acid acts inhibiting cyclo-oxygenase-1 and blocking the formation of thromboxane A2, inhibiting, therefore, platelet aggregation induced via this pathway. [20], [30] Its administration is associated with a decrease in death and MI in patients with UA and with a decrease in vascular events in patients with myocardial infarction and, therefore, acute treatment with aspirin is recommended in all patients with suspected ACS. [30], [34], [43] Continued use is also recommended, as it is associated with a long-term benefit. There exist, however, certain contraindications, such as allergy to acetylsalicylic acid, active peptic ulcer, local bleeding or haemorrhagic diatheses. [20], [30], [42]

Clopidogrel is an oral thienopyridine prodrug that requires activation in the liver via the cytochrome P450 system and that irreversibly inhibits the P2Y12 adenosine diphosphate receptor on the platelet, causing a reduction in platelet aggregation. Studies indicate that clopidogrel administration in patients with NSTEMI results in a reduction in combined event rate and mortality and that clopidogrel given 6 hours or more before elective PCI for patients with ACS without ST elevation reduces adverse ischemic events at 28 days. [22], [28], [41]

Ticagrelor is a non-thienopyridine drug, with a half-life of approximately 12 hours, that is a reversible antagonist of the P2Y12 adenosine diphosphate receptor on the platelet. Studies have reported an improvement in overall mortality and combined event rates with a marginal increase in bleeding the with administration of ticagrelor. [22], [28], [40]

Platelet GP IIb/IIIa inhibitors are specific inhibitors of platelet aggregation that act by interrupting the final common pathway of fibrinogen-mediated cross-linkage of platelets. Several trials have shown that these inhibitors have substantial benefit for patients at high risk and those undergoing PCI. [22]

Fibrinolytic therapy

Fibrinolytic therapy consists in the administration of clot-busting drugs such as alteplase, reteplase and tenecteplase, which dissolve existing thrombi by converting plasminogen to plasmin and degrading fibrin clots. This therapy is most effective when given within three hours after symptom onset and should be initiated within 30 minutes of medical evaluation. There are, however, certain contraindications, such as bleeding disorder, recent surgery or other invasive procedure, trauma, active peptic ulcer disease, use of anticoagulants, recent ischemic stroke, uncontrolled hypertension and brain tumor. [20], [24]

Coronary revascularization

There are two options for the coronary revascularization of patients presenting with ACS: percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). The decision to submit the patient to coronary revascularization and the choice of the most adequate technique depends on the extent and angiographic characteristics of the lesions present. [30]

PCI allows the mechanic stabilization of the disrupted plaque through the insertion of a catheter, normally through the femoral artery, into the occluded coronary artery. [20], [30] Percutaneous transluminal coronary angioplasty (PTCA) consists in the insertion of a catheter with a balloon tip that is then inflated, allowing the opening of the artery. [20] Various trials attest that the mortality rate associated with this procedure is very low and that the rate of success seems to be improved with the use of a stent, a metal device that keeps the artery open, and administration of GPIIb/IIIa receptor inhibitors, aspirin and heparin. [30] Some possible complications are, for instance, bleeding in the insertion site, decreased peripheral perfusion, retroperitoneal bleeding, cardiac arrhythmia, and acute renal failure. [20]

CABG is a technique in which bypass grafts, composed of other arteries and veins from the body, are attached onto a source of blood supply, most commonly the aorta, and onto the blocked coronary artery in a location beyond the blockage, providing an alternative

route for blood flow. In this technique advanced age is associated with higher morbidity and mortality, probably due to increased severity of coronary artery disease and increased frequency of comorbid medical conditions in elderly patients. [30], [42] In spite of this, elderly patients seem to present improved outcomes after CABG and, therefore, should not be denied CABG solely due to their age, although, in these cases, particular attention should be paid to baseline functional capacity and comorbid medical conditions. [42]

Patients with single-vessel disease are usually treated by PCI, with CABG normally only being a possibility in the case of, for instance, marked angulation or tortuosity of the vessel. On the other hand, in the case of left main or three-vessel disease, especially if associated left ventricular dysfunction, the choice is normally CABG if some of the lesions may not be appropriately managed with angioplasty. [30] However, the situation should always be evaluated on an individual patient basis. For instance, in the case of patients who need total revascularization, not possible with PCI, but in whom surgery poses an extremely high risk, the choice may be an initial percutaneous treatment of the 'culprit' lesion only and in the case of left main narrowing associated with severe co-morbidity, angioplasty may be the best choice in certain cases. [30]

1.2.8 – Risk factors

Obesity

Excessive accumulation of adipose tissue occurs when energy intake chronically exceeds energy expenditure, resulting from, for instance, an excessive intake of fat and sugar and a sedentary lifestyle. Obesity is a multifactorial disease in which metabolic, physiological, environmental, genetic, behavioral, and social factors play a role. [44], [45]

Obesity is associated with increased mortality and seems to have a strong correlation with lipoprotein levels, LDL in particular, and insulinemia and is a particularly important risk factor, especially because it is normally associated with two very important known risk factors for CVD, DM and hypertension. [44], [46], [47]

Various studies show an increase in the number of overweight children and adolescents in the past few decades, an increase associated with an increased risk of hypertension, lipid abnormalities, type II diabetes, and atherosclerotic lesions. [44]

It is, therefore, very important to prevent obesity with changes in diet, exercise and behavioral modification. It is important for this prevention to begin in the childhood, as children who are obese are more likely to become obese adults [44]

The waist/hip ratio and waist circumference are the most widely used measure of central adiposity and they seem to be better predictors of CVD than measures of overall adiposity such as the body mass index (BMI). [48]–[51]

Hypertension

Hypertension is one of the most important and common risk factors for CVD, with various studies indicating that it increases the risk of cardiovascular and atherosclerotic occurrences approximately two to three fold, independently of other risk factors. [48], [49]

It is a multifactorial disease, usually asymptomatic, one of the factors that makes its prevention and early diagnosis so important. A patient is diagnosed with hypertension normally when sistolic blood pressure or diastolic blood pressure are greater than the 95th percentile for sex, age, and height, plus 5 mmHg on 3 separate occasions. [44]

AngII and NO play an important role in the regulation of arterial blood pressure and are, as already discussed, also thought to be major interveners in the atherosclerotic process. Obesity also has a very prominent role in the development of hypertension, as approximately 30% of children and adolescents with overweight/obesity have hypertension. Smoking and alcohol consumption also seem to increase the risk of the development of hypertension. [44]

The best way to prevent the development of hypertension seems to be a healthy lifestyle with weight control, moderated sodium and alcohol intake and exercise. [44], [52]

Diabetes mellitus

DM is a metabolic disorder mainly characterized by elevated blood glucose levels and constitutes a strong risk factor for CVD and ischaemic heart disease, as cardiovascular complications are the leading cause of morbidity and mortality in patients with DM, with about 75–80% of adult diabetic patients dying of CVD. DM seems to have a greater associated risk of CVD in women, with a three to seven-fold increased risk, than in men, where it is associated with a two to three-fold increased risk. [48], [49], [53], [54]

As this is a disease that often coexists with other significant risk factors such as obesity, dyslipidemia, hypertension, and hyperuricaemia patients with DM are particularly predisposed to atherosclerotic disease and even modest elevations in blood glucose, without a diagnosis of DM, have been linked to an increased risk for development of CAD. [48], [55]

DM is associated with an increased mortality rate from myocardial infarction in women, both when comparing to women without DM and when comparing to men, with or without DM. It is also associated with alterations in the lipid profile, such as elevated triglycerides and low HLD and VLDL levels, that are predictive of coronary artery disease mortality in diabetic women but not in non diabetic women or in men. [49]

Various studies have shown that DM is also associated with a worse prognosis in patients with ACS, as DM increases the susceptibility of the heart to ischaemia/reperfusion injury. [56]

Dyslipidemia

Elevated levels of total cholesterol and LDL are associated with an increased risk of ACS both in men and women. It is especially important a control of LDL in postmenopausal women, as menopause is associated with a decline in the levels of estrogen, that result in a decrease in the activity of LDL receptors and, therefore, in an increase in LDL concentration. A reduction of a high cholesterol level in patients with coronary heart disease is thought to reduce major coronary events by 34%. [49]

Low levels of HDL are associated with an increased risk of coronary heart disease, especially in women, as it is thought that low levels of HDL are more predictive of coronary artery disease in women than in men. Recent studies show a decrease in HDL levels in women after menopause what, in combination with an increase in LDL levels, may explain the increase in coronary risk in postmenopausal women. Initially it was thought that low HDL levels, by themselves, in the absence of high levels of LDL or triglycerides, did not result in an increased risk of CVD, but recent studies indicate that isolated low HDL levels constitute a significant risk factor. [49]

Elevated triglycerides are also another important risk factor for CVD, although their role as an independent risk factor for CVD is not clear, due to their interactions with other lipid factors, with certain studies indicating that the measurement of serum triglycerides for the estimation of cardiovascular risk has no advantage over the measurement of cholesterol alone. [48], [49], [57] Certain meta-analysis studies, however, indicate a statistically significant increase in cardiovascular risk associated with a 1-mmol/l increase in triglycerides of 14% in men and 37% in women. [49], [57]

Lifestyle interventions such as reduction in total calories, weight loss and increased physical activity are important in the management of dyslipidemia, although pharmacological therapy may also be necessary. [58]

Homocysteine

Elevated levels of total plasma homocysteine seem to be associated with an increased risk of CVD both in women and in men, with meta-analysis indicating an odds-ration of 1.6 for men and 1.8 for women, in association with a 5-mmol/l increment. [48], [49], [57]

Plasma homocysteine levels seem to rise with age and be significantly higher in men than in women, possibly due to an increased body mass in men and to a lowering effect of estrogen in women, what may explain the increased levels in postmenopausal women, in relation to premenopausal women and even to men of the same age. [49]

The role of homocysteine as a risk factor may be explained by the fact that it is associated with endothelial dysfunction and injury and with vascular smooth-muscle cell

proliferation. It is also responsible for increasing thromboxane A2 formation and platelet aggregation and also has procoagulant effects. A potential increase in the levels of plasma homocysteine my be due to genetic, nutritional and environmental factors. [57], [59]

Fibrinogen

Various studies indicate a significant correlation between fibrinogen levels and CVD, with meta-analysis indicating that high fibrinogen levels have an odds ratio of 2.3 for cardiovascular events. [48], [49], [57]

Fibrinogen levels seem to be higher in women than in men, especially in postmenopausal women, and seem to rise with smoking, age obesity and physical inactivity. [49], [57] In patients with established coronary disease, the grade of increase in fibrinogen levels seems to be associated with the severity of the lesions and, in patients with UA, high fibrinogen levels are associated with a higher risk of death or myocardial infarction. [57]

Fibrinogen is associated with an increased risk of CVD because it seems to have mitogenic and angiogenic properties, due to its role in the coagulation cascade, in the stimulation of vascular smooth muscle cell migration and proliferation and in the promotion of platelet aggregation. [57]

Familiar history

Coronary heart disease seems to have a strong hereditary component. Therefore, positive familiar history of premature coronary heart disease is a known genetic risk factor, present in the majority of cases of premature-onset, that has been added to various risk prediction models. However, the analysis of familiar history as a risk factor for CVD is not always easy, as the definition and identification of a positive familiar history of CVD is difficult and because it is normally associated with other risk factors, what makes the assessment of the separate impacts of genetic and environmental factors difficult. [49], [59]–[61]

Family history of coronary heart disease seems to increase the probability of premature onset in women and men, with certain studies even indicating that the presence a familiar history of CVD could double the patient's risk of myocardial infarction. [49], [59]

At this point, however, the practical implications of the identification of families at risk are not clear, although, in the future, with the development of genetic research, it may be possible to determine different subtypes in the familial risk and specific therapy. [49]

Smoking and alcohol consumption

In smokers, the risk of CVD seems to be proportional to the number of cigarettes smoked and is apparently greater for women than men. It is also important to notice that there seems to be a substantial decrease in coronary heart disease mortality in former smokers compared with continuing smokers. [48], [62]

Smoking seems to be associated with oxidative stress, lipid oxidation, endothelial cell dysfunction and foam cell proliferation, as well as with an increase in inflammatory markers, what suggests that it is involved in the inflammatory process characteristic of atherosclerosis. [63]

Moderate alcohol intake seems to be protective for CVD, with a reduction of 20-40% in mortality and morbidity due to coronary heart disease, whereas more than two drinks a day seems to be associated with increased mortality. [45], [48], [64], [65] The risk reduction by moderate alcohol consumption may be explained by an increase HLD but is also related to levels of fibrinogen and glycated hemoglobin. [64]

1.3 – Biomarkers

1.3.1 – Inflammatory markers

CRP

CRP is the most important and the best studied inflammatory biomarker for ACS. It is synthesized essentially in the liver, although it may also be produced by other cells such as adipocytes, and is normally present in low, stable levels of less than 1 mg/L in the absence of an acute inflammatory stimulus. [66], [67]

CRP is involved in the inflammatory process by binding to endogenous and exogenous ligands, such as modified lipoproteins and apoptotic cells, thereby protecting against infection and tissue injury, and activating the complement cascade. [67]

It is thought that CRP has an important role in plaque formation and development, as it is normally associated with the presence of foam cells. Studies have demonstrated that CRP is associated with a decrease in endothelial NO synthase and an increase in endothelin-1 secretion, therefore leading to an increase in the expression of adhesion molecules such as ICAM-1,VCAM-1, E-selectin and P-selectin. CRP is also associated with and increase in LDL uptake and MCP-1 secretion, and with the induction of vascular smooth muscle cell apoptosis. These alterations are, as already discussed, key elements in the atherosclerotic process. [67], [68]

In spite of the doubts regarding the functional role of CRP in the pathogenesis of ACS, it is clear that it is a useful, sensitive biomarker in the detection of ACS, as a marker of a proinflammatory state and plaque instability. In myocardial infarction there is normally an accentuated rise in circulating CRP levels, directly correlated with the extension of myocardial injury, and an accumulation of CRP in the damaged myocardium, where it has a role in the opsonization of necrotic tissue. [67]–[70] CRP has the advantages of having relatively stable levels and a large availability of assays, although it must be taken into account that this is not a specific biomarker, as it may also be elevated in result from other inflammatory processes not associated with ACS. [67]

Adhesion molecules

As previously discussed, various adhesion molecules, including P-selectin, E-selectin, VCAM-1 and ICAM-1, are upregulated as a result of the endothelial cell activation characteristic of the atherosclerotic process. These adhesion molecules are associated with leukocyte recruitment and migration into the vessel wall and are, therefore, fundamental in the development of atherosclerotic plaques. Thus, these are important biomarkers for ACS, that are directly associated with the biological mechanisms that promote arterial thrombus and subsequent cardiovascular events. [67], [70]

VCAM-1 is involved in platelet activation and in the balance of fibrin formation and fibrinolysis, and seems to be associated with death and recurrent nonfatal ACS. [70]

Inflammatory cytokines and chemokines

Inflammatory cytokines and chemokines are also potential biomarkers for ACS, as they are particularly important in the inflammatory response verified in atherosclerosis. Foam cells, for instance, secrete a variety of cytokines, such as IL-1, Il-6 and TNF-α, and chemokines, such as MCP-1. This leads to the secretion, from endothelial cells, of adhesion molecules that promote leucocyte recruitment to the intima, perpetuating the inflammatory response.[67]

TNF-α IL-1, IL-6, and IL-18 are considered to be produced by nucleated cells in the heart in response to a precipitating event, such as ischemic cardiac injury, due to innate stress responses. The expression of these cytokines seems to lead to deleterious effects on left ventricular function and acceleration of the progression of heart failure, due to myocyte apoptosis and necrosis, with IL-6 being associated with hypertrophic response in myocytes and TNF-α with left ventricular hypertrophy, presumably due to activation of matrix metalloproteinases. [71]

1.3.2 – Markers of plaque rupture

sCD-40L

CD-40 is a cell surface receptor expressed in various cell types, including B-cells, macrophages, endothelial cells, vascular smooth muscle cells and platelets. CD-40 ligand (CD-40L) is a transmembrane protein structurally related to TNF-α that was originally identified on $CD4^+$ T cells, but is also found on activated platelets. [72]–[74]

With platelet activation CD-40L is recruited and clived into sCD-40L which binds to CD40 receptor in the endothelial membrane. Various studies suggest that interactions between CD-40 and CD-40L are associated with atherogenic and thrombotic mechanisms, inducing various inflammatory responses, matrix degradation, tissue factor expression on macrophages and a decrease in thrombomodulin expression, leading to a procoagulant and prothrombotic state. [72]–[74]

sCD-40L is, therefore, a marker of platelet activation and, thus, also a marker of plaque rupture and inflammatory thrombotic activity, with elevated levels being reported in patients with both UA and acute myocardial infarction. [72]–[74]

Placental growth factor

PlGF was originally discovered in the placenta, but is also present in a range of other tissues including the heart. It is a functional cytokine, associated with angiogenesis and atherogenic migration of monocytes/macrophages into the arterial wall. [75]

Recent studies have shown that PlGF is important in both early and advanced atherosclerotic lesions, possibly being an instigator of plaque instability during the acute phase of ACS and is, therefore, a potentially useful biomarker associated with plaque instability and rupture. Since PlGF is associated with the recruitment of machophages, important in the removal of necrotic tissue, it is thought that PlGF may be released into vulnerable plaques from damaged cardiomyocites. [76], [77]

1.3.3 – Markers of thrombosis

Plaminogen activator inhibitor-1

PAI-1 is a serine protease, synthesized in platelets endothelium and adipose tissue, that is important in the blockage of he conversion of plasminogen to plasmin and, therefore, in the inhibition of fibrinolysis. PAI-1 acts binding to tissue plasminogen activator (t-PA), forming a stable complex, that is then cleared from blood circulation in the liver. [78]

Studies have shown that the occurrence of myocardial infarction is sometimes preceded by a rise in the circulating level of PAI-1 and ACS patients usually present elevated plasma levels of PAI-1, in conformity with the prothrombotic state verified after plaque rupture. In patients with acute ST-elevated myocardial infarction this elevation of the plasma levels of PAI-1 is strongly associated with the risk of mortality during a 1 month period. [79]

It is however, important to have into account that the measurement of plasma PAI-1 levels does not exactly reflect the local release of PAI-1, from platelet granules, that prevents thrombolysis during thrombus formation. Studies indicate that, in patients with acute myocardial infaction, platelet-derived PAI-1 concentration is much higher than plasma PAI-1 and, therefore, the measurement of plasma PAI-1 may not accurately reflect the influence of PAI-1 in the formation and stability of an arterial thrombus. [80]

von Willebrand factor

von Willebrand factor (vWf) is a glicoprotein, produced almost exclusively by endothelial cells, that is involved in platelet aggregation and adhesion and presents an increased release with endothelial damage, what suggests an association with thrombogenesis and atherosclerotic vascular disease. [81]–[83]

vWf is extremely important in thrombus formation, with its deficiency causing severe hemophilia. In early stages of thrombus formation, with the exposition of the subendothelial matrix of the blood vessel, vWf binds to matrix components and platelets adhere to vWf through glycoprotein IIb r IIIa receptors, which promots platelet aggregation and the formation of a platelet plug. vWf also acts as a carrier protein for

factor VIII and when vWf binds to collagen in the subendothelial connective tissue conformational alterations occur in vWf that cause the release of factor VIII, also important in the fibrin clot formation. [81]–[83]

High concentrations of vWf may, therefore, be an indirect indicator of atherosclerosis and of thrombosis, with increased concentrations being found in patients with previous myocardial infarction and, in the case of UA, correlating with the clinical severity of angina. [81]

1.3.4 – Markers of ischaemia

Ischaemia modified albumin

Ischaemia modified albumin (IMA) is produced during myocardial ischaemia, due to structural changes in the N-terminal of serum albumin that make the N-terminal aminoacids unable to bind to transition metals, potentially as a result of the release of ROS during ischaemia. [84]–[86]

IMA is, therefore, a sensitive marker for the diagnosis of myocardial ischaemia and has a very important role in the detection of ACS in patients with chest pain, with studies indicating that IMA has a greater sensitivity in the diagnosis of ACS than ECG and cTnT, used alone or combined. [84], [87]

Brain natriuretic peptide

BNP is primarily secreted by the ventricles, in a response to left ventricular stretching or wall tension. It constitutes a homeostatic signal important in maintaining a stable blood pressure and plasma volume and in the prevention of excessive salt and water retention, exerting various functions, including natriuresis, vasodilatation and inhibition of RAS–aldosterone and sympathetic nervous system. [88], [89]

BNP levels constitute, therefore, a simple and objective way of assessment of cardiac function and a biomarker of myocardial injury. [88]

Choline

Elevated levels of whole-blood choline (WBCho), free plasma choline (PCho) and serum choline (SCho) are thought to be markers of plaque destabilization and ischaemia in patients with ACS, as studies have showed choline to be released together with troponin I from the myocardium. [90]

1.3.5 – Prognostic markers

Serum uric acid

Serum uric acid is the main end product of the metabolism of purins and an important prognostic biomarker associated with poor outcome, both in the general population and in patients with ACS, with studies indicating a strong relation between serum uric acid levels at the time of admission and in-hospital and short-term mortality in male patients with STEMI. [91]–[93]

An increased concentration of serum uric acid usually reflects an increase in the xanthine oxidase pathway activity. This pathway constitutes an important source of ROS, that has an important role in CVD. ROS, as previously discussed, is associated with impaired regulation of vascular tone, due to deficient NO production and endothelial dysfunction. Therefore, elevated levels of serum uric acid are a useful clinical indicator of oxidative stress and may be indirectly associated with endothelial dysfunction. [91], [92]

Patients usually present increased levels of uric acid, and it is theorized that these increased levels may constitute a compensatory mechanism and that, in early stages, uric acid may have antioxidant properties, that paradoxically become pro-oxidant in later stages of atherosclosis, when serum uric acid levels are increased, in a urate redox shuttle. [91], [93]

Elevated levels of serum uric acid may also be related to impaired uric acid excretion due to, for instance, low cardiac output and tissue hypoxia, with certain studies suggesting a strong correlation between serum uric acid levels and Killip classification. [92]

Procalcitonin

Procalcitonin (PCT) is a pro-hormone, involved in calcium metabolism, that is produced mainly by the medullary C-cells of the thyroid gland and is know to be an inflammatory biomarker, that is found in increased levels, for instance, in the case of bacterial infections, sepsis, major surgery, multiple trauma, cardiogenic shock and cardiac surgery. [94]

PCT is thought to be an alternative novel marker with prognostic value in ACS, with various recent studies indicating that higher PCT levels are associated with a poorer outcome and a higher risk of mortality in the following 6 months. [94]

Cystatin C

There seems to exist a close relationship between chronic kidney disease and subsequent cardiovascular events in patients with ACS. Creatinine concentration and estimation of creatinine clearance are the most used means for estimation of renal function. However, as creatinine concentration may be affected by various factors such as age and diet, it may be unsensitive to small decreases in glomerular filtration rate (GFR). [95], [96]

Cystatin C is a cysteine protease inhibitor, produced by all nucleated cells at a constant rate and filtred without subsequent reabsortion to the blood flow. Cystatin C concentration is not altered by age, sex, muscle mass, exercise or diet and, therefore, it is a good candidate for the estimation of GFR, with certain studies indicating that it may be a better endogenous marker of GFR than serum creatinine. Thus, cystatin C may be a promising new prognostic biomaker in patients with ACS, with higher concentrations being associated with renal dysfunction and, therefore, with a poorer prognosis and more subsequent cardiac events. [95], [96]

1.3.6 – Markers of necrosis

Troponins

Troponin, located on the thin filament of the myocardial contractile apparatus, is a regulatory complex of 3 protein subunits, designated troponin C, the calcium-binding component, troponin T, the tropomyosin-binding component, and troponin I, the inhibitory component. [97], [98]

Troponin T and troponin I constitute highly sensitive markers for myocardial injury. They present the advantage of having a low background concentration, being detected immediately 4 to 9 hours after the onset of chest pain and remaining elevated up to 14 days after infarction, what gives them a wide diagnostic window. They present, however, the inconvenient of not being specific for acute myocardial infarction being elevated also in other conditions that lead to myocardial injury, such as atrial fibrillation, congestive heart failure, myocarditis, and myocardial contusions. [97], [98]

Cardiac troponin levels seem to have a linear correlation with a worsening outcome, as levels greater than 0.4mg/mL are associated with a higher mortality rate within 42 days, are inversely correlated with LVEF and are useful in the prediction of infarct size. [97], [98]

Myoglobin

Myoglobin is a heme muscle protein abundant in the cytoplasm of cardiac and skeletal muscle cells, constituting approximately 2% of muscle protein in both skeletal and cardiac muscles. Due to its low molecular weight, myoglobin is rapidly released into the circulation after acute myocardial infarction, reaching levels 5 to 10 times greater than normal during the first 5 to 18 hours. [99]–[101]

Myoglobin presents the inconvenient of having poor specificity for acute miocardial infarction, due to its presence in skeletal muscle. [101], [102]

Creatine kinase

Creatine kinase (CK) is an enzyme present in many tissues, including myocardium and skeletal muscle, in the form of 3 isoenzymes: MM, MB, and BB. CK-MB is present in a relatively high concentration in the myocardium and in patients with acute miocardial infarction a rise to twice the normal levels may be detected 4 to 9 hours after the onset of chest pain, returning to baseline levels in 48 to 72 hours. CK-MB constitutes a marker of cardiac tissue necrosis, as it is only released from myocardial cells upon death, not being released with ischaemia. [98]–[100]

CK-MB should be determined as a percentage of total CK enzyme, in order to determine if the source of the enzyme is cardiac or skeletal muscle, as a rise in CK-MB levels is not specific to myocardial damage, occurring also in, for instance, skeletal muscle injury. A relative index greater than 3.5% is indicative of myocardial damage rather than skeletal muscle injury. CK-MB levels are also useful in the determination of infarct size and risk of re-infarction. [98], [100], [102]

1.4 – Aims

Risk stratification in patients with ACS is very important in the determination of the proper treatment strategy. Various clinical features are known to be associated with an increased risk of a worse outcome in the event of an ACS and are taken into account in various risk scores. The main aim of this work is the determination of clinical characteristics that are associated with a worse outcome in a group of patients with ACS admitted to the Cardiac Intensive Care Unit of Hospital Infante D. Pedro, in Centro Hospitalar do Baixo Vouga (CHBV), in order to identify potential prognostic markers in these patients, and the assessment of the association of these markers with other clinical characteristics, in order to determine their influence in the physiology of patients with ACS.

2 – METHODOLOGY

2.1 – Data collection

A prospective observational study was conducted in 980 patients with ACS admitted to the Cardiac Intensive Care Unit of Hospital Infante D. Pedro, in Centro Hospitalar do Baixo Vouga (CHBV), between January 2008 and June 2012.

Data collected included general clinical information and information regarding cardiac risk factors, general blood test, serum cardiac markers, LVEF, provided revascularization therapy and previous and posterior cardiac events.

2.1.1 – General clinical information

Data collected about the patient's general clinical information included date of admission, date of discharge, duration of the hospitalization, age, gender, race and reason of the hospitalization. The reason of the hospitalization was separated in UA, STEMI and NSTEMI

2.1.2 – Cardiac risk factors

The presence of cardiac risk factors was also determined. Risk factors evaluated included the presence of a familiar history of CVD, personal history of CVD, the presence of DM, obesity, hypertension or dyslipidemia and whether the patients were a smokers, ex-smokers or alcoholics.

Hypertension is defined as a persistent elevation of blood pressure to levels above 140 mm Hg in systolic blood pressure and/or above 90 mm Hg in diastolic blood pressure. [103]–[105]

Dyslipidemia consists in alterations in lipoprotein metabolism, such as lipoprotein overproduction and deficiency, that result in alterations in the lipid profile, such as elevated levels of LDL (> 110 mg/dL), elevated levels of triglyceride (> 150 mg/dL) and

decreased levels of HDL (< 40 mg/dL in men; < 60 mg/dL in women). Dyslipidemia is characterized by the presence of at least one of these alterations. [106]–[108]

DM is a metabolic disorder in which a defect in insulin secretion or action leads to hyperglycaemia and disturbances in carbohydrate, fat and protein metabolism. A patient is diagnosed with DM when presenting a fasting plasma glucose ≥ 126 mg/dL, a 2-hour plasma glucose ≥200 mg/dL following an oral glucose tolerance test, a glycated hemoglobin ≥ 6,5% or, in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, when presenting a random plasma glucose ≥200 mg/dL. In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing. [109], [110]

Obesity is defined as an excessive accumulation of body fat or adiposity. Although it does not quantify total body adiposity, BMI, in kg/m^2, is a weight-for-height index that presents a strong correlation with adiposity and is widely used in the assessment of obesity. According to World Health Organization (WHO) and National Institute of Health, a patient is considered overweight when presenting a BMI≥ 25,0 and obese with a BMI≥ 30,0. [106], [111]

2.1.3 – General blood test

Data related to general blood test was also assessed and included levels of hemoglobin (g/dL), glucose (mg/dL) and lipid profile.

The evaluation of hemoglobin levels is important, as bleeding is a common complication in patients with ACS. Anemia, defined by WHO as < 13 g/dL in men and < 12 g/dL in women, is common in patients with ACS and is associated with an increased probability of an adverse outcome. [112]–[114]

The assessment of glucose levels is important as elevated levels in patients without DM are associated with short-term adverse outcomes. Fasting plasma glucose levels should ideally be less than126 mg/dL. [115]–[117]

The evaluation of the patient's lipid profile is very important in cardiovascular risk prediction and has now become a routine test. This evaluation included measurements of the levels of total cholesterol (mg/dL) and LDL (mg/dL. [118] Lipide profile was measured in the first 24 hours after hospitalization, as studies indicate that measurements beyond this period are not valid and do not reflect its habitual value, insofar as there seems to be a reduction, that appears after 24 hours of onsent and remains for 2 to 3 months, in the levels of total cholesterol, LDL and HDL. [119]–[122]

2.1.4 – Biomarkers

As previously discussed, biomarkers provide valuable information both in diagnosis, in the determination of the extent of myocardial lesion and in prognosis. The biomarkers evaluated included troponin (ng/mL), CPR (mg/dL) and pro-brain natriuretic peptide (Pro-BNP) (pg/mL). In the case of troponin the level at time of admission and the maximum value reached were both registered.

Troponins, as previously mentioned, are cardiac markers of necrosis, important for diagnosis and determination of the extent of myocardial lesion. They seem to have a linear correlation with worsening outcome, with levels greater than 0.4mg/mL being associated with a higher mortality rate within 42 days. They are not normally detected in the serum of healthy individuals and, therefore, levels greater than 0,10 ng/ml are considered elevated. [123]

CRP is a useful, sensitive biomarker in the detection of ACS, as a marker of a proinflammatory state and plaque instability. In myocardial infarction there is normally an accentuated rise in circulating CRP levels, directly correlated with the extension of myocardial injury. CRP levels are considered elevated when they are greater than 6 mg/dL. [67]–[70], [124], [125]

Pro-BNP, levels constitute a simple and objective way of assessment of cardiac function and are an indicator of myocardial injury. A Pro-BNP of less than 125 pg/ml excludes cardiac dysfunction and heart failure whereas a greater value is indicative of cardiac dysfunction and is associated with cardiac complications. [88], [126]

2.1.5 – Left ventricular ejection fraction

LVEF was also determined as it is an important measurement in the evaluation of global contractile function. It was, therefore determined if patients presented a normal LVEF (>50%), a mildly reduced LVEF (35-50%) or a severely reduced LVEF (<35%). This evaluation is important as a low LVEF is associated with higher risk of cardiac arrest and arrhythmic death. [127], [128]

2.1.6 – Provided revascularization therapy

Data concerning the provided revascularization therapy was also assessed, and included the number of vases that presented and obstruction of more than 75% in the catheterization, if the patient underwent PTCA and the number of vases that were revascularizated.

2.1.7 – Events

The presence of previous and posterior cardiac events was also assessed, trough the consultation of the patient's medical records.

In the case of previous cardiac events it was registered if the patient had previously suffered from UA, NSTEMI, STEMI or stroke.

In the case of posterior cardiac events where characterized by date and type and were divided in ACS, stroke and others, such as FA, CHF or cardiogenic shock. In the case of multiple events only the first event was considered.

In the event of a death, date of death was registered, as well as whether death occurred during the hospitalization or not.

Patients were followed until January 2014 and their individual follow-up period was also registered. The mean follow-up period was 33,25 ± 25,60 months.

2.2 – Statistical analysis

Statistical analysis was performed using the version 19 of the software SPSS (SPSS Inc., Chicago, Illinois, USA).

Continue variable values were presented as mean ± standard deviation and categorical variable values were presented as frequencies.

In continuous variables differences between groups were assessed using One-way Anova or Kruskal-Wallis test, followed by the parametric Student's T-test. Anova analyzes variances, allowing the assessment of differences between several different groups without multiple comparisons between group means. Kruskal-Wallis is the advised non parametric alternative when One-way Anova assumptions are not met. [129]–[131]

Student's T-test is a parametric test presenting, thus, a stricter assumptions such as, in the case of independent variables, normal distribution and homogeneity of variances. [129], [132], [133]

Proportion differences in categorical variables were assessed using the asymptotic Pearson's X^2 test and Fisher's Exact test, the advised alternative for smaller samples. [129], [134], [135]

Hazard ratios, obtained through the stepwise Cox Proportional Hazards Model, a useful prognostic model in the prediction of clinical outcomes, were used in the evaluation of the prognostic impact of the predictors assessed. [136]

Survival curves, defined as the probability of surviving (absence of event) in a given length of time (considering time in small intervals) were obtained using the Kaplan-Meyer estimate. [137], [138]

Results were considered statistically significant when $p < 0,05$.

3 – RESULTS

The clinical characteristics of study participants are summarized in table 8 and in the figures 1-15.

The analyzed sample included 980 caucasian individuals that were hospitalized in CHBV between 2008 and 2012, 688 (70,2%) males and 292 (29,8%) females, from which 310 (31,6%) were hospitalized due to STEMI, 579 (59,1%) were hospitalized due to NSTEMI and 91 (9,3%) were hospitalized due to UA. These patients presented a mean age of 67,22 ± 12,99 years, with 798 (81,4%) of them being more than 55 years of age. The mean follow-up period was 33,25 ± 25,60 months and during this period 172 patients (17,6%) suffered a posterior event and 205 patients (20,9%) died, with 64 (6,5%) dying from cardiac causes. The 172 posterior events included 118 ACSs (12%), 19 strokes (1,9%) and 35 other events (3,6%).

In terms of risk factors, 41 (4,2%) patients had family history of ACS, 252 (25,7%) patients had a previous case of ACS or stroke, 681 (69,5%) patients suffered from hypertension, 565 (57,7%) patients suffered from dyslipidemia, 308 (31,4%) patients suffered from DM, 173 (17,7%) patients had a BMI greater than 30, 137 (14%) patients were smokers, 93 (9,5%) patients were ex-smokers and 27 (2,8%) patients suffered from alcoholism.

The mean hemoglobin value was 13,67 ± 1,84 g/dL, with 30 patients (3,2%) presenting a value of less than 10 g/dL, 138 patients (14,9%) presenting a value between 10 and 12 g/dL and 757 patients (81,8%) presenting a value greater than 12 g/dL, what translated in 222 anemic patients (24%). The mean glucose value was 151,61 ± 69,98 mg/dL, with 155 patients (16,7%) presenting a value of less than 100 mg/dL, 228 patients (31,1%) presenting a value between 100 and 126 mg/dL and 484 patients (52,2%) presenting a value greater than 126 mg/dL. The mean initial troponin value was 9,58 ± 23,61 ng/mL. The mean maximum troponin value was 31,12 ± 44,71 ng/mL. The mean Pro-BNP value was 3696,40 ± 9608,60 pg/mL. The mean total cholesterol value was 183,55 ± 46,79 mg/dL. The mean LDL value was 115,94 ± 39,02 mg/dL, with 711 patients (89,2%) presenting avalue greater than 70 mg/dL. The mean CRP value was 2,02 ± 4,48 mg/dL.

PTCA was performed in 441 patients (59%), with 356 patients (57,4%) revascularizating one blood vessel, 73 patients (12,1%) revascularizating 2 blood vessels and 10 patients (1,7%) revascularizating 3 blood vessels

Table 8 – Clinical characteristics of study participants

Sample description		
Age (years)	67,22 ±12,99	
Age Class (n, %)	< 55 years	182 (18,6%)
	> 55 years	798 (81,4%)
Gender (n, %)	Male	688 (70,2%)
	Female	292 (29,8%)
Hospitalization Motive (n, %)	STEMI	310 (31,6%)
	NSTEMI	579 (59,1%)
	UA	91 (9,3%)
Family History of ACS (n, %)	No	939 (95,8%)
	Yes	41 (4,2%)
Previous event (n, %)	No	728 (74,3%)
	Yes	252 (25,7%)
Type of Previous Event (n, %)	None	728 (74,3%)
	ACS	202 (20,6%)
	Stroke	41 (4,2%)
	ACS+Stroke	9 (0,9%)
Hypertension (n, %)	No	299 (30,5%)
	Yes	681 (69,5%)
Dyslipidemia (n, %)	No	415 (42,3%)
	Yes	565 (57,7%)
BMI (n, %)	< 30	807 (82,3%)
	> 30	173 (17,7%)
DM (n, %)	No	672 (68,6%)
	Yes	308 (31,4%)

Note. Values are presented as mean ± SD for continuous variables and as frequencies for categorical variables. ACS: acute coronary syndrome; BMI: body mass index; DM: diabetes mellitus; NSTEMI: non–ST-segment elevation acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

(continued)

Table 8 – Clinical characteristics of study participants (continued)

Sample description		
Smoker (n, %)	No	843 (86%)
	Yes	137 (14%)
Ex-smoker (n, %)	No	887 (90,5%)
	Yes	93 (9,5%)
Alcoholic (n, %)	No	953 (97,2%)
	Yes	27 (2,8%)
Hemoglobin (g/dL)	13,67 ±1,84	
Hemoglobin Class (n, %)	< 10 g/dL	30 (3,2%)
	10 -12 g/dL	138 (14,9%)
	> 12 g/dL	757 (81,8%)
Anemia (n, %)	No	703 (76%)
	Yes	222 (24%)
Glucose (mg/dL)	151,61 ± 69,98	
Glucose Class (n, %)	< 100 mg/dL	155 (16,7%)
	100 – 126 mg/dL	228 (31,1%)
	> 126 mg/dL	484 (52,2%)
Inicial Troponin (ng/mL)	9,58 ± 23,61	
Maximum Troponin (ng/mL)	31,12 ± 44,71	
Pro-BNP (pg/mL)	3696,40 ± 9608,60	
Total Cholesterol (mg/dL)	183,55 ± 46,80	
LDL (mg/dL)	115,94 ± 39,02	
LDL Class (n, %)	< 70 mg/dL	86 (10,8%)
	> 70 mg/dL	711 (89,2%)
CRP (mg/dL)	2,02 ± 4,48	
Obstructed Blood vessels (n, %)	0	139 (18,8%)
	1	317 (42,8%)
	2	175 (23,6%)
	3	110 (14,8%)
PTCA (n, %)	No	306 (41%)
	Yes	441 (59%)
Revascularizated blood vessels (n, %)	0	174 (28,9%)
	1	356 (57,4%)
	2	73 (12,1%)
	3	10 (1,7%)

Note. Values are presented as mean ± SD for continuous variables and as frequencies for categorical variables. CRP: c reacive protein; LDL: low density lipoprotein; PTCA: percutaneous transluminal coronary angioplasty; Pro-BNP: pro-brain natriuretic peptide

(continued)

Table 8 – Clinical characteristics of study participants (continued)

Sample description		
LVEF Class (n, %)	> 50%	353 (67,5%)
	35 – 50%	108 (20,7%)
	< 35%	62 (11,9%)
Posterior Event (n, %)	No	808 (82,4%)
	Yes	172 (17,6%)
Type of Posterior Event (n, %)	No event	808 (82,4%)
	ACS	118 (12%)
	Stroke	19 (1,9%)
	Other	35 (3,6%)
Death (n, %)	No	775 (79,1%)
	Yes	205 (20,9%)
Cardiac Death(n, %)	No	916 (93,5%)
	Yes	64 (6,5%)
Follow-up (Months)	33,25 ± 25,60	

Note. Values are presented as mean ± SD for continuous variables and frequencies for categorical variables. ACS: acute coronary syndrome; LVEF left ventricular ejection fraction

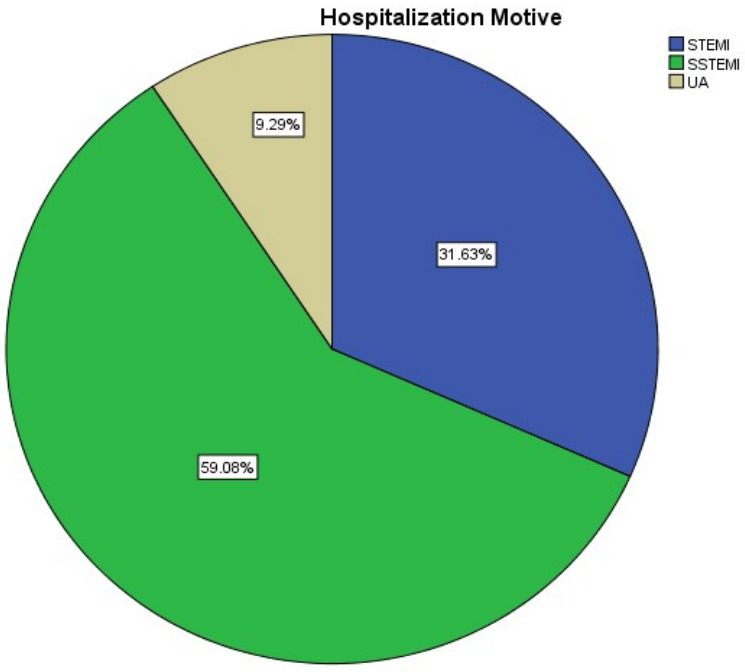

Figure 1 – Distribution (%) according to the hospitalization motive

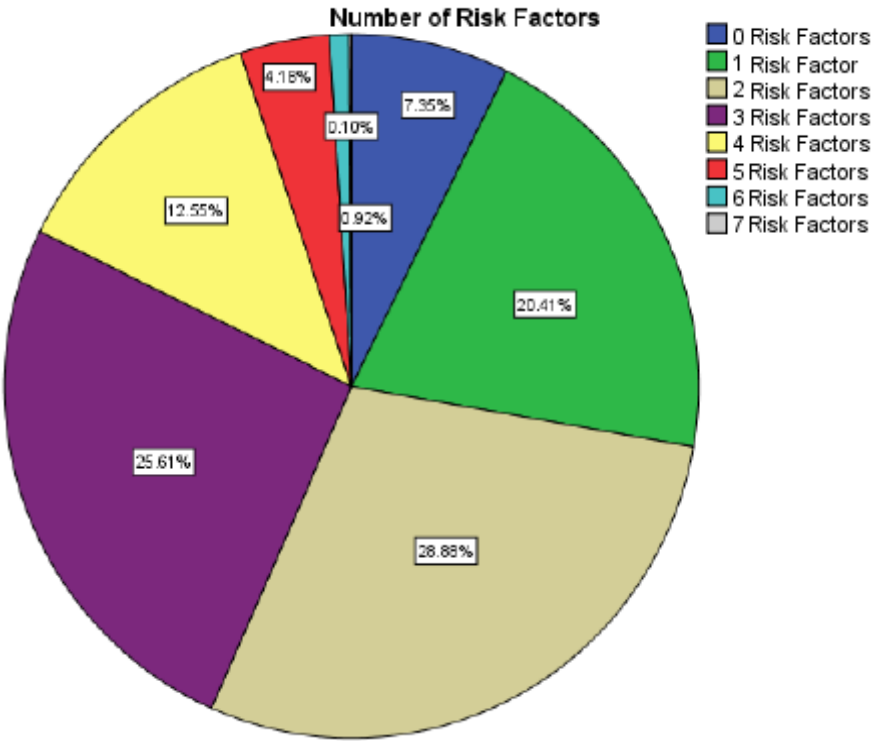

Figure 2 – Distribution (%) according to the number of risk factors

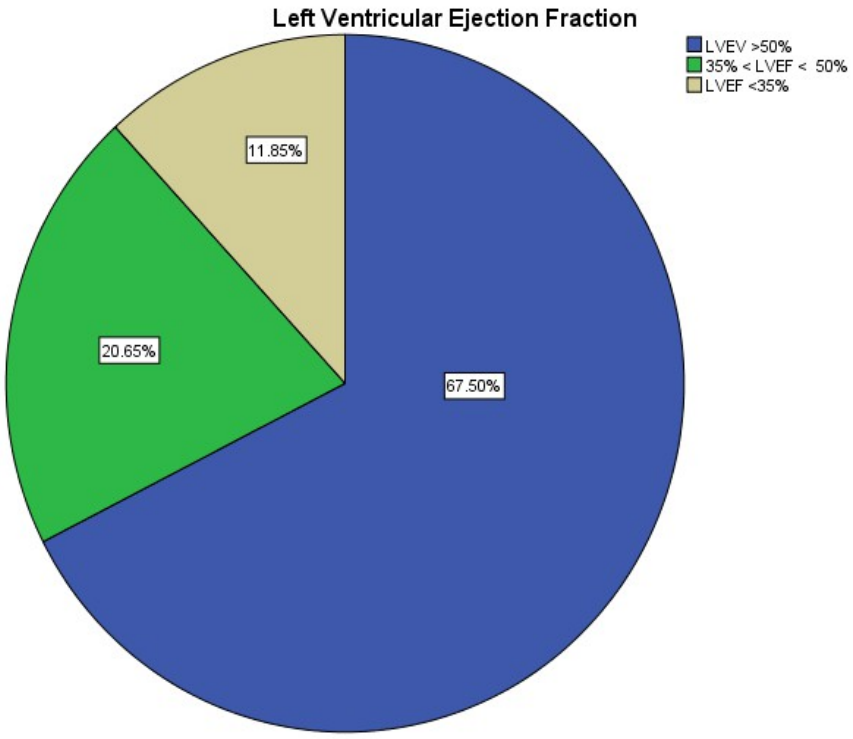

Figure 3 – Distribution (%) according to the left ventricular ejection fraction

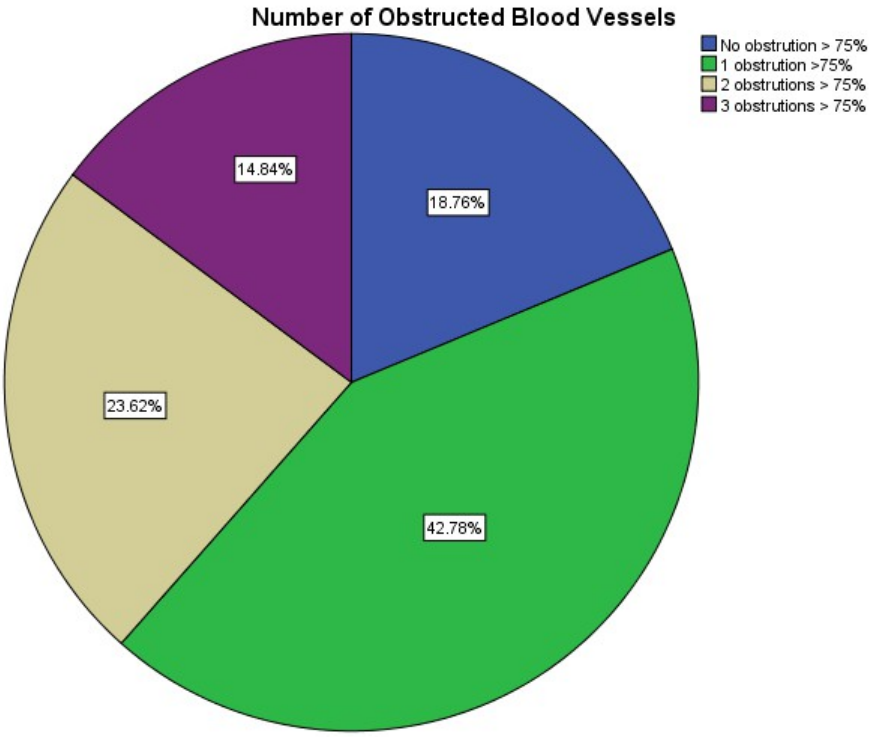

Figure 4 – Distribution (%) according to the number of obstructed blood vessels

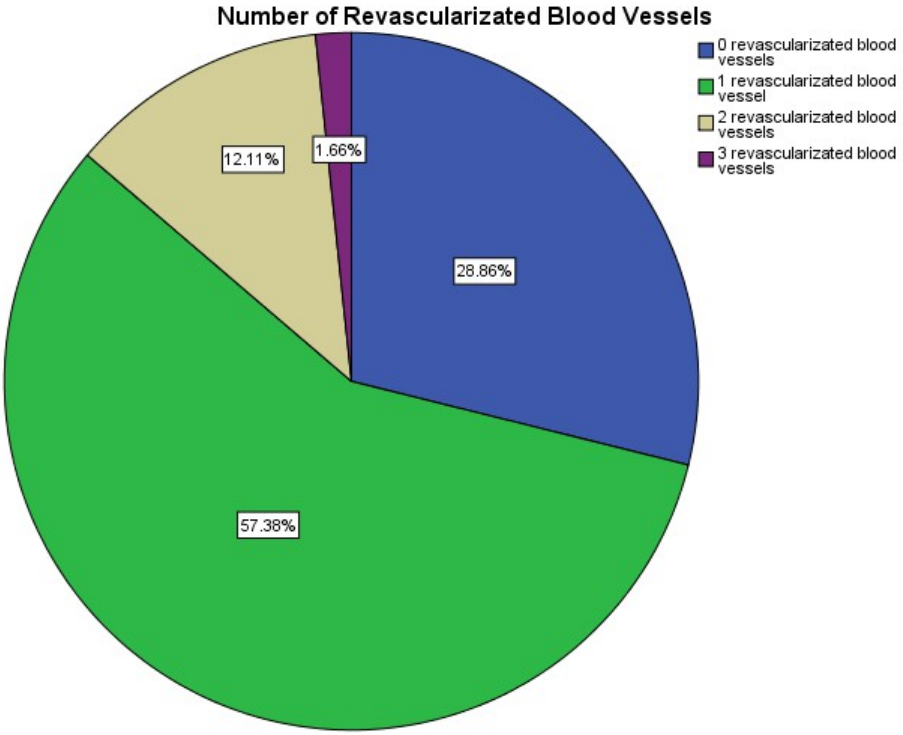

Figure 5 – Distribution (%) according to the number of revascularizated blood vessels

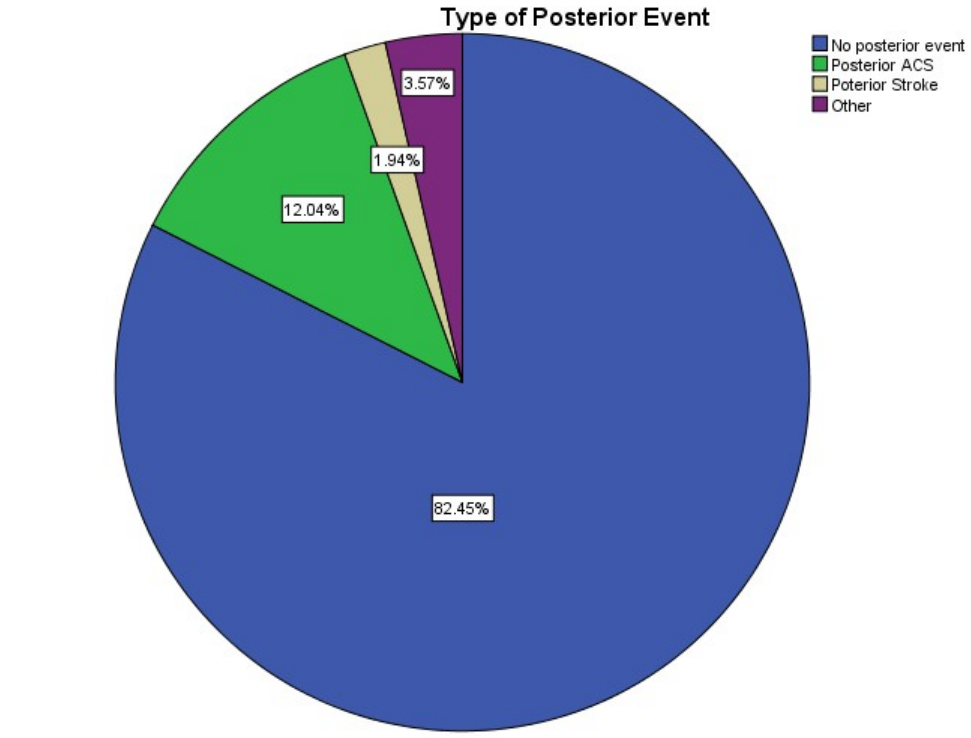

Figure 6 – Distribution (%) according to the type of posterior event

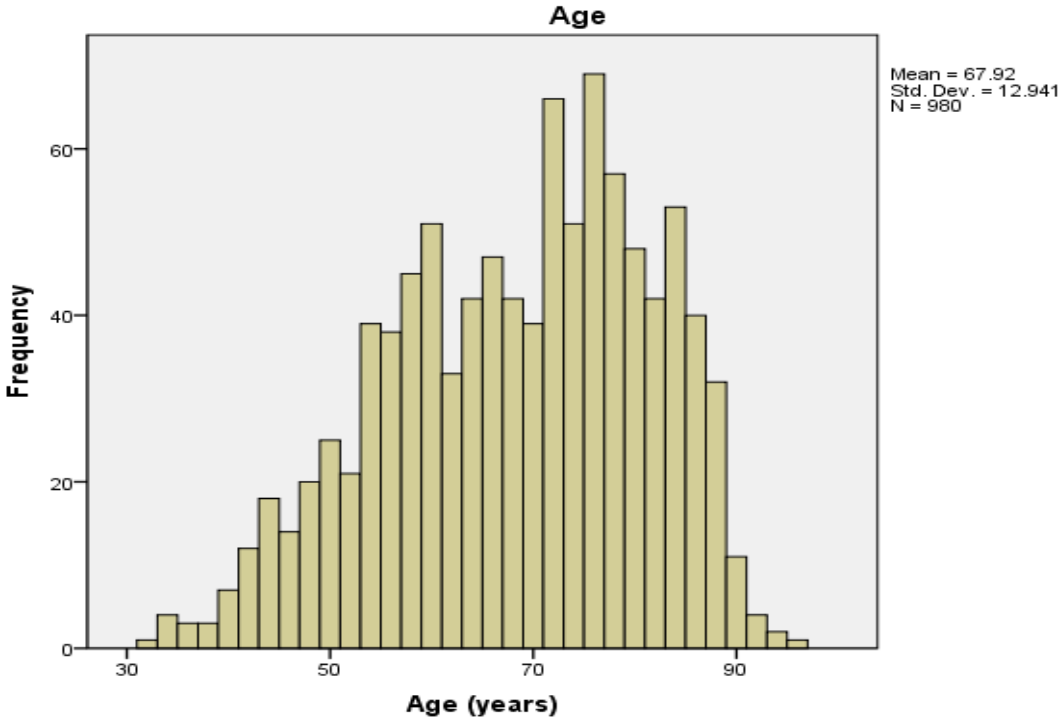

Figure 7 – Histogram of age distribution (years)

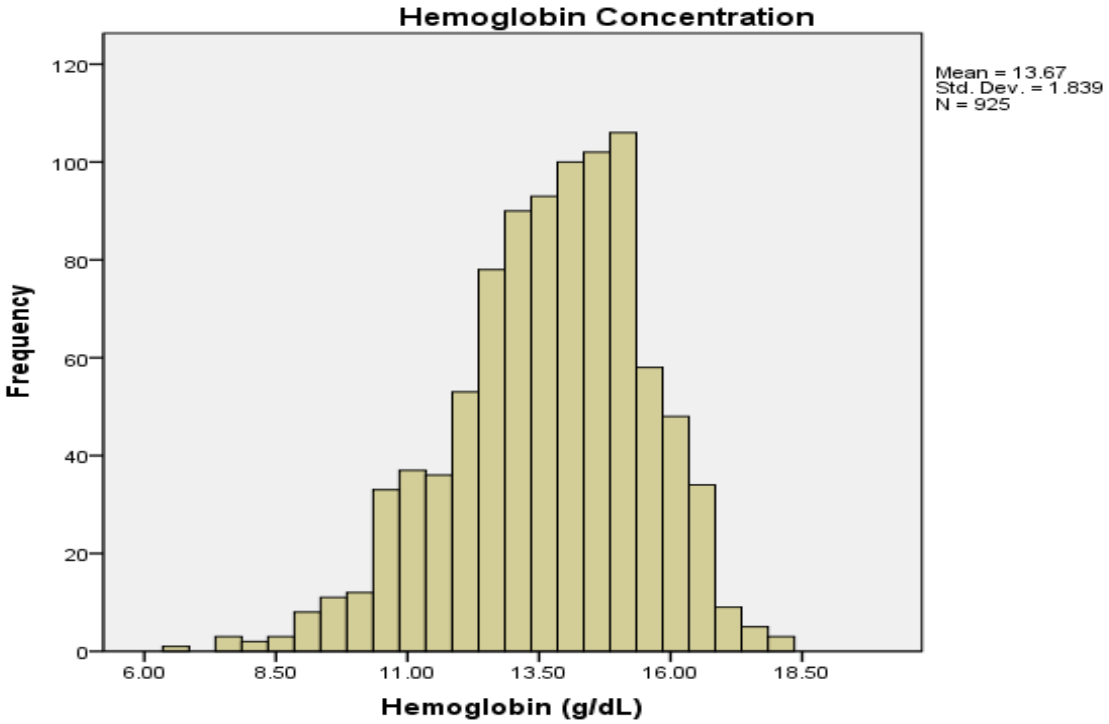

Figure 8 – Histogram of hemoglobin concentration distribution (g/dL)

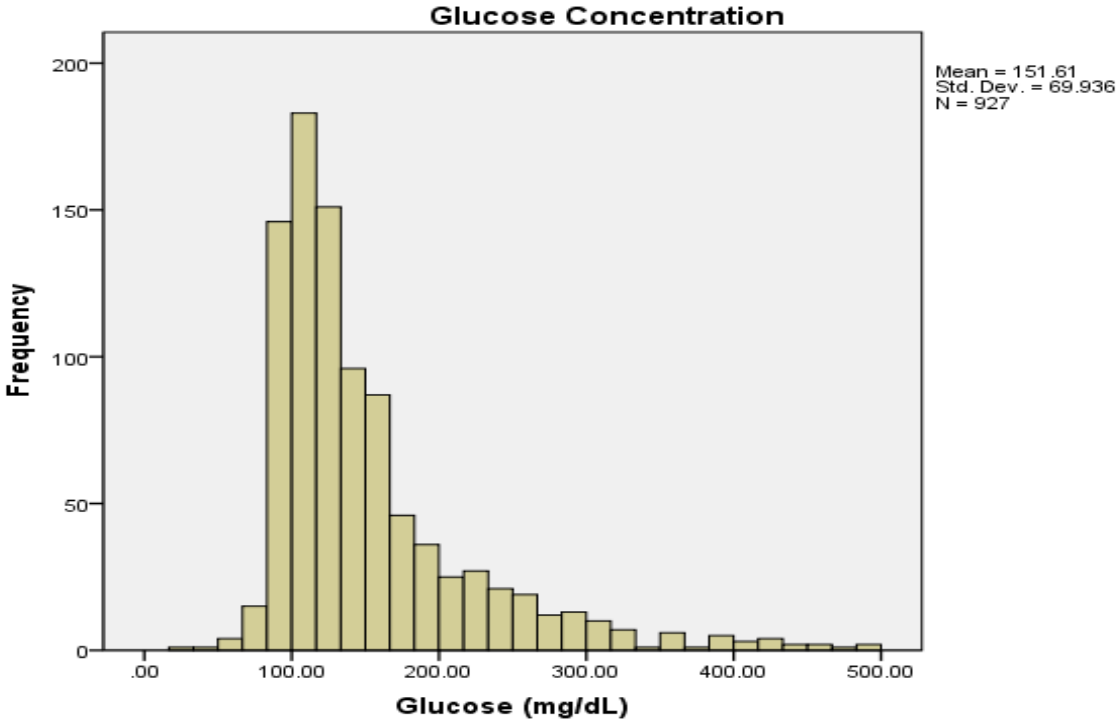

Figure 9 – Histogram of glucose concentration distribution (mg/dL)

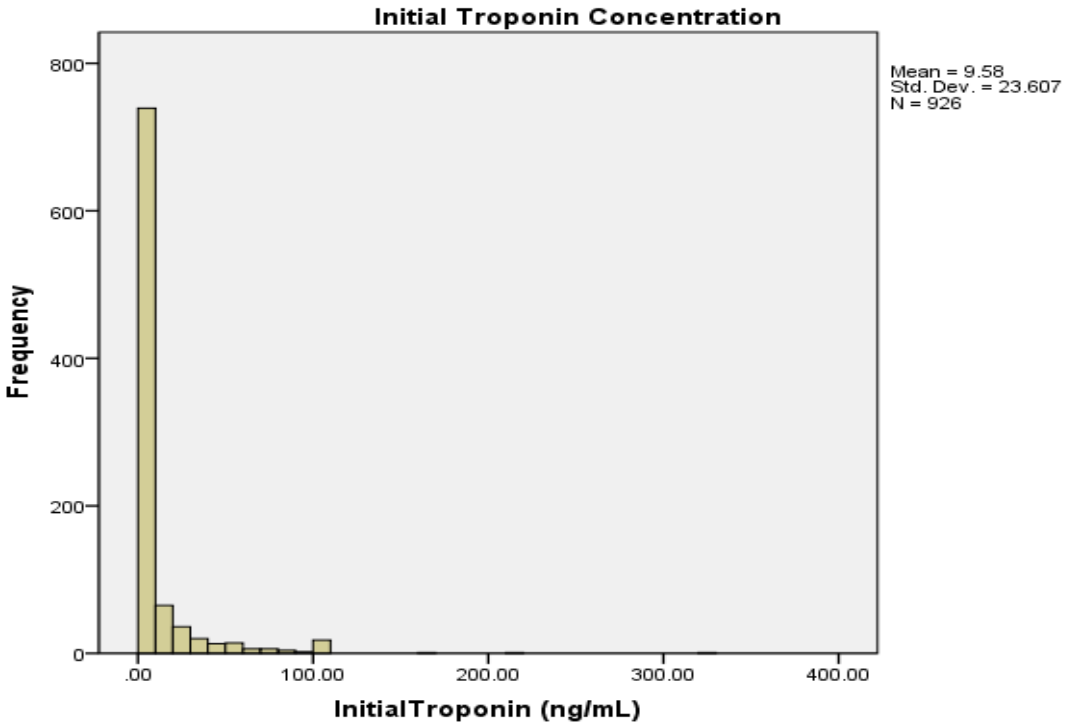

Figure 10 – Histogram of initial troponin concentration distribution (ng/mL)

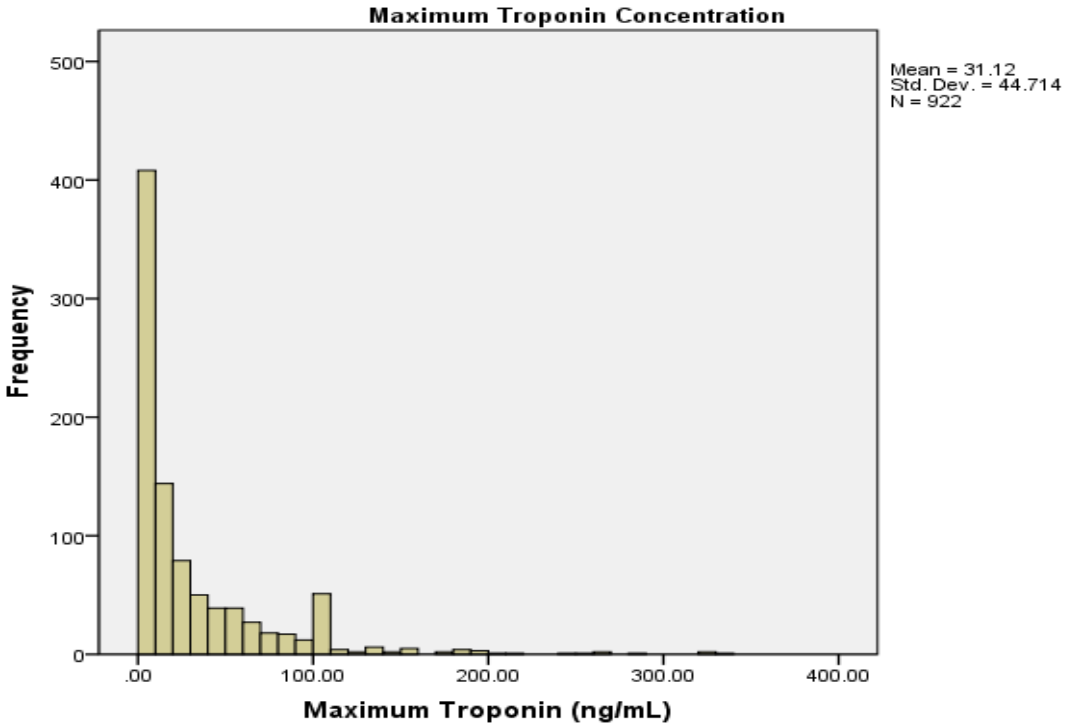

Figure 11 – Histogram of maximum troponin concentration distribution (ng/mL)

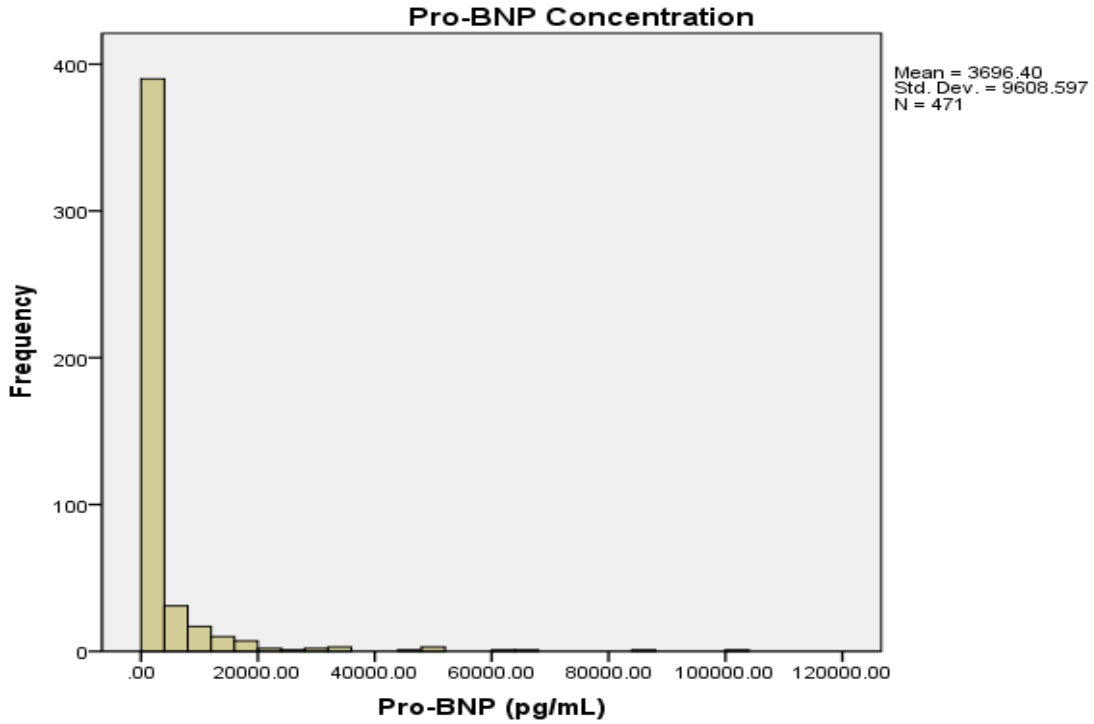

Figure 12 – Histogram of Pro-BNP concentration distribution (pg/mL)

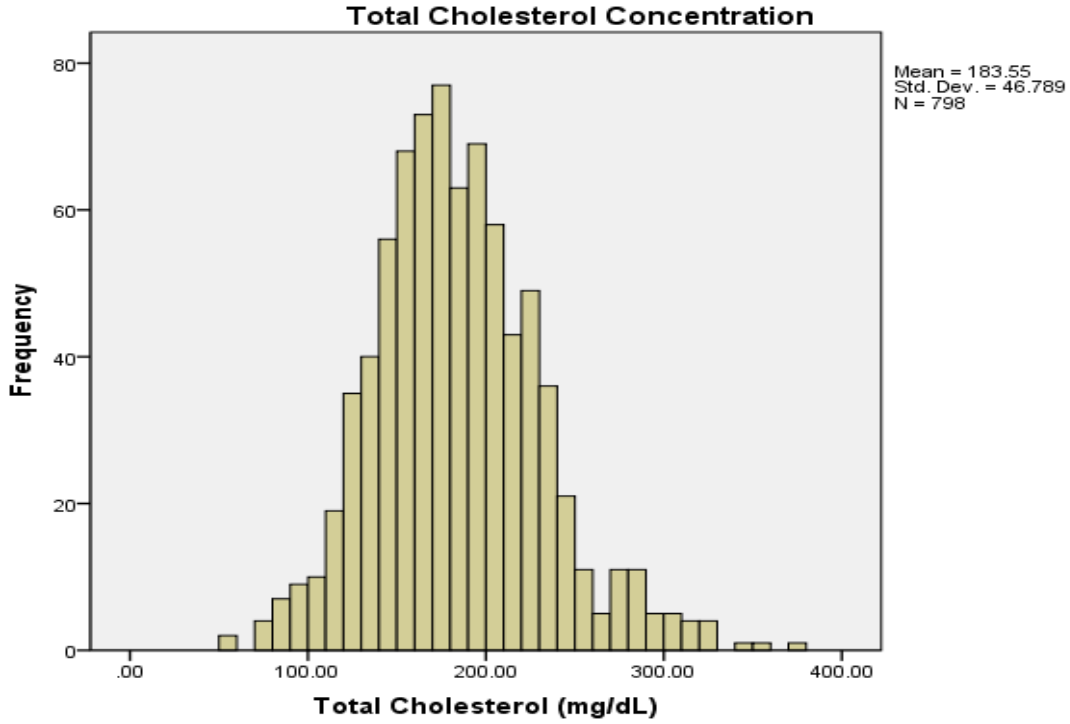

Figure 13 – Histogram of total cholesterol concentration distribution (mg/dL)

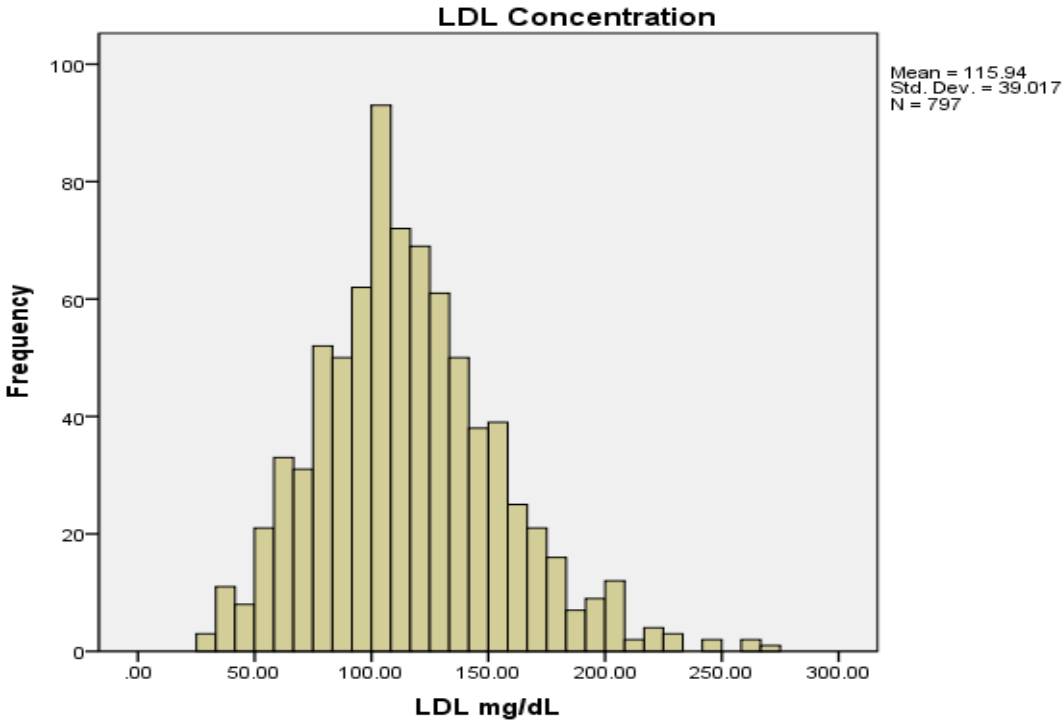

Figure 14 – Histogram of LDL concentration distribution (mg/dL)

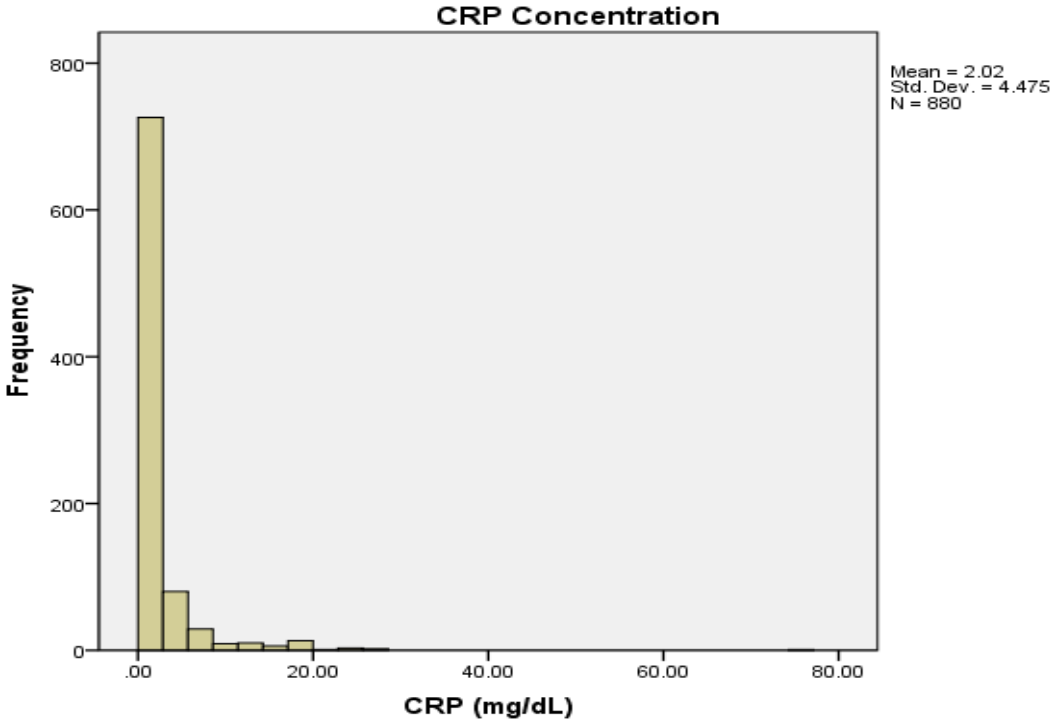

Figure 15 – Histogram of CRP concentration distribution (mg/dL)

The assessment of significant differences in the mean values of age, hemoglobin, glucose, initial troponin, maximum troponin, Pro-BNP, total cholesterol, LDL and CRP in different groups of patients, using Student's T-Test presented various statistically significant results, that are summarized in table 9.

Patients that had a posterior event were older and presented significantly lower hemoglobin concentrations than patients that did not suffer a posterior event.

Patients that had a posterior stroke were older and presented significantly lower hemoglobin concentrations than patients that did not suffer a posterior stroke.

Patients that suffered another other type of posterior event were significantly older than patients that did not suffer any other type of posterior events

Male patients were younger and presented significantly higher hemoglobin concentrations and lower Pro-BNP concentrations than female patients.

Patients younger than 55 years of age presented significantly higher hemoglobin, total cholesterol and LDL concentrations and lower initial troponin and Pro-BNP concentrations than patients older than 55 years of age.

Anemic patients were older and presented significantly higher initial troponin, Pro-BNP and CRP concentrations and lower total cholesterol and LDL concentrations than non anemic patients.

Patients that did underwent PTCA were younger and presented significantly higher hemoglobin and maximum troponin concentrations than the patients that did not underwent PTCA.

Patients that died were older and presented significantly lower hemoglobin, total cholesterol and LDL concentrations and higher glucose, initial troponin, Pro-BNP and CRP concentrations than the patients that did not died.

Patients that died due to cardiac reasons were older and presented significantly lower hemoglobin concentrations and higher initial troponin, maximum troponin, Pro-BNP and CRP concentrations than the patients that did not die due to cardiac reasons.

Table 9 – Comparison of the mean values of age, hemoglobin, glucose, initial troponin, maximum troponin, Pro-BNP, total cholesterol, LDL and CRP in different groups of patients

	Mean ± SD		T	p Value
	No Posterior Event	**Posterior Event**		
Age	67,18 ± 13,05	71,18 ± 11,87	-4,137	0,000
Hemoglobin	13,76 ± 1,79	13,20 ± 1,995	3,408	0,001
	No Posterior Stroke	**Posterior Stroke**		
Age	67,71 ± 12,93	78.3 ± 8,32	-5,594	0,000
Hemoglobin	13,70 ± 1,83	12,13 ± 1,68	3,586	0,003
	No Other Posterior Events	**Other Posterior Events**		
Age	67,67 ± 13,02	74,83 ± 8,02	-5,045	0,000
	Male	**Female**		
Age	65,52 ± 12,85	73,57 ± 11,31	-9,776	0,000
Hemoglobin	14,12 ± 1,72	12,59 ± 1,65	12,473	0,000
Pro-BNP	2952,60 ± 8144,44	5402,46 ± 12191,14	-2,119	0,029
	< 55 Years of Age	**> 55 Years of Age**		
Hemoglobin	14,75 ± 1,36	13,42 ± 1,85	10,833	0,000
Initial Troponin	5,13 ± 14,40	10,63 ± 25,19	-3,869	0,000
Pro-BNP	710,84 ± 1211,38	4353,84 ±10487,48	-6,627	0,000
Total Cholesterol	201,14 ± 48,85	178,96 ± 45,16	5,523	0,000
LDL	130,39 ± 40,12	112,17 ± 37,86	5,437	0,000
	No anemia	**Anemia**		
Age	65,31 ± 12,92	75,42 ± 10,188	-12,041	0,000
Initial Troponin	7,48 ± 18,28	16,22 ± 34,87	-3,576	0,000
Pro-BNP	2369,89 ± 5812,83	7850,49 ± 15955,83	-3,592	0,000
Total Cholesterol	189,05 ± 45,68	164,20 ± 45,40	6,310	0,000
LDL	120,33 ± 38,34	100,44 ± 37,496	6,039	0,000
CRP	1,65 ± 4,195	3,28 ± 5,17	-4,074	0,000

Note. Student's T-test results are presented as Mean ± SD, and statistics T and p Value. Results were considered statically significant when $p < 0,005$. CRP: C reactive protein; LDL: low density lipoprotein; Pro-BNP: pro-brain natriuretic peptide

(continued)

Table 9 – Comparison of the mean values of age, hemoglobin, glucose, initial troponin, maximum troponin, Pro-BNP, total cholesterol, LDL and CRP in different groups of patients (continued)

	Mean ± SD		t	p Value
	Did not underwent PTCA	**Underwent PTCA**		
Age	68,04 ± 11,77	64,00 ± 12,26	4,501	0,000
Hemoglobin	13,69 ± 1,81	14,08 ± 1,72	-2,907	0,000
Maximum Troponin	21,28 ± 28,22	40,84 ± 56,30	-6,099	0,000
	Did not Die	**Died**		
Age	65,39 ± 12,66	77,49 ± 8,91	-15,700	0,000
Hemoglobin	13,98 ± 1,68	12,41 ± 1,92	10,070	0,000
Glucose	148,65 ± 68,11	163,87 ±76,05	-2,457	0,015
Initial Troponin	7,22 ±17,86	19,31 ± 37,78	-4,193	0,000
Pro-BNP	2338,17 ± 7029,42	11101,56 ± 16261,19	-4,528	0,000
Total Cholesterol	186,92 ± 45,46	165,03 ± 49,74	4,838	0,000
LDL	118,36 ± 37,88	102,53 ± 42,53	4,168	0,000
CRP	1,63 ± 4.13	3,70 ± 5,41	-4,650	0,000
	Without Cardiac Death	**With Cardiac Death**		
Age	67,25 ± 12,96	77,53 ± 7.90	-6,264	0,000
Hemoglobin	13,76 ± 1,80	12,41 ± 1,97	5.164	0,000
Initial Troponin	8,45 ±21.78	26,28 ± 38,71	-5,711	0,000
Maximum Troponin	7,22 ±17,86	19,31 ± 37,78	-2,017	0,048
Pro-BNP	3085,70 ± 8329,34	15070,79 ± 19976,59	-4,528	0,000
CRP	1,84 ± 4.29	4,65 ± 6,11	-4,600	0,000

Note. Student's T-test results are presented as Mean ± SD, and statistics T and p Value. Results were considered statically significant when $p < 0,005$. CRP: C reactive protein; LDL: low density lipoprotein; PTCA: percutaneous transluminal coronary angioplasty; Pro-BNP: pro-brain natriuretic peptide

The assessment of significant differences in the values of age hemoglobin, glucose, initial troponin, maximum troponin, Pro-BNP, total cholesterol, LDL and CRP according to the patient´s hospitalization motive, LVEF and type of posterior event was done using One-way Anova in the cases where Levine's test confirmed the homogeneity of variances and the Kruskal-Wallis test in the cases where Levine's test did not confirm the homogeneity of variances. The significant results of these tests are summarized in table 10.

In the case of the hospitalization motive, there was a statistically significant difference between groups in age and in the levels of hemoglobin, initial troponin, maximum

troponin, Pro-BNP and CRP.

In the case of the LVEF, there was a significant difference between groups in age and in the levels of hemoglobin, initial troponin, maximum troponin, Pro-BNP and CRP.

In the case of the type of posterior event, there was a statistically significant difference between groups in age and in the levels of hemoglobin and Pro-BNP.

Table 10 – Assessment of differences in the values of age hemoglobin, glucose, initial troponin, maximum troponin, Pro-BNP, total cholesterol, LDL and CRP between different groups of patients

Groups		**Kruskal-Wallis**		**One-way Anova**	
		H	**p Value**	**F**	**p Value**
Hospitalization Motive	Age	11,212	0,004		
	Hemoglobin			3,582	0,028
	Initial Troponin	81,193	0,000		
	Maximum Troponin	229,589	0,000		
	Pro-BNP	22,143	0.000		
	CRP	11,650	0,003		
LVEF	Age	24,002	0,000		
	Hemoglobin	17,143	0,000		
	Initial Troponin	14,077	0,001		
	Maximum Troponin	13,164	0,001		
	Pro-BNP	52,894	0,000		
	CRP	16,670	0,000		
Posterior Event	Age	28,190	0,000		
	Hemoglobin			5,924	0,001
	Pro-BNP	16,494	0,001		

Note. One-way Anova was used in the cases where Levine's test confirmed the homogeneity of variances and in the cases where Levine's test did not confirm the homogeneity of variances the Kruskal-Wallis test was used. Results were considered statically significant when $p < 0,005$. CRP: C reactive protein; LVEF: left ventricular ejection fraction; Pro-BNP: pro-brain natriuretic peptide

Pearson's X^2 test was used in the assessment of associations between the presence of a posterior event, gender, age, anemia, PTCA death and other clinical variables. When, in Pearson's X^2 test, there were more than 20% of cells with an expected count of less than

5, Fisher's exact test was used instead. The significant results of these tests are summarized in table 11.

There was a statistically significant association between posterior event and age, gender, presence of a previous event, hypertension, dyslipidemia, BMI, being an ex-smoker, hemoglobin class, anemia, LVEF class and with death. Patients that suffered a posterior event were older and more prone to be female; had a higher prevalence of hypertension, dyslipidemia and anemia; had a higher BMI, a lower hemoglobin class and a lower LVEF class; were more prone to have had a previous event, less prone to being ex-smokers and more prone to death.

Posterior ACS presented a statistically significant association with previous event, dyslipidemia, BMI, anemia, glucose class and with LVEF class. Patients that suffered a posterior ACS were more prone to have had a previous event; had a higher prevalence of dyslipidemia and anemia; had a higher BMI, a lower glucose class and a lower LVEF class.

Posterior stroke presented a statistically significant association with age, gender, previous event, hypertension, hemoglobin class, anemia and death. Patients that suffered a posterior stroke were older, more prone to be female, more prone to have had a previous event and more prone to death; had a higher prevalence of hypertension and a higher hemoglobin class.

Patient gender presented a statistically significant association with, age, hypertension, being a smoker, being an ex-smoker, alcoholism, hemoglobin class, anemia, number of obstructed blood vessels and death. Male patients were younger and more prone to be smokers and ex-smokers; had a lower prevalence of hypertension and anemia and a higher prevalence of alcoholism; had a higher hemoglobin class and a higher number of obstructed vases and were less prone to death.

There was a statistically significant association between age and family history of ACS, previous event, hypertension, DM, being a smoker, being an ex-smoker, alcoholism, hemoglobin class, anemia, LDL class, number of obstructed blood vessels, PTCA, number of revascularizated blood vessels, LVEF and death. Older patients were less prone to have family history of ACS, less prone to be smokers and ex-smokers and more prone to have

had a previous event; had a higher prevalence of hypertension, DM and anemia and a lower prevalence of alcoholism; had a lower hemoglobin class, a lower LDL class, a lower LVEF class and a higher number of obstructed blood vessels and revascularizated blood vessels; were less prone to have had a PTCA and more prone to death.

There was a statistically significant association between anemia and hospitalization motive family history of ACS, previous event, hypertension, DM, being a smoker, LDL class, number of obstructed blood vessels, PTCA, number of revascularizated blood vessels, LVEF class and death. Anemic patients were more prone to have been hospitalized due to STEMI, more prone to have had a previous event, less prone to have a family history of ACS and less prone to be smokers; had a higher prevalence of hypertension and DM; had a lower LDL a lower LVEF class and a higher number of obstructed blood vessels and revascularizated blood vessels; were less prone to have had a PTCA and more prone to death.

There was a statistically significant association between PTCA and hospitalization motive, previous event, hypertension, being a smoker and number of obstructed blood vessels. Patients that underwent PTCA were more prone to have been hospitalized due to STEMI, more prone to be smokers and less prone to have had a previous event; had a lower prevalence of HTA and a higher number of obstructed blood vessels.

There was a statistically significant association between death and hospitalization motive, family history of ACS, previous event, dyslipidemia, BMI, DM, being a smoker, being an ex-smoker, hemoglobin class, LDL class, number of obstructed blood vessels, number of revascularizated blood vessels and LVEF class. Patients that died were less prone to have been hospitalized due to UA, less prone to have a family history of ACS and less prone to be smokers or ex-smokers and were more prone to have had a previous event; had a lower prevalence of dyslipidemia and a higher prevalence of DM; had a lower BMI, a lower hemoglobin class, a lower LDL class, a lower LVEF class and a higher number of obstructed blood vessels and revascularizated blood vessels. Patients that died due to cardiac reasons were older, more prone to be female and less prone to be smokers; had a lower prevalence of dyslipidemia and DM and a higher prevalence of anemia; had a lower hemoglobin class, a lower LDL class and a lower LVEF class.

There was a statistically significant association between LVEF and hospitalization motive and previous event. Patients with a lower LVEF class were more prone ho have been hospitalized due to STEMI and more prone to have had a previous event.

Table 11 – Assessment of the association between various clinical characteristics

	N(%)		Pearson's X^2 test		Fisher's exact test
			X^2	P value	
	No Posterior Event	**Posterior Event**			
>55 years of age	647 (80,1%)	151 (87,8%)	5,584	0,018	
Female gender	226 (28,0%)	66 (38,8%)	7,335	0,007	
Previous Event	175 (21,7%)	77(48,8%)	39,646	0,000	
Hypertension	544 (67,7%)	137 (79,5%)	10,160	0,001	
Dyslipidemia	448 (55,4%)	117 (68,0%)	9,189	0.002	
BMI > 30	129 (16,0%)	44 (25,6%)	9,021	0,003	
Ex-Smoker	85(10,5%)	8 (4,7%)	5,686	0,017	
Hemoglobin < 10g/L	22 (2,8%)	8 (5,3%)	12,581	0,002	
Anemia	169 (21,9%)	53 (34,9%)	11,779	0,001	
LVEF <35%	43 (9,6%)	19 (24,7%)	26,747	0,000	
Death	149 (18,4%)	56 (32,6%)	17,086	0,000	
	No Posterior ACS	**Posterior ACS**			
Previous event	200 (23,2%)	52 (44,1%)	23,657	0,000	
Dyslipidemia	481 (55,8%)	84 (71,2%)	10,064	0,002	
BMI > 30	140 (16,2%)	33 (28.0%)	9,815	0,002	
Anemia	185 (22,6%)	37 (34,9%)	7,806	0,005	
Glucose < 100 mg/dL	135 (15,2%)	30 (28,0%)	11,154	0,004	
LVEF <35%	55 (11,5%)	7 (15,2%)	15,211	0,000	
	No Posterior Stroke	**Posterior Stroke**			
>55 years of age	779 (81,1)	19 (100%)			0,034
Female gender	282 (29,3%)	10 (52,6%)	4,830	0,028	
Previous event	242 (25,2%)	10 (52,6%)			0,014
Hypertension	663 (69,0%)	18 (94,7%)	5,825	0,016	
Hemoglobin > 12 g/L	750 (82,4%)	7 (46,7%)			0,003
Death	195 (20,3%)	10 (52,6%)			0,002

Note: Pearson's X^2 test was used in the assessment of associations between various variables. When, in Pearson's X^2 test, there were more than 20% of cells with an expected count of less than 5, Fisher's exact test was used. Results were considered statically significant when $p < 0,005$. ACS: acute coronary syndrome; BMI: body mass index; LVEF: left ventricular ejection fraction;

(continued)

Table 11 – Assessment of association between various clinical characteristics (continued)

	N (%)		Pearson's X^2 test		Fisher's exact test
			X^2	P value	
	Male	**Female**			
< 55 years of age	158 (23,0%)	24 (8,2%)	29,476	0,000	
Hypertension	462 (67,2%)	219 (75%)	5,956	0,015	
Smoker	121 (17,6%)	16 (5,5%)	24,991	0,000	
Ex-smoker	90 (13,1%)	3 (1,0%)	34,678	0,000	
Alcoholism	24 (3,5%)	3 (1,0%)	4,634	0,031	
Hemoglobin > 12 g/dL	574 (87,8%)	183 (67,5%)	52,824	0,000	
Anemia	140 (21,4%)	82 (30,3%)	8,230	0,004	
3 obstructed blood Vessels	88 (15,9%)	22 (11,8%)	7,913	0,048	
Death	131 (19,0%)	74 (25,3%)	4,921	0,027	
	< 55 years of age	**> 55 years of age**			
Family history of ACS	17 (9,3%)	24 (3,0%)	14,828	0,000	
Previous event	30 (17,6%)	220 (27,6%)	7,737	0,005	
Hypertension	100 (54,9%)	581 (72,8%)	22,302	0,000	
DM	45 (24,7%)	263 (33,0%)	4,660	0,031	
Smoker	82 (45,1%)	55 (6,9%)	179,486	0,000	
Ex-smoker	27 (14,8%)	66 (8,3%)	7,435	0,006	
Alcoholism	12 (6,6%)	15 (1,9%)	12,290	0,000	
Hemoglobin < 10 g/dL	1 (0,6%)	29 (3,9%)	37,261	0,000	
Anemia	12 (6,8%)	210 (2,8,1%)	35,585	0,000	
LDL > 70 mg/dL	155 (93,9%)	556 (88,0%)	4,836	0,028	
3 obstructed blood vessels	15 (9,3%)	95 (16,4%)	18,275	0,000	
PTCA	106 (66,3%)	335 (57,1%)	4,381	0,036	
3 revascularizated blood vessels	1 (0,8%)	9 (1,9%)	8,397	0,038	
LVEF < 35%	5 (4,8%)	57 (13,6%)	6,277	0,043	
Death	4 (2,2%)	201 (25,2%)	47,351	0,000	

Note. Pearson's X^2 test was used in the assessment of associations between various variables. When, in Pearson's X^2 test, there were more than 20% of cells with an expected count of less than 5, Fisher's exact test was used. Results were considered statically significant when p < 0,005. ACS: acute coronary syndrome; DM: diabetes mellitus; LDL: low density lipoprotein; LVEF: left ventricular ejection fraction; PTCA: percutaneous transluminal coronary angioplasty

(continued)

Table 11 – Assessment of association between various clinical characteristics (continued)

	N (%)		Pearson's X^2 test		Fisher's exact test
			X^2	P value	
	No Anemia	**Anemia**			
Family history of ACS	37 (5,7%)	4 (1,8%)	4,772	0,029	
Previous event	151 (21,5%)	79 (35,6%)	17,970	0,000	
Hypertension	462 (65,7%)	175 (78,8%)	13,526	0,000	
Hospitalization due to NSTEMI	397 (56,7%)	149 (67,1%)	7,959	0,019	
DM	190 (27,0%)	94 (42,3%)	18,601	0,000	
Smoker	124 (17,2%)	14 (6,3%)	16,099	0,000	
LDL > 70 mg/dL	576 (92,3%)	134 (78,4%)	27,335	0,000	
3 obstructed blood vessels	80 (14,1%)	25 (18,1%)	11,681	0,009	
PTCA	356 (62,2%)	71 (50,7%)	6,222	0,013	
3 revascularizated blood vessels	2 (0,4%)	8 (7,7%)	36,965	0,000	
LVEF < 35%	35 (8,7%)	25 (22,7%)	17,060	0,000	
Death	86 (12,2%)	94 (42,3%)	97,592	0,000	
	No PTCA	**PTCA**			
Hospitalization due to STEMI	63 (20,6%)	197 (44,7%)	47,213	0,000	
Previous event	90 (29,4%)	94 (21,3%)	6,379	0,012	
Hypertension	236 (77,1%)	290 (65,8%)	11,200	0,001	
Smoker	33 (10,8%)	87 (19,7%)	10,717	0,001	
2 obstructed blood vessels	54 (18,5%)	119 (27,0%)	256,982	0,000	
	Did not die	**Died**			
Hospitalization due to NSTEMI	446 (57,5%)	133 (64,9%)	9,578	0,008	
Family history of ACS	40 (5,2%)	1 (0,5%)	8,833	0,003	
Previous event	180 (23,2%)	72 (35,1%)	12,011	0,001	
Dyslipidemia	466 (60,1%)	99 (48,3%)	9,303	0,002	
BMI < 30	148 (19,1%)	25 (12,2%)	5,312	0,021	
DM	226 (29,2%)	82 (40,0%)	8,837	0,003	
Smoker	127 (16,4%)	10 (4,9%)	17,857	0,000	
Ex-smoker	83 (10,7%)	10 (4,9%)	6,419	0,011	
Hemoglobin < 10 g/dL	14 (1,9%)	16 (8,9%)	100,447	0,000	
LDL > 70	618 (91,6%)	93 (76,2%)	25,212	0,000	
3 obstructed blood vessels	93 (14,4%)	17 (17,5%)	14,763	0,002	
3 revascularizated blood vessels	8 (1,5%)	2 (2,4%)	13,740	0,003	
LVEF < 35%	32 (7,1%)	30 (40,5%)	72,337	0,000	

Note. Pearson's X^2 test was used in the assessment of associations between various variables. When, in Pearson's X^2 test, there were more than 20% of cells with an expected count of less than 5, Fisher's exact test was used. Results were considered statically significant when p < 0,005. BMI: body mass index; DM: diabetes mellitus; LDL: low density lipoprotein; LVEF: left ventricular ejection fraction; NSTEMI: non–ST-segment elevation acute myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; STEMI: ST segment elevation myocardial infarction; UA: unstable angin

(continued)

Table 11 – Assessment of association between various clinical characteristics (continued)

	N (%)		Pearson's X^2 test		Fisher's exact test
			X^2	P value	
	Without cardiac death	**Cardiac Death**			
>55 years of age	735 (80,2%)	64 (98,4%)	13,99	0,000	
Female Gender	265 (27,8%)	137 (42,2%)	5,026	0,025	
Hypertension	645 (70,4%)	36 (56,3%)	5,661	0,017	
Dyslipidemia	538 (58,7%)	27 (42,2%)	6,708	0,012	
Smoker	134 (14,6%)	*3* (4,7%)	4,916	0,027	
Hemoglobin < 10 g/dL	24 (2,8%)	16 (10%)	28,582	0,000	
Anemia	446 (57,5%)	137 (64,9%)	23,779	0,000	
LVEF < 35%	52 (10,3%)	10 (52,8%)	37,254	0,000	
	LVEF < 35%	**LVEF > 50%**			
Hospitalization due to STEMI	40 (64,5%)	196 (55,5%)	20,240	0,000	
Previous event	21 (33,9%)	10 (%)	6,484	0,039	

Note. Pearson's X^2 test was used in the assessment of associations between various variables. When, in Pearson's X^2 test, there were more than 20% of cells with an expected count of less than 5, Fisher's exact test was used. Results were considered statically significant when p < 0,005. LVEF: left ventricular ejection fraction; STEMI: ST-segment elevation myocardial infarction

The Kaplan-Meier estimate allowed the assessment of significant differences in survival distribution in function of gender, age, hemoglobin class, presence of anemia, LVEF class, motive of hospitalization, presence of a family history of ACS, presence of a previous event, type of previous event, presence of hypertension, presence of dyslipidemia, presence of DM, BMI, being a smoker, being an ex-smoker, presence of alcoholism, LDL class, glucose class and PTCA, as reported in the survival-curves in the figures 16-26.

There was a statistically significant difference in survival distribution in function of age, gender, presence or absence of a previous event, type of previous event, presence or absence of hypertension, presence or absence of dyslipidemia, BMI, being an ex-smoker, hemoglobin class, presence of anemia and LVEF class.

Younger age, male gender, absence of a previous event, absence of hypertension, absence of dyslipidemia, lower BMI class, being an ex-smoker, higher hemoglobin class, absence of anemia and a lower LVEF class are statistically associated with a higher probability of absence of a posterior event.

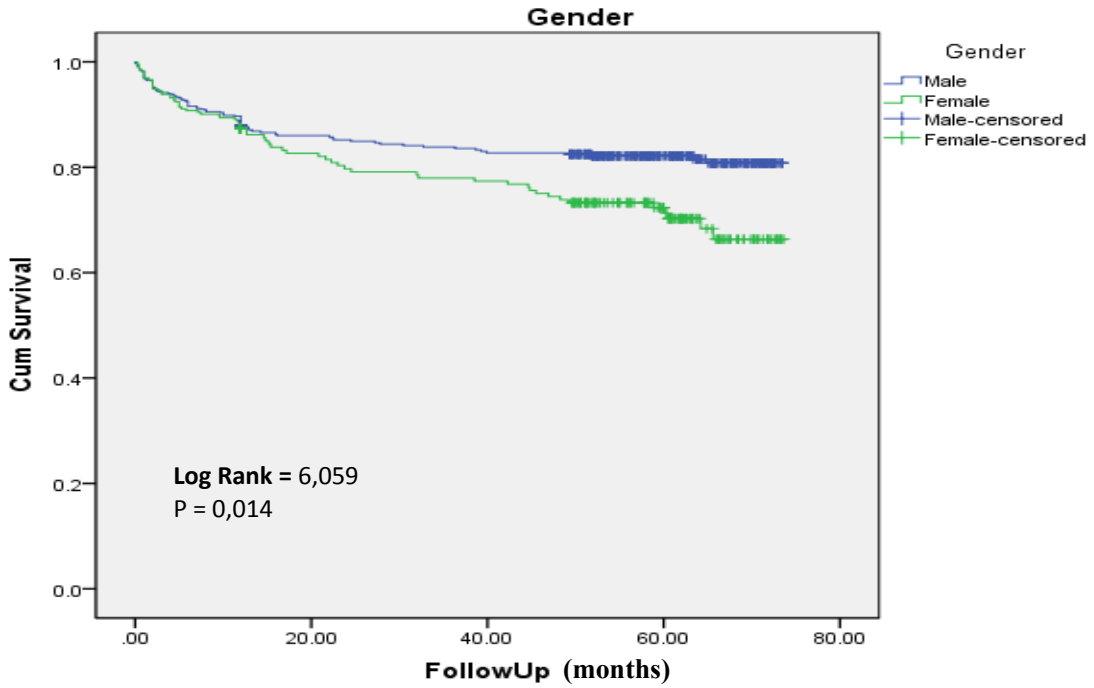

Figure 16 - Curves of the probability of absence of a posterior event in male and female patients

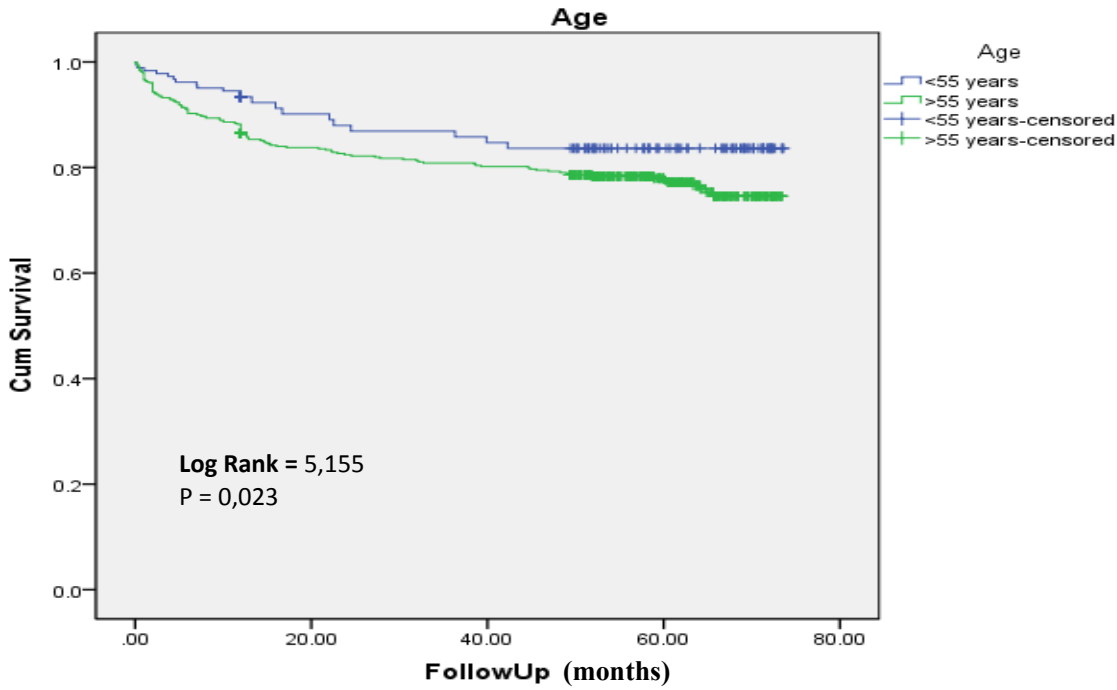

Figure 17 – Curves of the probability of absence of a posterior event in patients younger than 55 years of age and in patients older than 55 years of age

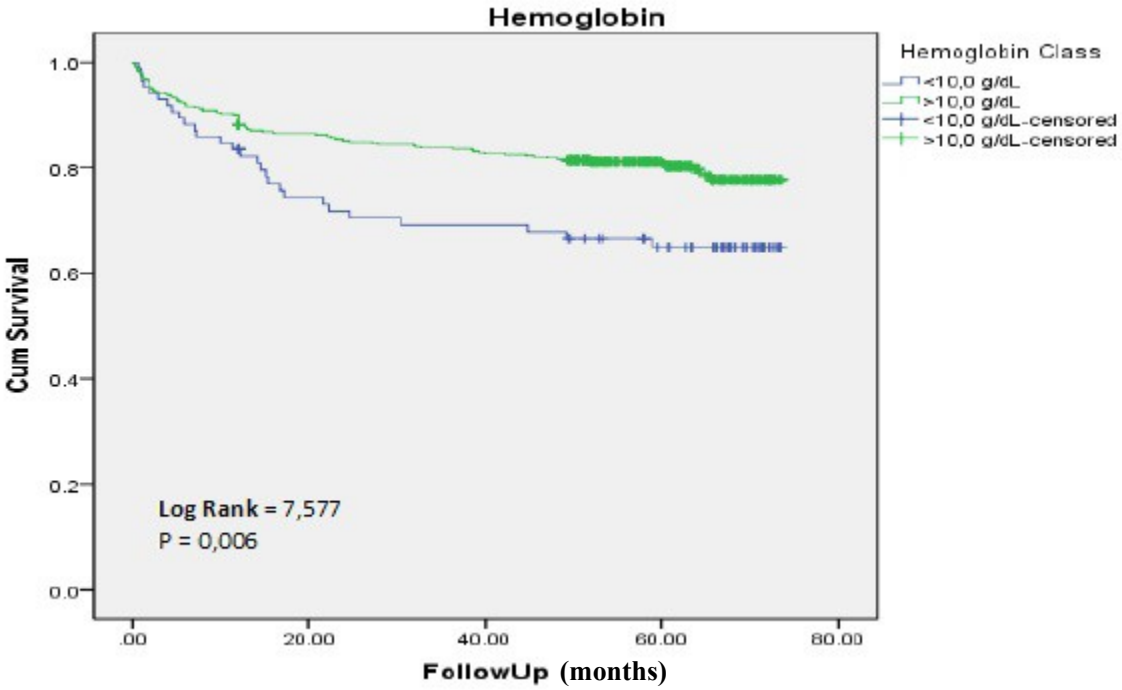

Figure 18 – Curves of the probability of absence of a posterior event according to the patient's hemoglobin class

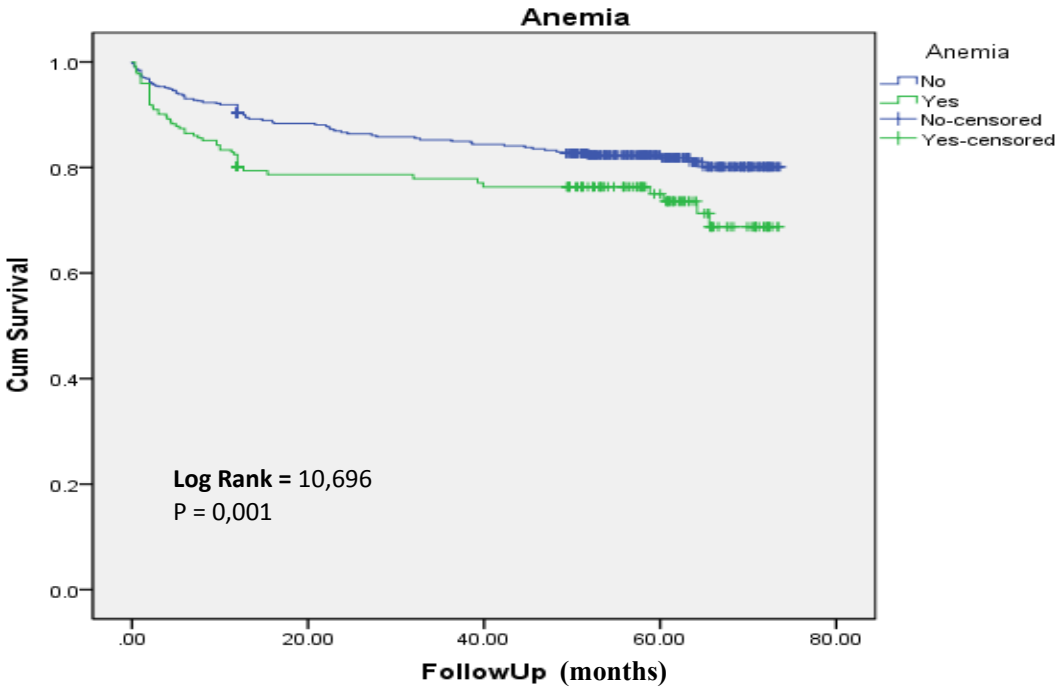

Figure 19 – Curves of the probability of absence of a posterior event in patients with and without anemia

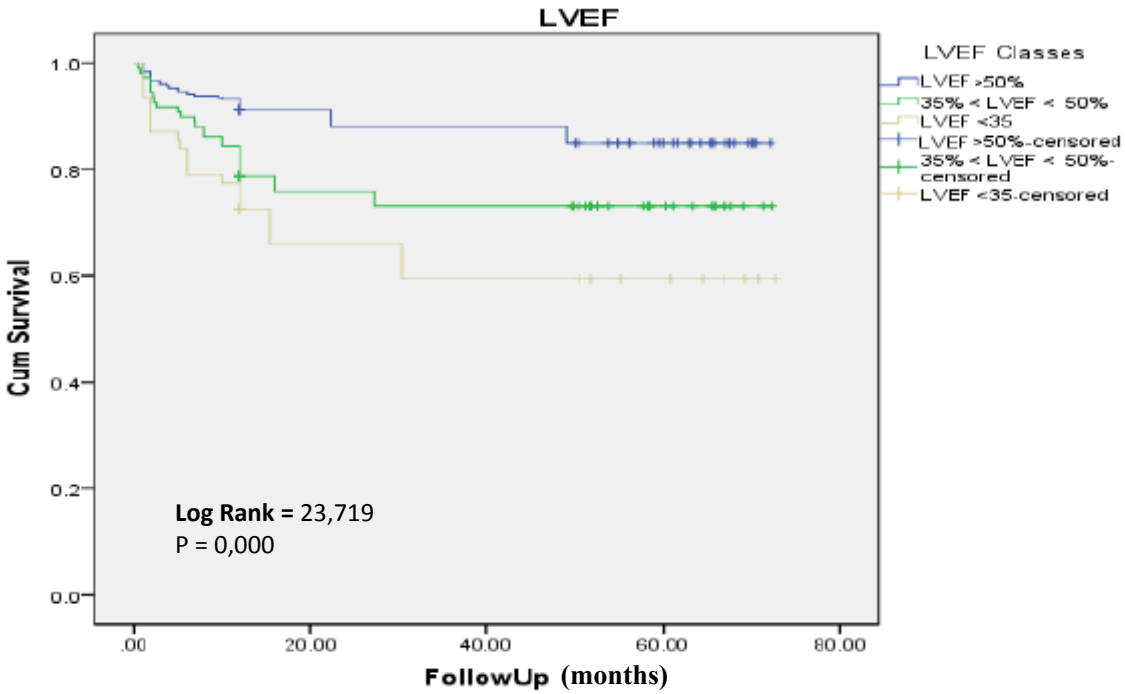

Figure 20 – Curves of the probability of absence of a posterior according to the patient's LVEF class

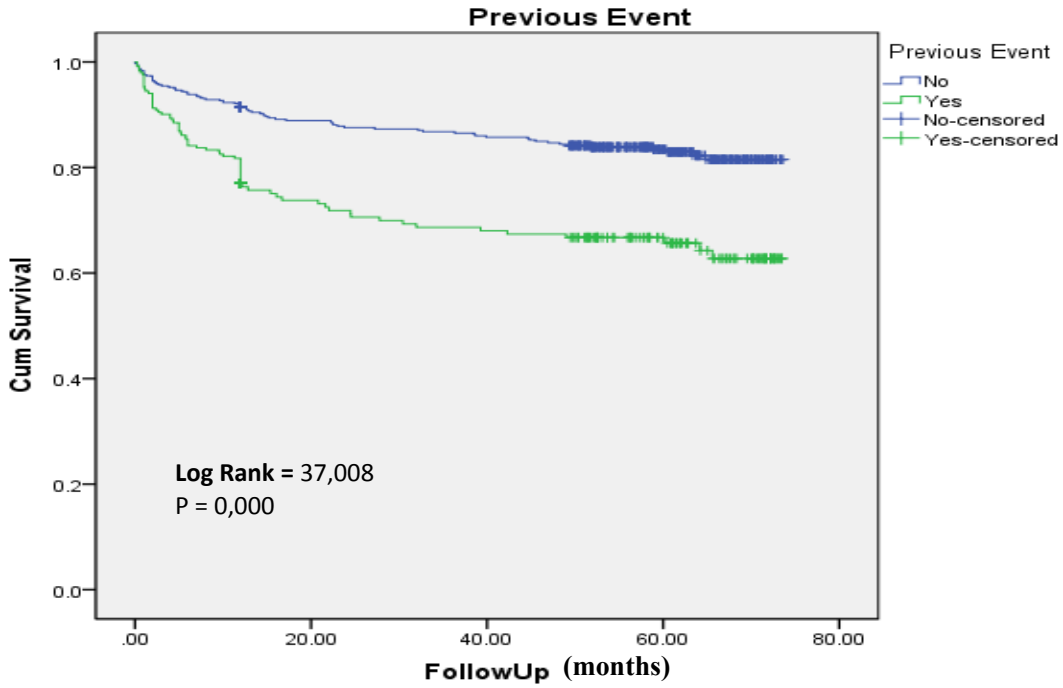

Figure 21 – Curves of the probability of absence of a posterior event in patients that suffered and did not suffer a previous event

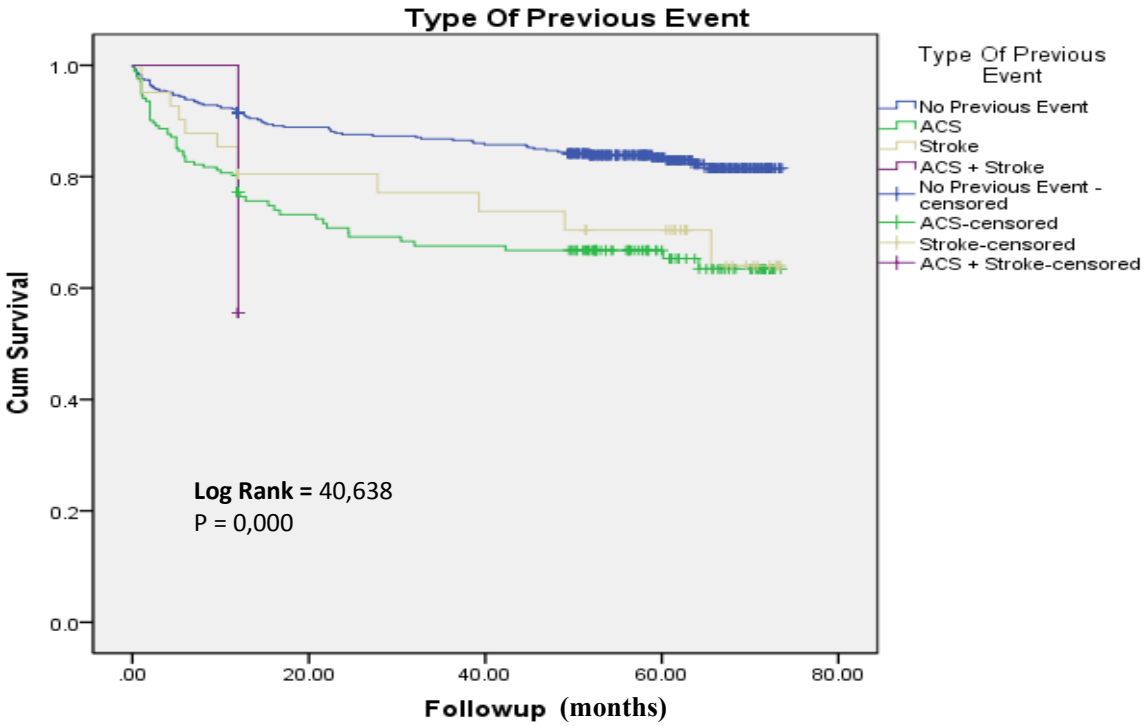

Figure 22 – Curves of the probability of absence of a posterior event according to the type of previous event

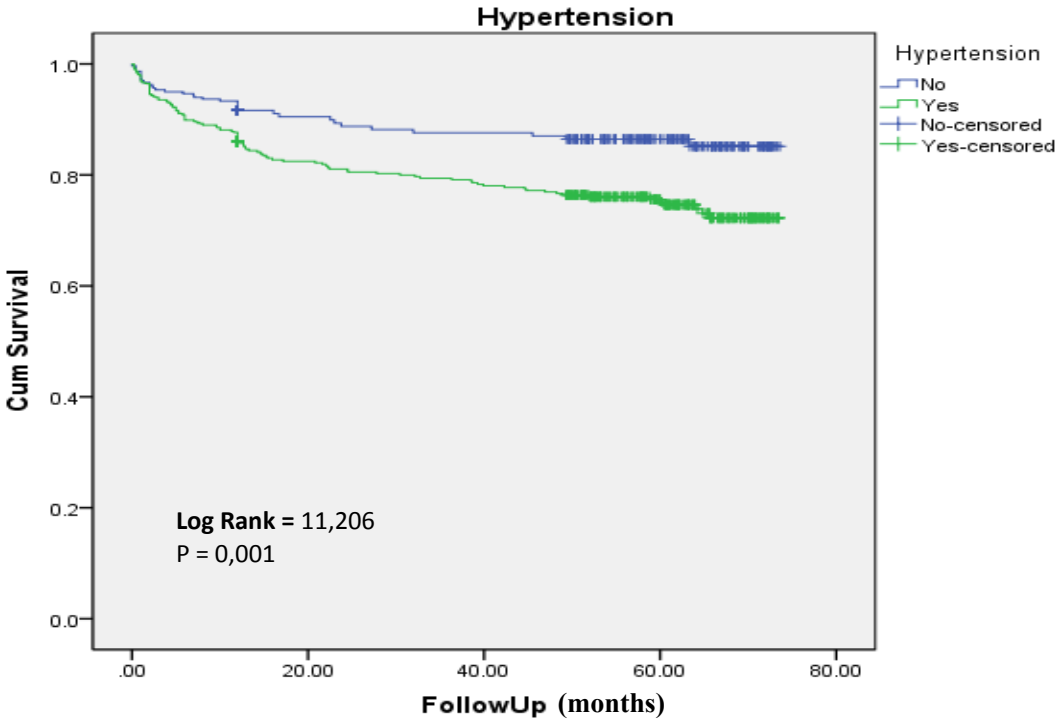

Figure 23 – Curves of the probability of absence of a posterior event in patients with and without hypertension

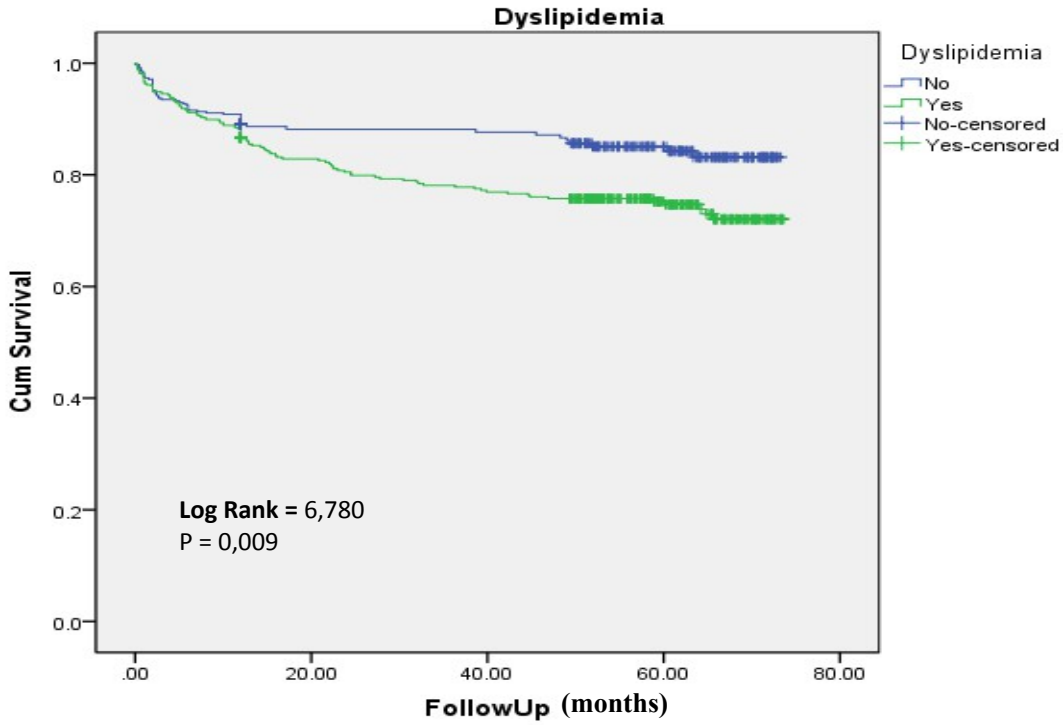

Figure 24 – Curves of the probability of absence of a posterior event in patients with and without dyslipidemia

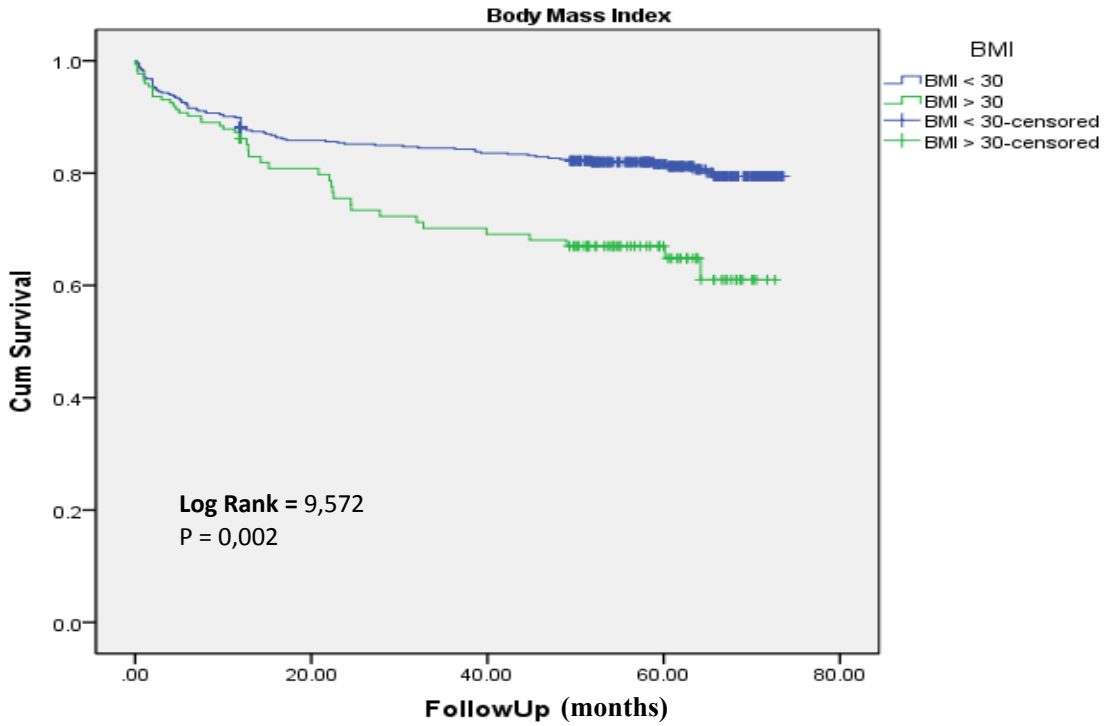

Figure 25 – Curves of the probability of absence of a posterior event in patients with and without a BMI greater than 30

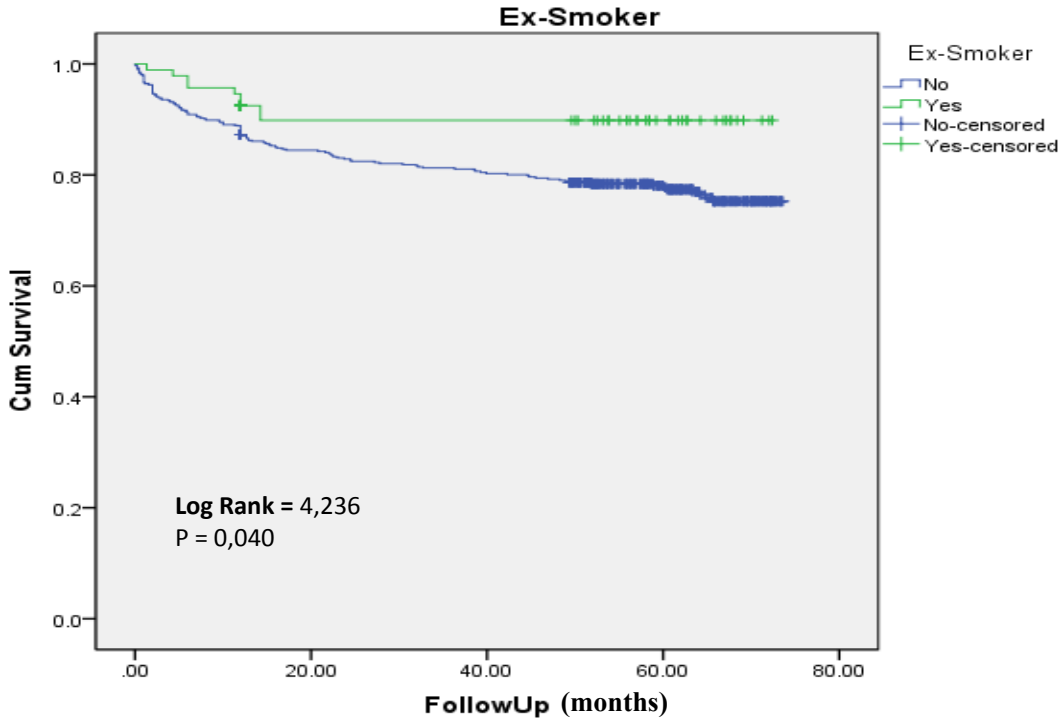

Figure 26 – Curves of the probability of absence of a posterior event in patients that are and aren't ex-smokers

The Cox proportional hazards model was used in the evaluation of the relative risk associated with age, hemoglobin, glucose, initial troponin, maximum troponin, Pro-BNP, total cholesterol, LDL and CRP.

Without adjustment for other variables, older age, lower hemoglobin levels and higher Pro-BNP levels are associated with an increased risk of occurrence a posterior event.

With the adjustment for gender, previous event, DM, BMI and number of risk factors, older age was associated with an increased risk of occurrence of a posterior event. With the adjustment for age, gender, previous event, DM, BMI and number of risk factors, higher Pro-BNP levels are associated with an increased risk of occurrence a posterior event. These results are summarized in table 12.

TABLE 12 – Adjusted and unadjusted relative hazard ratios (95% CI) for the occurrence of a posterior event according to age, hemoglobin and pro-BNP concentrations

	Variable	Hazard Ratio	p Value
Model 1	Age	1,023 (1,010 – 1,036)	0,000
	Hemoglobin	0,876 (0,807 – 0,949)	0,001
	Pro-BNP	1,000 (1,000 – 1,000)	0,038
Model 2	Age	1,026 (1,012 – 1,041)	0,000
Model 3	Pro-BNP	1,000 (1,000 – 1,000)	0,019

Note: Model 1: Without adjustment; Model 2: After adjustment for gender, presence of previous event, DM,BMI and number of risk factors; Model 3: After adjustment for age, gender, presence of previous event, DM,BMI and number of risk factors. Pro-BNP: pro-brain natriuretic peptide

4 – DISCUSSION

4.1 – Gender

The risk of CVD in women is often underestimated due to the perception that females are protected against ACS. However, CVD is the leading cause of death in both man and women, with data from WHO indicating that, in Europe, it is responsible for 43% of all deaths in men and 55% of all deaths in women. Various studies also indicate that female gender in associated with a worse outcome in the event of an ACS, despite the fact that females are less likely to have significant coronary narrowing and relatively more often have preserved left ventricular function, what constitutes a "gender-paradox". [139], [140]

Our results indicate that men with ACS are significantly younger than women and that the proportion of female patients with ACS seems to rise with age. This corroborates the notion that women in fertile age have a lower risk of cardiac events that increases with menopause. The repercussion of coronary risk factors in women, especially during menopause, is different than in male, due to specific hormonal effects during menopausal period. Menopause is associated with a decline in the levels of estrogen, that result in a decrease in the activity of LDL receptors and, therefore, in an increase in LDL concentration that, associated with a decrease in HDL levels, may explain the increase in coronary risk in postmenopausal women. This is corroborated by the fact that total cholesterol levels in women normally reach a peak between 55 and 65 years of age, about a decade later than in men. [49], [140]

In our study, men presented significantly higher hemoglobin concentrations, while women presented a higher prevalence of anemia, which may play a role in the worse prognosis verified in women, as anemia is a known indicator of an adverse outcome in ACS, leading to to a greater reduction in oxygen flow to the miocardium.

It is also important to notice that women presented statistically significant higher concentrations of Pro-BNP, what may be an indicator of a greater infarct size and cardiac dysfunction in women, although various studies have showed that the levels of Pro-BNP

are gender dependent, with higher levels in women being independent of other baseline variables such as blood pressure or renal function. [141]

In women there is normally a higher prevalence of risk factors and co-morbidities, what may also contribute to a worse outcome. That was also verified with our results, as women presented a higher prevalence of hypertension and anemia. It is, however, interesting to notice that our study found no significant differences between men and women in the prevalence of obesity, dyslipidemia and DM, in spite of the higher prevalence in women reported by various studies. Men presented a greater prevalence of smoking and alcoholism, possibly due to socio-cultural factors.

There was also higher incidence of death and posterior events in women and survival curves revealed a significantly higher probability of the occurrence of a posterior event in the case of women, what indicates that women have a worse prognosis after ACS. This may be explained by a worse clinical profile as, at presentation, women are older and have more co-morbidities such as hypertension, DM, dyslipidemia and anemia. Also, there is a higher incidence of silent ischaemia or atypical symptoms in women, possibly due to older age and more co-morbidities, what may cause an increase in treatment-seeking delay and result in a greater infarct size in the case of an acute myocardial infarction and more serious consequences, what could explain the greater Pro-BNP concentrations found in women. Finally, studies indicate that in women there is normally a less invasive diagnostic approach and that women with ACS generally receive less aggressive treatment and are less likely to undergo coronary angiography or have revascularization what may also explain contribute to their worse prognosis. [139], [141], [142] It is, however, interesting to notice that our study found no significant gender bias in utilization of invasive revascularization procedures or in the number of revascularizated blood vessels.

4.2 – Age

Age is a very important determinant in the outcome of ACS, taken into account in various risk assessment scores. Older age is not only an important risk factor for ACS but has also a very important association with a poorer prognosis, what was also verified in our study, where older age was significantly associated with a higher incidence of death and posterior events and where survival curves also revealed a significantly higher probability of the occurrence of a posterior event in the case of older patients. Various factors are associated with this worse outcome in older patients.

An accurate recognition of ACS on initial presentation is a key for the minimization of morbidity and mortality. Older patients frequently have a more atypical clinical presentation, a higher incidence of silent ischaemia and their initial ECGs are less likely diagnostic of ACS what may result in an increase in treatment-seeking delay in an uncertainty about the initial diagnosis, potentially hindering timely ACS therapies, what may lead to a greater infarct size in the case of an acute myocardial infarction.[143] This could explain the higher concentrations of initial troponin and Pro-BNP that we found in older patients. This is corroborated by the findings of *Boersma et al.* [144], as they found a more pronounced association between older age and mortality in patients with acute myocardial infarction rather than in those with UA, what suggests that the relation between age and outcome is associated with the presence and extent of myocardial necrosis at admission.

Older patients also presented a higher prevalence of cor-morbilities and risk factors, such as hypertension, DM and anemia, and had higher concentrations of LDL and total cholesterol what may also contribute to a worse outcome. The exceptions were the lower prevalence in older patients of smoking and alcoholism.

Furthermore, older patients presented a lower LVEF, what indicates that they have a less preserved left ventricular systolic function, possibly due to greater infarction sizes and due to the greater prevalence of previous events that may have result in an already impaired LVEF, what further contributes to a poor prognosis.

It is also important to notice that older patients normally have a greater frequency of physiological and cognitive impairment or disability and, as previously mentioned, present a greater number of co-morbidities which enhance their age-related risk. Elderly patients may also present varied drug metabolism and a greater prevalence of renal impairment and decreasing lean body weight what may difficult the correct dosing of medication. All these factors may increase the tendency to a more conservative option of treatment, in spite of these being higher risk ACS patients, what may also contribute to a worse outcome. [143] Elderly patients have been shown to receive less aggressive anti-ischaemic therapy and to be less likely to undergo coronary angiography and revascularization procedures. This was also verified in our study where, in spite of having a greater number of obstructed blood vessels, older patients were significantly less likely to undergo PTCA. The elderly patients that did undergo PTCA presented a greater number of revascularizated blood vessels than younger patients.

Finally, it is very interesting to notice there was a higher prevalence of family history of ACS in younger patients, what seems to indicate that, in fact, genetic factors may have an important role in the pathogenesis of ACS and, therefore, certain genetic characteristics may make individuals more prone to ACS, leading to an earlier onset of the disease. The determination of these genetic factors is, therefore, very important, in order to allow an earlier determination of families at a higher risk and an earlier clinical intervention in order to modify risk factors and prevent the development of the disease.

4.3 – Anemia

Anemia is known to be a strong indicator of a higher probability of an adverse outcome in patients with ACS what is corroborated by our findings as there was a significant association between anemia and death or occurrence of a posterior event. We also found significant lower concentrations of hemoglobin in patients that died or had any kind of posterior event when compared to those who didn't. Also the survival curves and hazard ratios obtained confirmed that lower hemoglobin concentrations and anemia are associated with a higher probability of occurrence of a posterior event.

Anemia causes a decrease blood oxygen levels, what may be arrhythmogenic, directly exacerbate myocardial ischaemia or activate the sympathetic nervous system and result in hypoperfusion. On one side, a reduction in hemoglobin levels means that blood will have a lower capacity of oxygen delivery, what will decrease even further the oxygen supply to the myocardium. On the other side, if tissue oxygen needs are not met, heart rate will rise in order to increase cardiac output, what may increase myocardial oxigen neads and potentially worsen the myocardial oxygen supply-demand mismatch. [145]

The meta-analisys by *Liu et al* [146] demonstrated a higher risk of major bleeding in anemic patients, that may also contribute to their poorer outcome. Bleeding is one of the most common complications of ACS, and may result in hypotension and in a hyperadrenergic state that may contribute to myocardial ischaemia by further decreasing myocardial oxygen supply. [147]

Anemic patients are also more prone to have more associated co-morbidities and high risk features, as observed in our results, where anemic patients were older, had a higher prevalence of hypertension and DM and were more prone to have had a previous event, what may also contribute to a worse outcome. The exceptions were their lower tendency to have a family history of ACS and to be smokers.

We also found a significantly higher concentration of initial troponin, Pro-BNP and CRP in anemic patients, what may indicate a more severe ischaemic disease and a greater delay in treatment-seeking, possibly due to, as previously mentioned, a higher prevalence of

atypical symptoms or silent ischaemia. The higher concentration of CRP in anemic patients is particularly interesting, as it constitutes an indicator of a more marked systemic inflammation. This may be significant, as cytokines are known to inhibit erythropoietin production, thus reducing reduced red blood cell production. [113]

The idea that anemic patients may have a more severe ischaemic disease and a greater delay in treatment-seeking is also suported by the fact that these patients presented a significantly lower LVEF class, what may indicate a greater ischaemic lesion. Another factor that may contribute to this lower LVEF class is the greater incidence of previous events, that may have already impaired LVEF, found in this patients.

The meta-analisys by *Liu Y. et al.* [146] also found that differences in therapeutic options may also have a role in the worse prognosis of patients with anaemia. In the case of anemic patients, doctors often prefer a more conservative approach of treatment, possibly due to a higher prevalence of contraindications to revascularization procedures and to their higher risk of bleeding. Therefore, anemic patients are less likely to be treated with aspirin and β-blockers and less likely to receive reperfusion therapy, that are known to increase long-term survival and decrease the chances of ischaemic complications. This was also comproved by our findings, where anemic patients, in spite of having a greater number of obstructed blood vessels, were significantly less likely to undergo PTCA. The anemic patients that did undergo PTCA presented, however, a greater number of revascularizated blood vessels than non-anemic patients.

As we have seen, anemia is associated with older age and with a higher prevalence of co-morbidities and cardiovascular risk factors, what may contribute to the poorer prognosis of anemic patients. However the adjusted hazard ratio for hemoglobin concentrations showed that the increased risk of lower hemoglobin concentrations persisted after adjustment for potential confounders, what indicates that an independent association between anemia and mortality in patients with ACS.

4.4 – PTCA

In spite of being associated with a higher risk of complications, especially bleeding, PTCA is known to improve the outcome in patients with ACS, with various trials suggesting that an invasive strategy of treatment normally leads to better outcomes than a conservative strategy. [148] This improvement provided by PTCA in the outcome of patients with ACS was not, however, verified in our study, as we found no significant effect of PTCA in death or in the probability of occurrence of a posterior event. A possible explanation for this may be the fact that we did not take into account the concomitant pharmacological therapy and the amount of time that passed until PTCA, what may also influence patient's outcome, as current guidelines for the treatment of ACS recommend rapid PCI under the protection of a platelet GP IIb/IIIa receptor antagonist. [148]

A study by *Berger et al.* [149] found that 30 day mortality was significantly lower in patients that reveaved PTCA within 60 minutes and progressively higher in patients with a greater delay. That study found that the time from enrollment to first balloon inflation was a significant predictor of 30 day mortality even after adjustment for age, systolic blood pressure, baseline Killip class, smoking status, and diagnosis or treatment of cancer in the last 5 years, with each time interval was associated with a 1.6 times (95% CI, 1.13 to 2.26;P =0.008) greater risk of death than the interval preceding it.

Our results indicate that patients that underwent PTCA were younger, presented higher hemoglobin concentrations and a lower prevalence of HTA and previous events, what corroborates the fact that patients that are older, anemic or have a higher prevalence of co-morbidities and cardiovascular risk factors tend to receive a more conservative treatment and are less prone to undergo PTCA, probably to their higher risk of bleeding.

We also found that patients that were hospitalized due to STEMI were significantly more prone to receive PTCA than the patients that were hospitalized due to NSTEMI or UA, what may constitute an indicator that STEMI is, in fact, associated with a higher degree of blood vessel obstruction and, therefore, with a greater need for PTCA. This corroborate the notion that UA and NSTEMI normally result from a partially occluded artery and STMI from a fully occluded artery.

Finally, patients that did undergo PTCA had a significantly higher number of obstructed blood vessels, what may indicate that, in patients with a higher number of obstructed blood vessels, the improvement in the outcome provided by PTCA supplants the risk of complications and, therefore, doctors more commonly submit these patients to this revascularization procedure.

4.5 – LVEF

Our results indicate that a lower class of LVEF is associated with a higher probability of death or occurrence of a posterior event. This is not surprising, as a lower LVEF is an indicator of a greater ischaemic lesion and a lower global contractile function, what is associated with higher risk of cardiac arrest and arrhythmic death.

The assumption that a lower LVEF class is an indicator of a greater ischaemic lesion is also supported by the differences found in the concentrations of Initial troponin, maximum troponin, Pro-BNP and CRP found between the different classes of LVEF.

Patients that had a lower LVEF class were older and more prone to anemia what may also have an influence in their worse prognosis. These patients also presented a greater incidence of previous events, what was also expected, as these previous events may have resulted in myocardial lesion and in an already impaired global contractile function.

4.6 – Hospitalization motive

Our results indicate that patients that were hospitalized due to UA were significantly less prone to death than the patients that were hospitalized due to STEMI or NSTEMI, what suggests that hospitalization motive has a significant impact in the probablitity of death. We did not, however, find a significant influence of hospitalization motive in the probability of occurrence of a posterior event.

There was also a significant difference between hospitalization motives in the concentrations of initial troponin, maximum troponin, and Pro-BNP, what was expected, as markers of myocardial necrosis and ischaemia are normally elevated in myocardial infarction but not in UA. A similar difference between hospitalization motives was also found in the levels of CRP, what may be explained by the finds of Irfan et al, that observed that patients with UA presented presented low-levels of CRP when compared with patients hospitalized due to STEMI or NSTEMI. This suggests that CRP, besides being a marker of inflammation, may also have an important role in plaque disruption leading to STEMI and NSTEMI.

Patients that were hospitalized due to UA also presented a higher LVEF class and were less less prone to anemia. The fact that that these patients presented a higher LVEF class is no surprise, as UA is not commonly associated with myocardial necrosis and, therefore presents a more preserved global contractile function. The lower prevalence of anemia in these patients may, in part, be explained by their lower levels of CRP, what indicates a lower degree of systemic inflammation, that may, as previously mentioned, be responsible for an impairment in red blood cell production.

4.7 – Risk factors

4.7.1 – Family history of ACS

Our study found no significant association between the presence of a family history of ACS and the probability of occurrence of a posterior event. Patients with a family history of ACS were, however, less prone to death, what may be explained by their younger age and by the lower prevalence of anemia in these patients.

These results indicate that, in spite of having an important role in the pathogenesis of ACS and in making individuals more prone to this disease leading, therefore, to an earlier onset, genetic factors do not seem to have an impact in the occurrence of a posterior event.

4.7.2 – Previous event

We found a significant association between the presence of a previous event and a worse outcome in patients with ACS, as these patients were more prone to death and had a higher probability of occurrence of a posterior event. Survival curves showed that the type of previous event was also determinant in the probability of occurrence of a posterior event, as patients that had a previous ACS presented a higher probability of occurrence of a posterior event than the patients that had a previous stroke.

The worse outcome verified in patients with a previous event is not unexpected, as this previous event may have already result in an important myocardial lesion. We verified that patients that had a previous event presented a lower LVEF class, what may indicate that the previous event sustained by these patients may have, in fact, resulted in significant myocardial ischaemia and, therefore, in an impairment of global contractile function. Our results also indicate that the presence of a previous event is associated with older age and a higher prevalence of anemia what may further contribute to a poorer outcome.

Finally, the findings by *Motivala et al*. [150] suggest that the presence of a previous myocardial infarction is associated with a higher prevalence of co-morbidities and cardiovascular risk factors, but not with worse in-hospital outcomes during the recurrent ACS episode, what indicates that clinical presentation has a greater effect in in-hospital outcomes than cardiovascular risk factors.

4.7.3 – Hypertension

Several studies indicate that hypertension is the most important risk factor for an earlier onset of stroke and is associated with an increased prevalence of adverse outcomes. This was also evidenced by our results as the survival curves obtained indicate that the presence of hypertension is associated with an increased probability of occurrence of a posterior event. There was not, however, an association between hypertension and death. [151], [152]

Patients with hypertension were older and more prone to be female, what may be associated with an increased prevalence of co-morbidities and cardiovascular risk factors what, in association with the higher prevalence of anemia in these patients, may also play a role in their higher probability of having a posterior event. Finally, hypertensive patients were less prone to receive PTCA, possibly due to a higher incidence of co-morbidies and cardiovascular risk factors, what may also influence their risk of having a posterior event.

4.7.4 – Dyslipidemia

Our study found a significant relationship between dyslipidemia and a poorer outcome, with a higher probability of death or occurrence of a posterior event, what may in part be explaned by the findings of *Kato et al*. [153], that reported a relationship between higher levels of LDL and lower levels of HDL and a higher prevalence of multiple complex coronary lesions in male ACS patients, what may lead to an increased incidence of posterior events.

4.7.5 – Body mass index

We found a significant relationship betweem a BMI greather than 30 and a poorer outcome, with a higher probability of death or occurrence of a posterior event. Various studies have, however, reported better prognosis in overweight patients in a so called “obesity paradox”. Other studies have reported a U-shaped relationship, with underweight and obese patients presenting worse outcomes than overweight patients. [154]

One possible explanation for this paradox Is that overweight patients are usually younger and treated more aggressively, what may possibly contributing to improved outcomes. Another hypothesis is that obese patients may present a larger coronary artery diameter. It is however, important to take into account that BMI does not allow the distinction between muscle and fat mass and, therefore, certain overweight patients may have more muscle mass. Certain researchers consider that this obesity paradox may disappear in the cases where BMI is very high and better reflects body adiposity, what would also explain why such paradox was not found in our trial, as we only differentiated obese and no obese patients, not distinguishing underweight normal weight and overweight patients. [154], [155]

4.7.6 – Diabetes mellitus

Our results indicate that there is no significant association between DM and the probability of occurrence of a posterior event. Patients with a family history of DM were, however, more prone to death, what comes as no surprise, as it is well known that DM is associated with an increase of 2-4 fold in the mortality rate. [152] Two important factors that may have contributed to this higher mortality rate in the case of patients with DM may be the older age and the lower prevalence of anemia in these patients.

A study by *AlNemer et al.* [156] also found a higher prevalence of cardiovascular risk factor and co-morbidities in diabetic patients, what may also contribute to their worse outcome.

4.7.7 – Smoking

In spite of being a very important cardiovascular risk factor, various studies have reported lower mortality rates after ACS in smokers, what may indicate a protective effect of smoking that would make smokers more prone to suffer ACS but also more likely to survive. [157]

Our trial presented similar results, with smokers and ex-smokers having a lower probability of death, and ex-smoker having a lower probability of occurrence of a posterior event. It is however important to take into account that smokers and ex-smokers were younger and more prone to be males, what suggests that they may present a lower prevalence of cardiovascular risk factors and co-morbidities. These patients also presented a lower prevalence of anemia and underwent PTCA more frequently, what may also have contributed to a more favorable outcome. These assumptions are supported by the findings of *Gaspar et al.* [157], that reported that patients with a history of tabagism were younger, more frequently men, presented a lower prevalence of DM, hypertension and renal insufficiency and were more often referred for PTCA.

4.8 – Biomarkers

4.8.1 – Troponin

Cardiac troponins are widely used in the diagnosis and risk stratification of patients with ACS.

In our trial we found significantly higher initial troponin concentrations in older patients and anemic patients. This supports the theory that a higher prevalence of co-morbidities in these patients may make them more prone to a more atypical presentation and increased treatment-seeking delay, what would explain the higher initial levels of troponin in these patients.

Patients that died also presented higher initial troponin concentrations, what suggests that this delay in treatment seeking is associated with poorer outcomes. There was not, however, a significant influence of troponin concentrations in the probability of occurrence of a posterior event.

It is particularly interesting to notice that we did not find a significant association between maximum troponin concentrations and death, what may be due to the fact that we did not stratify troponin concentrations in terciles, as in a study by *Knight et al.* [158] the upper tertile of cTnT (>1.1 mg/l) presented a significantly greater risk of death than that of all the other troponin groups ($p = 0,003$).

We also found that patients with higher maximum troponin concentrations were more prone to undergo PTCA, what may indicate that higher troponin concentrations are associated with a more severe blood vessel obstruction and, therefore, with a higher need for PTCA.

Finally, there were also significant differences in the maximum levels of troponin according to LVEF class, what may indicate that higher troponin concentrations are associated with a higher degree of myocardial necrosis and with a more compromised global contractile capacity.

4.8.2 – Pro-BNP

Higher concentrations of Pro-BNP presented a significant association with an increased probability of occurrence of a posterior event and the patients that died presented significantly higher concentrations of Pro-BNP when compared to the patients that did not die, what suggests that higher levels of Pro-BNP are associated with a worse outcome. This comes as no surprise, as higher levels of Pro-BNP are indicative of more severe myocardial injury and greater cardiac dysfunction, what Is proved by the differences found in Pro-BNP concentrations according to LVEF class.

It is important to notice that higher Pro-BNP concentrations were also found in older patients, women and patients with anemia, what suggest that the higher prevalence of cardiovascular risk factors and co-morbidities characteristic of these patients may contribute to a greater myocardial injury and cardiac dysfunction.

5 – CONCLUSION

ACS is one of the most common initial manifestations of CVD, having reached pandemic levels in developed countries. In the last couple of years there has been a reduction in the mortality rate due to ischaemic heart disease, specially in developed countries, but, nonetheless, this disease is still responsible for approximately one third of all deaths in persons older than 35 years of age.

This is a multifactorial disease, with a complex pathogenesis. However, in recent years, there has been an evolution in the understanding of the molecular mechanisms involved in ACS. This allowed the uncovering of various biomarkers that may be used in diagnosis and in the evaluation of the extent of the myocardial damage. Also, various features are know to be associated with an increased risk of development of ACS and with a worse outcome and are, thus, taken into account in various risk scores.

The evaluation of 980 patients with ACS hospitalized in CHBV allowed the confirmation that various factors are associated with an increased risk of a worse outcome in patients with ACS, such as older age, female gender, presence of anemia, low LVEF, hypertension, dyslipidemia, obesity and the presence of a previous event. High levels of specific biomarkers were also associated with a worse outcome, particularly in the case of Pro-BNP, what comes as no surprise, as they are indicative of greater areas of ischaemic lesion. It is also important to notice that various of these features also presented an association with other risk factors and co-morbidities, what may render the determination of their specific predictive value in ACS difficult.

Risk assessment is very useful in patients with ACS, as patients at higher risk may need a more aggressive approach of treatment and, therefore, risk scores should be used to help the physician in determining the better treatment option. Patients with a higher risk of worse outcome normally also have a greater risk of complications with the use of a more aggressive treatment and, therefore, a risk/benefit evaluation should always be done.

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