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CORSO DI LAUREA IN MEDICINA E CHIRURGIA

Tesi di Laurea

Coronary Plaque Healing in Patients with and without Diabetes: An Optical Coherence Tomography Study

Relatore

Chiar.mo Prof. Italo Porto

Correlatore

Prof. Rocco Vergallo

Candidata

Bianca Varaldo

Matricola

5005442

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1 INTRODUCTION

1.1 Coronary circulation

The heart is vascularized by the coronary circulation, which normally receives 5% of the cardiac output. The coronary circulation consists of the right and left coronary arteries, which with their ramifications run on the external surface of the heart, covered by the epicardium. The thinner branches then deepen into the thickness of the myocardium to form the capillary networks at the level of the interstitial connective tissue and reaching the subendocardial layer. In addition, coronary circulation takes place mainly during the diastolic phase of the cardiac cycle, since during systole it is prevented by the contraction of the cardiac muscles. The coronary arteries originate from the ascending aorta at the aortic sinuses, just above the aortic valve (1).

Another concept worth mentioning is that of dominance: we speak of right or left dominance based on the origin of the posterior interventricular artery. In the majority of cases (90%) there is a right dominance while, in 10% of cases, the posterior interventricular is supplied by the left coronary artery and so we speak of left dominance; only in 1% of cases is there a balanced circulation, consisting of two parallel branches (1).

The right coronary artery, after originating from the coronary sinus, runs in the coronary sulcus between the right auricle and the sterno-costal face of the right ventricle and reaches the crux cordis. Once at this level, in 90% of cases, it gives rise to the posterior interventricular artery; it then continues in the homonymous furrow until the apex of the heart. In the case of left dominance, on the other hand, the right coronary artery is finished before reaching the crux cordis. During its course, it also provides important branches including atrial branches, atrioventricular branches and the branch for the conus arteriosus (1).

The left coronary artery, on the other hand, after originating from the aortic sinus, heads obliquely downwards and to the left and once it reaches the coronary sulcus it divides into its two terminal branches: the anterior interventricular artery and the circumflex artery. The first continues its course in the anterior interventricular sulcus and provides the branches for the sternocostal face of the right and left ventricles and those for the interventricular septum; the circumflex branch, on the other hand, runs into the coronary sulcus, finishing itself before the crux cordis, except in cases of left dominance, in which it reaches the coronary sulcus

and generates the posterior ventricular artery. It also supplies atrial and ventricular branches such as the left marginal branch (1).

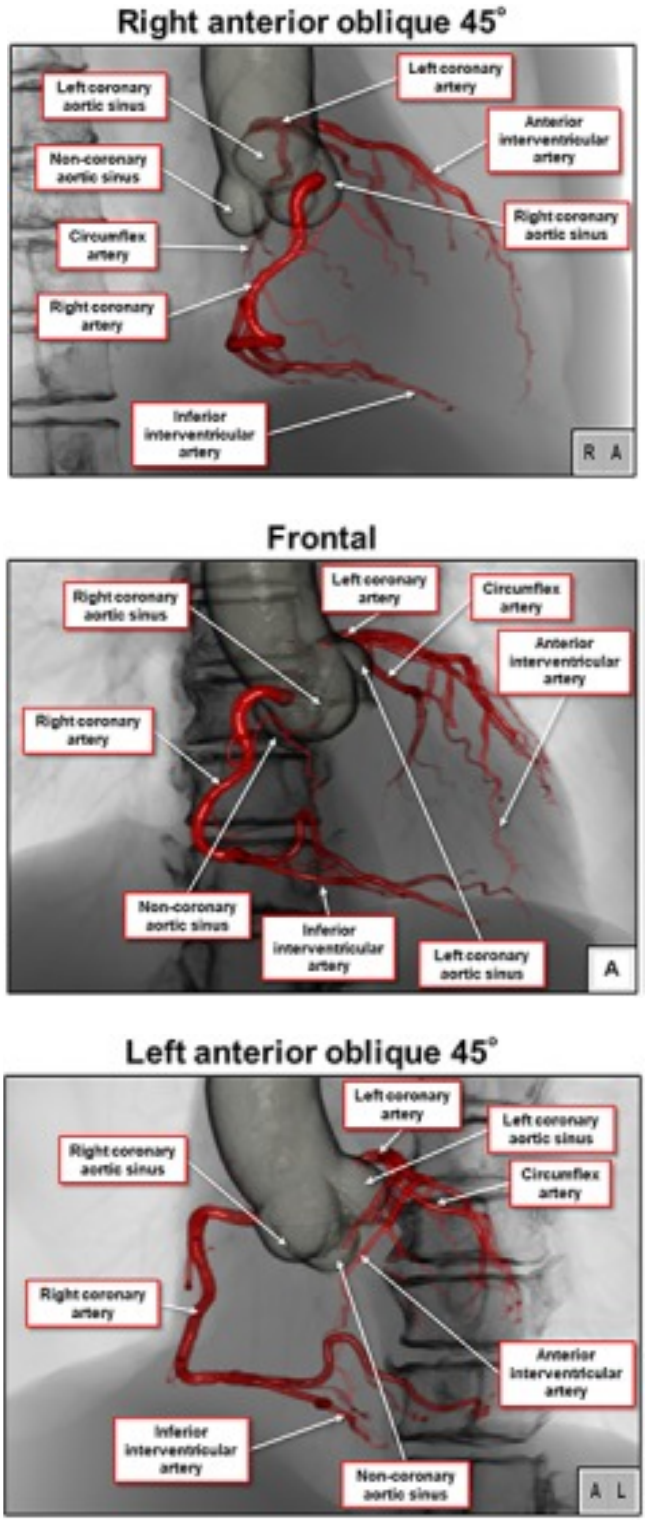


FIG 1: Coronary arteries as viewed from the frontal and right and left anterior oblique 45 degrees direction (Mori S. et Al. "What is the real cardiac anatomy?" *Clinical anatomy (New York, N.Y.)* vol. 32,3 (2019): 288-309. doi: 10.1002/ca.23340)

1.2 Ischaemic cardiopathy

Ischaemic heart disease presents a wide range of symptoms depending, as we will see, on the characteristics of the atherosclerotic plaques causing it. A distinction can be made between stable manifestations, in particular stable angina, and unstable manifestations, which include unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) (2).

1.2.1 Stable angina

Stable angina occurs when there is an unbalance between the myocardium's demand for oxygen and the supply of oxygen delivered by the coronary circulation; this generally occurs in the presence of atherosclerotic plaques, which cause stenosis of the coronary lumen and a consequent reduction in blood flow. At rest, coronary perfusion is usually sufficient to satisfy the myocardial metabolic demands; however, in situations characterised by increased oxygen consumption, such as during physical exercise or under emotional stress, coronary blood flow may become inadequate, leading to myocardial ischaemia.

From a clinical perspective, angina typically presents as recurrent retrosternal chest discomfort that may radiate to the neck, jaw, arms (often the left), or the epigastric region. Furthermore, as we have mentioned, it is predictably triggered by physical exercise, anxiety or stress; it increases progressively over a few minutes and subsides rapidly with rest or nitroglycerin (2-3).

1.2.2 Acute coronary syndromes

Acute coronary syndromes are conditions caused by a sudden reduction of blood flow to the heart, leading to myocardial ischaemia.

Within acute coronary syndromes, various entities are identified: conditions characterised by the absence of ST-segment elevation, which are in turn divided into unstable angina (troponin-negative) and NSTEMI myocardial infarction (characterised by elevated plasma troponin levels); and STEMI myocardial infarction (4).

Cardiovascular diseases are the leading cause of mortality and morbidity worldwide, and acute coronary syndromes are often their first manifestation (5).

It is estimated, indeed, that every year more than 7 million people worldwide are diagnosed with acute coronary syndrome (4, 6, 7) and that, despite significant advances in their diagnosis and treatment, they remain one of the leading causes of death globally (8-10).

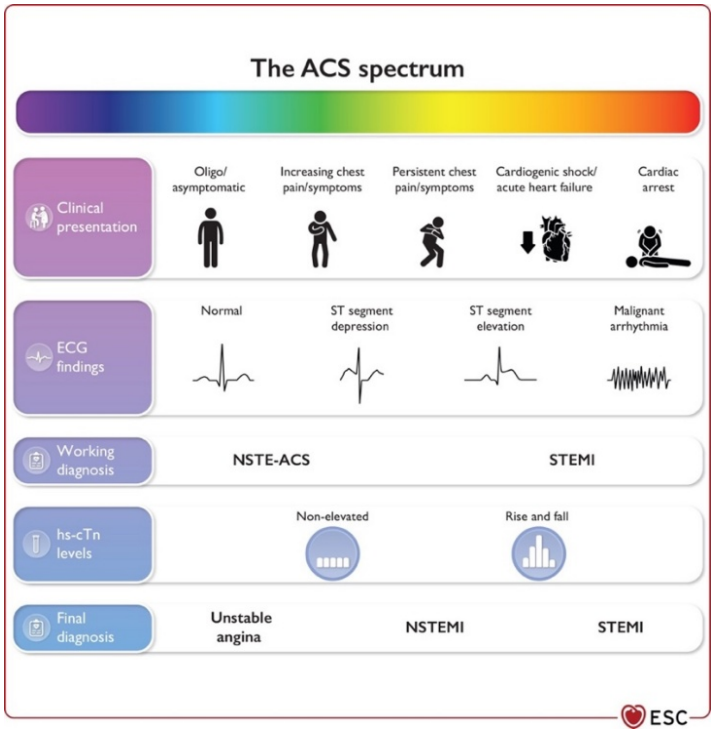


FIG 2: The ACS spectrum (2023 ESC Guidelines for the management of acute coronary syndromes.)

The most common clinical manifestation of acute coronary syndromes is chest pain/discomfort: as stated in the review (4) that included 1.226,163 patients from 27 observational studies demonstrated the presence of chest pain in 79% of men and 74% of women with ACS."

Despite this, there is a wide range of clinical presentations (often related to the severity of the thrombosis causing the ischaemia) ranging from cardiac arrest and cardiogenic shock to more insidious or silent presentations, as seen in diabetic and geriatric patients (5).

Unstable angina

Unstable angina is defined as a condition in which myocardial ischaemia occurs at rest or following minimal physical exercise, but without acute damage or necrosis of the cardiomyocytes.

We can speak of unstable angina in cases where pain occurs at rest and lasts for more than 20 minutes, or in cases where angina increases in frequency or duration or occurs at lower exercise thresholds than usual. We also speak of new-onset angina in cases of pain at rest occurring within the previous two months in a previously asymptomatic patient, or of post-infarction angina if it occurs following a recent episode of myocardial infarction (5).

NSTEMI myocardial infarction

A myocardial infarction without ST-segment elevation occurs when the thrombus does not completely occlude the vessel but only partially (5).

In this case, unlike in unstable angina, the ischaemia causes necrosis of the myocardium and, in particular, of the subendocardial layers of the affected area; this is therefore termed a subendocardial infarction.

Nowadays, this type of infarction represents the dominant phenotype, thanks to improvements in primary prevention strategies and greater awareness of the risk factors for coronary artery disease (11-12).

STEMI myocardial infarction

Acute myocardial infarction with ST-segment elevation, on the other hand, is defined as necrosis of cardiomyocytes in the clinical context of acute myocardial ischaemia caused by complete vessel occlusion (5). In this case, the necrosis involves the entire thickness of the myocardium and is therefore defined as a transmural infarction.

It typically presents as oppressive, retrosternal pain lasting longer than 30 minutes, which may radiate to the neck, mandible, infrascapular region, left shoulder and arm, or the epigastrium. It may also be associated with dyspnoea and autonomic symptoms such as nausea, vomiting, dizziness, palpitations and profuse sweating (4).

2 ATHEROSCLEROSIS

2.1 Epidemiology

Atherosclerosis is a vascular disorder characterized by progressive thickening and stiffening of the arterial wall, leading to gradual narrowing of the lumen and the development of ischemic manifestations in the affected vascular territories. It predominantly involves large- and medium-sized elastic and muscular arteries, particularly the coronary and cerebral vessels. The disease progresses slowly over decades, following a non-linear course marked by phases of relative stability alternating with periods of accelerated progression (13-14).

Atherosclerosis is one of the leading causes of morbidity and mortality worldwide, in both industrialised and developing countries. Cardiovascular diseases are responsible for approximately 17.9 million deaths worldwide each year. The expansion of the global economy, combined with the increasing prevalence of Western lifestyles and dietary habits, has contributed to a rise in the incidence and mortality associated with vascular diseases. Consequently, atherosclerosis is now one of the most significant public health issues, representing not only a highly prevalent condition in the adult population but also one of the leading causes of death worldwide (15).

2.2 Risk factors

Risk factors associated with the development of atherosclerosis can be divided into two main categories: non-modifiable factors and modifiable factors. Non-modifiable constitutional factors include age, sex (with a higher predisposition observed in males) and genetic background. Modifiable risk factors, on the other hand, comprise hyperlipidaemia, hypertension, smoking, diabetes mellitus, and physical inactivity. These represent the primary targets of research aimed at preventing and limiting the development of atherosclerotic plaques (16).

Atherosclerotic disease is closely associated to the main components of metabolic syndrome, a clinical condition characterised by the coexistence of multiple cardiovascular risk factors, including abdominal obesity, insulin resistance, impaired glucose metabolism, hypertension, and dyslipidaemia. In particular, metabolic syndrome is linked to an increased proportion of small, dense LDL particles, which are highly atherogenic. These particles are more susceptible to oxidation and have a greater ability to penetrate the arterial wall, contributing

to the inflammatory response and the progression of the atherosclerotic process, even in the presence of plasma LDL cholesterol concentrations that appear to be within normal limits.
Elevated levels of cholesterol carried by low-density lipoproteins (LDL-C) in the bloodstream play a central role in the pathogenesis of atherosclerosis. Conditions characterized by markedly increased LDL-C concentrations, such as familial hypercholesterolemia (FH), are therefore associated with the early onset of atherosclerotic cardiovascular disease (16-18).
Diabetes mellitus further contributes to the progression of atherosclerosis, partly through the development of diabetic nephropathy. This condition may lead to a reduced glomerular filtration rate (GFR), promote a chronic inflammatory state, and increase the risk of premature atherosclerosis. In the context of atherosclerosis etiology, additional relevant factors should also be considered, including sleep deprivation, air pollution, passive smoking, and the gut microbiota, whose bacterial metabolites are involved in cholesterol homeostasis (13, 14, 16, 19).

2.3 Pathogenesis

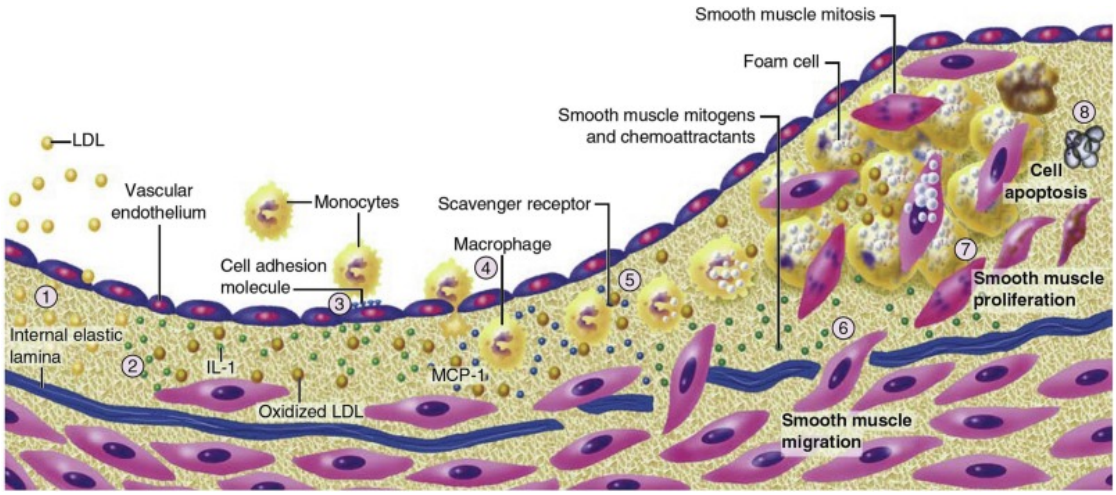


FIG 3: Evolution of the atherosclerotic plaque (*Braunwald's Heart Disease*, Volume 12, Figure 24-6).

An atherosclerotic plaque is composed of extracellular lipid deposits, foam cells, and cellular debris that accumulate within the intimal layer of the arterial wall, forming a lipid-rich or necrotic core. This core is encased in a collagen-dense matrix containing smooth muscle cells and is covered by endothelial cells, collectively referred to as the fibrous cap (20-22).

The fibrous cap exhibits variability in thickness and cellular composition among different plaques within the same individual, and heterogeneity can also be observed within distinct regions of a single cap.

The process that leads to the formation of such atherosclerotic plaques begins early in human life: the interaction between atherogenic lipoproteins and cells of the vessel wall leads to initial alterations of the intimate tunic, such as diffuse intimal thickening (DIT) and the appearance of the so-called lipid striae, and progresses over time to the formation of complex and potentially unstable plaques.

The earliest event of the process is the damage that occurs at the level of the endothelium: This can be determined by various conditions such as hypertension, hyperlipidaemia, hyperglycaemia, smoking, turbulent flow or the presence of reactive oxygen species; This initial insult alters endothelial physiology, which does not normally involve the adhesion of leukocytes, monocytes or other molecules to the vessel wall (15).

This endothelial damage allows, on the one hand, low-density lipoproteins (LDL) and triglycerides to enter, deposit and accumulate in the intimate layer of the vascular wall. On the other hand, the endothelium is not only a physical barrier between blood and tissues but is a real autocrine and paracrine organ essential for vascular homeostasis and in the defence against atherosclerosis: among the main processes that it regulates there are indeed vascular tone, cell composition of the wall, leukocyte trafficking, coagulation, inflammation and angiogenesis.

Under physiological conditions, there is a balance between vasodilatory factors (mainly nitric oxide and prostacyclin) and vasoconstrictors (endothelin-1, thromboxane A2, prostaglandin F2α); endothelial dysfunction, on the contrary, predisposes the vascular system vasoconstriction, mainly caused by reduced bioavailability of nitric oxide (13).

Undoubtedly, together with endothelial dysfunction, lipid homeostasis also plays a fundamental role in the initiation of the atherogenesis process: high levels of low-density lipoproteins (LDL) and triglycerides in plasma favour their accumulation in the subendothelial space, and especially in areas of hemodynamic turbulence.

In addition to this phenomenon, dysfunctional endothelium increases the expression of adhesion molecules (such as VCAM-1, ICAM-1 and E-selectin) and chemokines, promoting the adhesion of circulating mononuclear cells, predominantly monocytes, with a smaller proportion of lymphocytes, to endothelial cells (13).

This is followed by the transmigration of these cells into the subintimal space, where monocytes subsequently differentiate into macrophages.

These macrophages play a central role in lesion initiation and progression, as they internalize, thanks to scavenger receptors, lipids, including oxidized LDL and other atherogenic lipoproteins, acquiring a foam cell phenotype.

The accumulation of foam cells leads to the formation of so-called fatty streaks, the principal hallmark of early atherosclerosis, and through their subsequent interactions with other cellular components in the arterial wall, establishes the foundation for the development of atherosclerotic plaque.

As the disease progresses, oxidative stress contributes to the death of macrophages and smooth muscle cells by generating an accumulation of cellular debris, which feeds the lipid necrotic core.

In addition, several studies have shown that iron overload represents an additional pathogenic factor: free iron accelerates lipid peroxidation through the Fenton reaction, increasing oxidative stress and promoting ferroptosis, a form of iron-dependent regulated cell death characterized by the accumulation of peroxidized lipids. Ferroptosis has been implicated in several processes such as endothelial dysfunction, death of macrophages and smooth muscle cells, expansion of necrotic core, and increased inflammation.

Parallel to this, the pro-inflammatory and oxidizing elements induce a differentiation of muscle cells, which change their phenotype from contractile to secretory and migrate from the middle to the intimate tunic starting to deposit collagen and elastin. This process then leads to the formation of the fibrous capsule, which incorporates the necrotic lipid material and cellular debris (13, 115, 23, 24).

2.4 Clinical phenotypes and plaque progression

So, as we have said, plaques consist of multiple structural and cellular components, including extracellular matrix elements (such as collagen, proteoglycans, fibronectin, and elastic fibres), lipids (cholesterol crystals, cholesterol esters, and phospholipids), inflammatory cells (monocyte-derived macrophages and T lymphocytes), vascular smooth muscle cells, thrombotic material, and calcific deposits. The relative proportion of these constituents varies considerably among plaques, giving rise to a broad spectrum of lesion phenotypes.

Atherosclerotic plaques can be classified, based on their phenotypic characteristics and their potential evolution, into two families: stable and unstable plaques.

2.4.1 Stable plaque

A plaque is defined as stable when it is not the cause of acute ischemic manifestations; in fact, it is often asymptomatic. In addition, it has specific characteristics from a histopathological point of view, such as lower cellularity and a prevalence of fibrosclerotic tissue composed of a matrix of collagen and elastin fibres (25).

2.4.2 Unstable plaque

Unstable plaque, on the other hand, is defined as a plaque prone to various complications such as plaque rupture, plaque erosion and calcified nodule which lead to clinically symptomatic luminal thrombosis (26).

This type of plaque is characterized by a large necrotic core, which develops due to dysregulated cell death and reduced elimination of cellular debris. This process, often initiated by cholesterol-overloaded macrophages, plays a crucial role in plaque progression and vulnerability.

In fact, we speak of vulnerable or high-risk plaque when a plaque is characterized by a large central lipid nucleus, rich in inflammatory cells (macrophages and T lymphocytes), few smooth muscle cells and a thin fibrous cap (26, 27).

T lymphocytes, although less numerous than macrophages, secrete cytokines such as interferon gamma that instruct macrophages to express genes implicated in the progression of atheroma by encoding collagenolytic enzymes that degrade the tightly wound triple-helical interstitial collagen conferring strength to the plaque's protective fibrous cap, thereby promoting cap fragility.

In addition, thin-cap fibroatheroma (TCFA) is defined when the thickness of the fibrous cap is < 65 micrometres and macrophage infiltration is > 25 cells per 0.3 mm diameter field (28).

The morphological characteristics of plaque rupture and thin-cap fibroatheromas are shown in figure 4.

Plaque type	Necrotic core, %	Fibrous cap thickness, μm	MΦs %	SMCs %	T-lymph	Calcification Score
Rupture	34 ± 17	23 ± 19	26 ± 20	0.002 ± 0.004	4.9 ± 4.3	1.53 ± 1.03
Thin-cap fibroatheroma	23 ± 17	<65 μm	14 ± 10	6.6 ± 10.4	6.6 ± 10.4	0.97 ± 1.1
P value	ns		0.005	ns	ns	0.014

Mean values are represented ± standard deviation. MΦs, macrophages; SMCs, smooth muscle cells; T-lymph, T-lymphocytes.

Fig 4: Morphologic characteristics of plaque rupture and thin-cap fibroatheromas (28)

2.4.3 The concept of the High-Risk Plaque

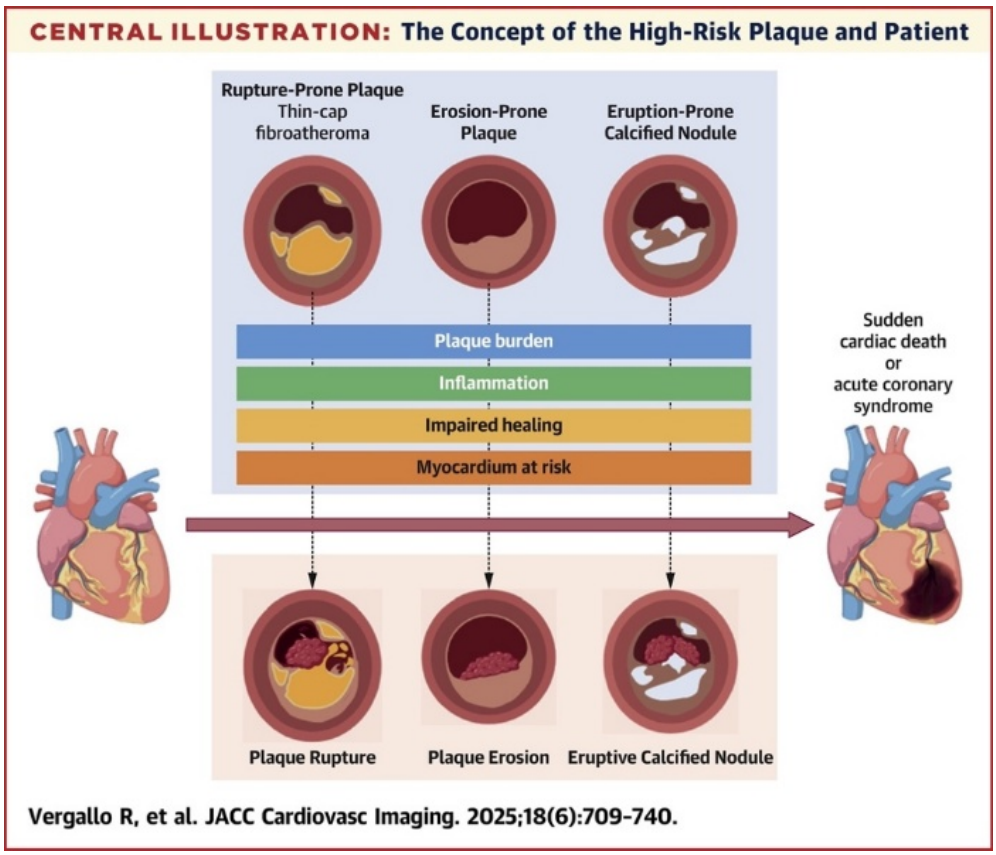


FIG 5: The concept of the Hight-Risk Plaque and Patient (29)

We can therefore define the "high-risk plaque", as can be read in the article "Vulnerable or High-Risk Plaque" by Rocco Vergallo et al. (29), “a plaque with increased propensity to evolve into a clinically relevant thrombosis, and to cause ACS (mostly ST segment elevation MI or type 1 non–ST-segment elevation MI) or cardiac death, on the basis of its morphology, burden, biological activity, intrinsic thrombogenicity, and location" (30).

In contrast to previous decades, when plaque vulnerability was associated exclusively with plaque rupture, it is now recognised that plaque erosion and eruptive calcified nodules also play a key role in the pathogenesis of acute coronary syndromes (29).

Based on currently available evidence and in vivo studies, the man risk factors for high-risk plaque can be classified into major and minor categories.

Major risk factors include thin fibrous cap, large lipid/necrotic core, large plaque burden, active plaque inflammation (macrophages) and endothelial damage/denudation.
Minor criteria, on the other hand, include superficial protruding calcified nodules, intraplaque haemorrhage, neovascularisation, cholesterol crystals, positive remodelling, absence of healed plaque, disturbed local haemodynamics (shear stress, shear stress gradient) and location in a proximal or mid-coronary artery (large area at risk) (29).
More specifically, it has been highlighted that the thickness of the fibrous cap is the main discriminating factor between unruptured and ruptured plaques; plaque burden and luminal obstruction, on the other hand, are key factors in determining the acute clinical manifestation of the thrombotic complication (29).
Evidence from pathological and vivo studies has consistently shown that not only plaque morphology, but also plaque volume and burden and severity of stenosis are important in determining the risk of major adverse cardiovascular events (MACE). In many studies, such as the PROSPECT study (Providing Regional Observations to Study-Predictors of Events in the Coronary Tree) and the VIVA study (VH-IVUS in Vulnerable Atherosclerosis), plaque burden has emerged as the single most important predictor of plaque instability. Nevertheless, as stated in the PROSPECT II study, plaque burden alone is not sufficient to identify a plaque at risk of future cardiovascular events, but it must also be lipid-rich (29).
While TCFA is frequently associated with plaque rupture, the characteristic precursor lesion of plaque erosion is fibrous plaque or, less frequently, a thicker cap-like fibroatheroma. Plaques prone to erosion are also typically eccentric and rarely calcified (29).
Finally, the precursor lesions of eruptive calcific nodules, although there is less evidence on this, are typically characterised by protruding nodular calcifications, followed subsequently by rupture of the fibrous cap and the formation of the overlying thrombus (29).

2.4.4 The role of macrophages

Recent studies have shown that macrophages play a fundamental role in the distinction between stable and unstable plaque and in particular their plasticity and polarization capacity. As we have seen, macrophages represent one of the main components of atherosclerotic plaque, but it has been observed that there is a phenotypic heterogeneity of these within different areas of the plaque.

Macrophages are indeed a cell population that has a wide phenotypic spectrum at the poles of which there are cell types with opposite roles: on the one hand there is the M1 family, polarized in the T-helper 1 sense, on the other the M2 family, polarized in the T-helper 2 sense. Each of these families can then be divided into different subtypes, the M2 macrophages for example, depending on the markers they express and their specializations, are divided into M2a, M2b, M2c and M2d.

Thanks to this plasticity, therefore, macrophages can polarize according to the stimuli they receive from the microenvironment in which they are located: there are pro-inflammatory cytokines and chemokines such as TNF-α, IL-1β, IL-6, IL-12, IL-23, CXCL9, CXCL10 and CXCL11 that lead to an M1 polarization, while others such as IL-10, IL-4 and IL-13 towards M2 polarization (26).

Each phenotype also corresponds to a different function, M1 macrophages play a pro-inflammatory role and cause degradation of the fibrous cap matrix with consequent destabilization of the plaque, while M2 macrophages play a role in tissue remodelling, angiogenesis and immunoregulation.

Interestingly, these macrophage families have different localizations within the plaque: M1 macrophages are found primarily in the lipid core; M2 macrophages, on the other hand, are more resistant to lipid accumulation and are found predominantly in the fibrous cap. This suggests that the M1 phenotype is more involved in plaque progression and destabilization (26, 27, 31).

3 PATHOGENESIS OF CORONARY SYNDROMES

As described by Filippo Crea and Peter Libby (32), there are three main pathological pathways that lead to acute coronary syndrome: plaque rupture with or without systemic inflammation, plaque erosion, and the pathway in the absence of thrombosis (such as due to a functional alteration of the coronary circulation, as in vasospastic angina, or dynamic spasm obstruction of an epicardial coronary vessel, coronary embolism, or coronary artery dissection).

Furthermore, calcific nodules have also been shown to be implicated in the pathogenesis of acute coronary syndromes (29).

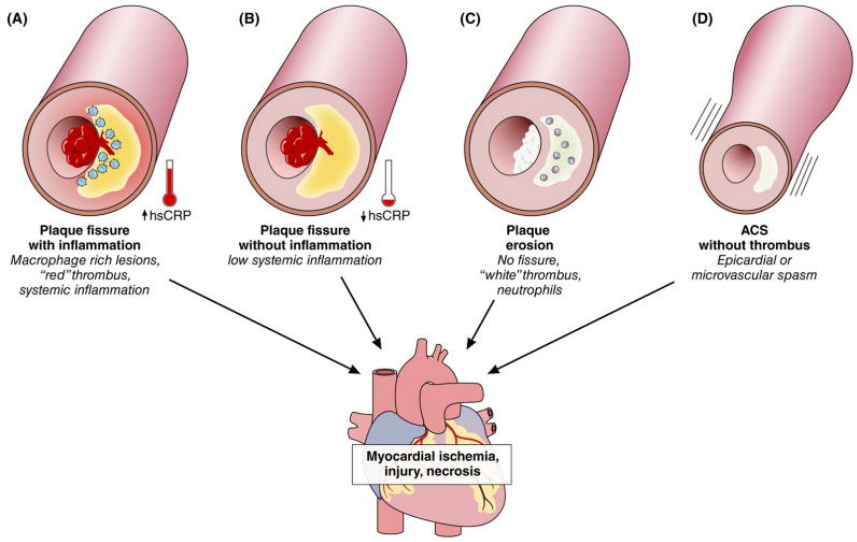


FIG 6: Mechanisms of acute coronary syndromes (32)

3.1 Plaque rupture

Recent data obtained using Optical Coherence Tomography (OCT) recognise plaque rupture as the cause of 60% of acute coronary syndromes (33).

As stated in the article "Diagnosis and Treatment of Acute Coronary Syndromes A Review" by Bhatt et al. "(34), coronary atherosclerotic plaque rupture with thrombus formation accounts for approximately 70% of fatal acute MIs and sudden coronary deaths.

Numerous studies have demonstrated that inflammation plays a fundamental role in plaque destabilization. M1 macrophages, through the production of metalloproteinases and cathepsins, degrade the components of the fibrous cap, causing its fragility; this process is also promoted by a reduction in endogenous inhibitors of these enzymes, such as tissue inhibitors of metalloproteinases and cystatins.

Not only innate immunity is altered, but also adaptive immunity: there is an increase in pro-inflammatory CD4+ T cells and a reduction in type 17 T helper cells (Th17) and regulatory T cells (T reg).

Finally, systemic inflammation also plays a role, as demonstrated by increased levels of C-reactive protein in approximately half of patients with acute coronary syndrome (32).

All these pro-inflammatory phenomena ultimately lead to plaque fissure and communication of the highly thrombogenic necrotic core with the vascular lumen and blood flow (20).

This leads to the activation of the endogenous haemostatic system, with, first, the recruitment of platelets, which bind to von Willebrand factor and their degranulation of autocrine and paracrine mediators that allow clot formation. The coagulation cascade is then activated, which, through the intrinsic and extrinsic pathways, leads to the formation of the definitive thrombus within the vessel and subsequent tissue ischemia.

The thrombus that arises from plaque rupture has well-defined characteristics, which, as we will see, are different from those of thrombi originating from eroded plaques: it is composed predominantly of fibrin and erythrocytes and, to a lesser extent, platelets, taking on a typical "red" appearance (35).

However, it is possible that plaque rupture can also occur in the absence of systemic inflammatory activation, such as in situations of severe emotional stress, intense physical exertion, or mechanical stress on the arterial wall. These factors remain poorly studied and understood, but it is hypothesized that there is a relationship between them and the activation of the sympathetic nervous system and the release of catecholamines (which result in an increase in heart rate, blood pressure, and coronary vasoconstriction (32, 36).

3.2 Plaque erosion

It is estimated that approximately one-third of acute coronary syndromes are currently caused by plaque erosion, particularly NSTEMIs; this prevalence is thought to have increased in recent decades thanks to the growing use of effective therapies to reduce plasma LDL cholesterol and consequently plaque lipid content (33, 37, 38).

Autopsy studies have shown that fatal plaque erosions were more frequently associated with hypertriglyceridemia, diabetes mellitus, female gender, and young subjects.

The morphological and phenotypic characteristics of eroded plaques are very different from those of ruptured plaques: they contain fewer macrophages and inflammatory cells while being composed of large quantities of proteoglycans such as versican, glycosaminoglycans, and smooth muscle cells. Eroding plaques also typically have a lower lipid content and are more fibrous.

It has been hypothesized that thrombosis following plaque erosion occurs in two phases: the first involves a compromised endothelial viability and a disruption of the integrity of the monolayer overlying the atherosclerotic plaque, leading to platelet recruitment; the second phase involves platelet activation, caused by contact with collagen and other plaque components, and their degranulation of chemotactic factors (35, 39).

Supporting this, it has been observed that eroded lesions tend to be more frequently located near bifurcations, where there is greater endothelial stress due to blood flow; these conditions can lead to increased expression of the TLR-2 receptor, an innate immune signalling receptor involved in endothelial damage (33).

Chemotactic factors then lead to the recruitment of polymorphonuclear leukocytes, which, in this inflammatory context, can release structures known as NETs (Neutrophil Extracellular Traps). These networks consist of nuclear DNA, granular and cytoplasmic proteins, tissue factor, and pro-oxidant enzymes that trap platelets and fibrin filaments, generating a thrombus (32, 40-42).

Neutrophil activation, therefore, appears to play a fundamental role in the plaque erosion process; this has been demonstrated by studies that observed patients diagnosed with plaque erosion by OCT, whose myeloperoxidase levels were higher than those of patients with plaque rupture (32, 35).

Furthermore, as previously mentioned, different plaque phenotypes (eroded or ruptured) are associated with thrombi with different compositions: thrombus originating from plaque erosion is defined as "white" because it is composed predominantly of platelets and poor in erythrocytes (35).

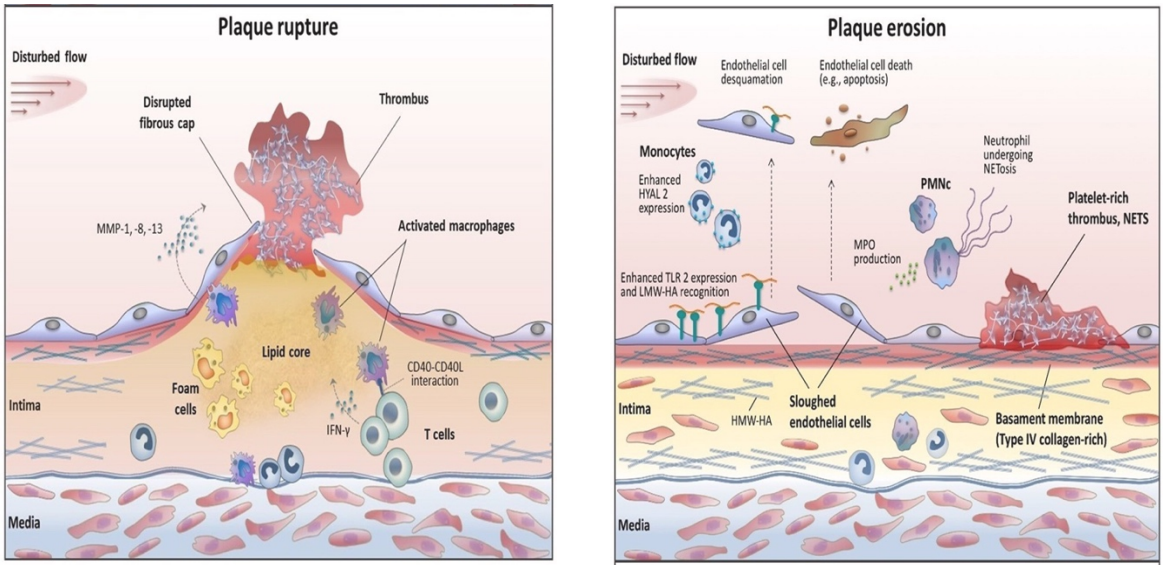


FIG 7: Plaque rupture and plaque erosion (40)

3.3 Calcific nodule

Calcific nodules are a less common cause of coronary thrombosis and are estimated to account for approximately 2%-8% of acute coronary syndromes (29, 43, 44).

Atherosclerotic plaques characterized by protruding nodular calcifications, especially in elderly patients and those with chronic kidney disease, may be present. These plaques cause the fibrous cap to rupture and form an overlying thrombus. This thrombus is composed primarily of fibrin and platelets, with the addition of calcification fragments, as it forms following intraplaque haemorrhage caused by calcium damage to the surrounding capillaries and arterioles (29, 45).

The lesion preceding these nodules is typically an eccentric plaque with a calcified necrotic core lacking mechanical resistance adjacent to areas of greater stability. The fragility of this area therefore favours the eruption of calcium fragments in situations of external mechanical forces, such as the movements of the coronary vessel during the cardiac cycle (29).

In particular, these lesions are most frequently located in the proximal and middle segments of the right coronary artery, particularly in tortuous areas and at hinge points. Furthermore, another common site for calcified nodules is the left main bifurcation (29).

3.4 Plaque healing

Pathological studies have shown that many, if not most, plaques become unstable without giving rise to an acute clinical event: symptomatic coronary syndrome occurs, indeed, when plaque rupture or erosion takes place in a pro-thrombotic environment, leading to occlusive or sub-occlusive thrombosis. If, on the other hand, anti-thrombotic factors prevail, thrombus formation is limited and the phenomenon known as plaque healing occurs.

In this process, the endogenous fibrinolytic system plays a fundamental role, including soluble mediators produced by endothelial cells such as tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), or those produced by circulating blood cells such as elastase and cathepsin G released by neutrophils and monocytes (20, 45).

If these systems are intact and functional, they are therefore able, when a rupture of the fibrous cap occurs, to restore its integrity through three successive phases: a phase of thrombus lysis, a phase of granulation tissue formation, and a phase of re-endothelialisation of the vessel.

In addition to the endogenous fibrinolytic system, other factors also play an important role in the plaque repair process, such as the structural properties of the fibrin fibres forming the thrombus (the thicker they are, the more susceptible they are to lysis) and the dispersing effect produced by laminar blood flow.

A proliferative response of smooth muscle cells then occurs, mediated by growth factors such as PDGF-BB and TGF-β and mitogenic factors such as thrombin produced by platelets, which promotes the synthesis of a provisional extracellular matrix formed by granulation tissue rich in proteoglycans and type III collagen, which is then gradually replaced by type I collagen. The plaque stabilisation process ultimately concludes with the re-endothelialisation of the surface and the formation of a neointima, as shown in Figure 8 (20, 46).

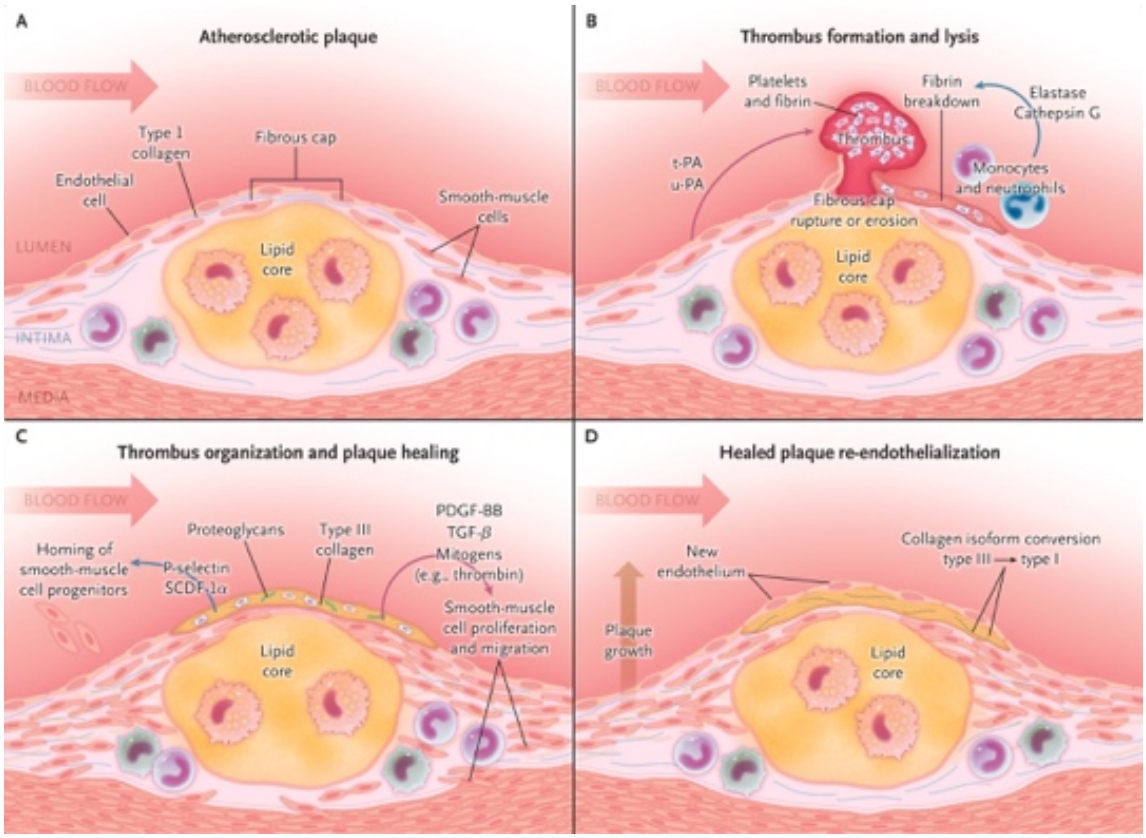


FIG 8: Mechanisms of Atherosclerotic Plaque Healing (20)

3.4.1 The double-hit theory

Thanks to new studies on the progression of atherosclerosis, the so-called 'double-hit' theory has been proposed: this theory states that for acute coronary syndrome to occur, with occlusive thrombosis of the vessel, it is not only necessary for the plaque to become unstable through rupture or erosion of the fibrous cap (first hit), but also for endogenous fibrinolytic and healing capacity to be compromised (second hit).

Once the plaque has become stable, it may subsequently become unstable again: this leads to silent stenotic progression of the coronary lumen, which can also result in high-grade coronary occlusions, in the absence of acute coronary events (20, 47).

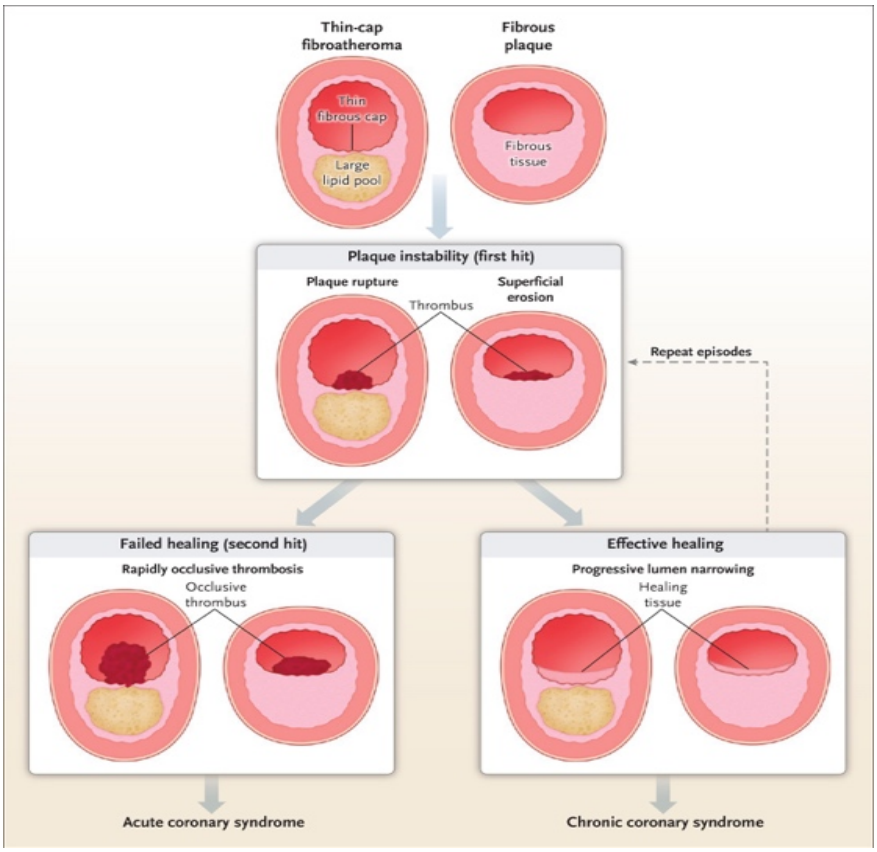


FIG 9: Role of Plaque Healing in the Natural History of Ischemic Heart Disease (20)

3.4.2 Prevalence of healed plaques

In recent decades, research has focused primarily on the mechanisms underlying plaque instability; however, the difficulty in predicting the risk of acute myocardial infarction or sudden cardiac death suggests the involvement of additional pathogenic mechanisms. In this context, the role of plaque healing has attracted increasing interest, partly due to the development of advanced imaging techniques, such as OCT, IVUS and cardiovascular magnetic resonance imaging, which allow for the in vivo study of the morphological characteristics of atherosclerotic lesions.

The reported prevalence varies considerably from < 5% to > 80%, depending on the detection method, the vascular bed assessed and the clinical presentation; however, several studies have shown that the prevalence of such plaques is considerably higher in patients with chronic manifestations of atherosclerotic disease (20).

About one out of three to four patients with ACS have layered (‘healed’) plaques at the culprit site, suggesting that many disrupted lesions do not result in an ACS (48,49).

Several observations have also led to the hypothesis that plaque erosion is more commonly associated with the healing process than with plaque rupture: an anatopathological study of 111 patients who died suddenly of coronary causes showed that almost half of the thrombi overlying plaque ruptures showed no evidence of healing while the remaining half showed various stages of healing; in contrast, more than 85% of the thrombi overlying plaque erosions showed late stages of healing (50).

In addiction another study by Geary et al (51) analysed healing thrombi formed after experimental angioplasty of the left iliac artery in non-human primates and showed that the thrombus was replaced by smooth muscle cells expressing hyaluronan and an associated protein, versican, which are known to be specifically involved in the pathogenesis of erosion.

Another point to consider is that healed coronary plaques are rarely observed in patients with a history of recurrent acute coronary syndromes, whereas they are much more common in patients with long-standing stable coronary artery disease or a history of a single acute myocardial infarction, as demonstrated by the study conducted by Vergallo et al. (47).

3.4.3 Inflammation and healing

The link between inflammation and plaque healing is not yet fully understood; nevertheless, it is thought that inflammation may play a crucial role in modulating the balance between instability and healing: Th1 lymphocytes, through the production of interferon-γ, inhibit collagen synthesis by smooth muscle cells, whilst the CD40–CD40L interaction between T lymphocytes and macrophages stimulates the production of metalloproteinases (MMP-1, -8, -13), promoting collagen degradation and the weakening of the fibrous cap. Conversely, M2 macrophages, induced by Th2 cytokines (interleukin-4 and -13), produce anti-inflammatory mediators and profibrotic factors (fibronectin, IGF-1, TGF-β), promoting tissue repair (20, 21, 52). These mechanisms are shown in Figure 10.

3.4.4 Neoangiogenesis and healing

Neoangiogenesis also plays an important role in thrombus organisation and tissue repair, as it delivers oxygen and nutrients to the healing tissue. Indeed, the growth of microvessels within the plaque has been documented more frequently in healed plaques than in unhealed ones (20).

Mark Brezinski et al also state (53) that intimal angiogenesis represents the line of supply for reparative cells and plays an important role in plaque healing and in the prevention of intimal thinning and the development of acute coronary syndrome. This hypothesis is further supported by data showing that angiogenesis-inhibiting drugs such as Sutinib and Sorafenib increase the risk of vascular occlusion in humans (50, 53, 54).

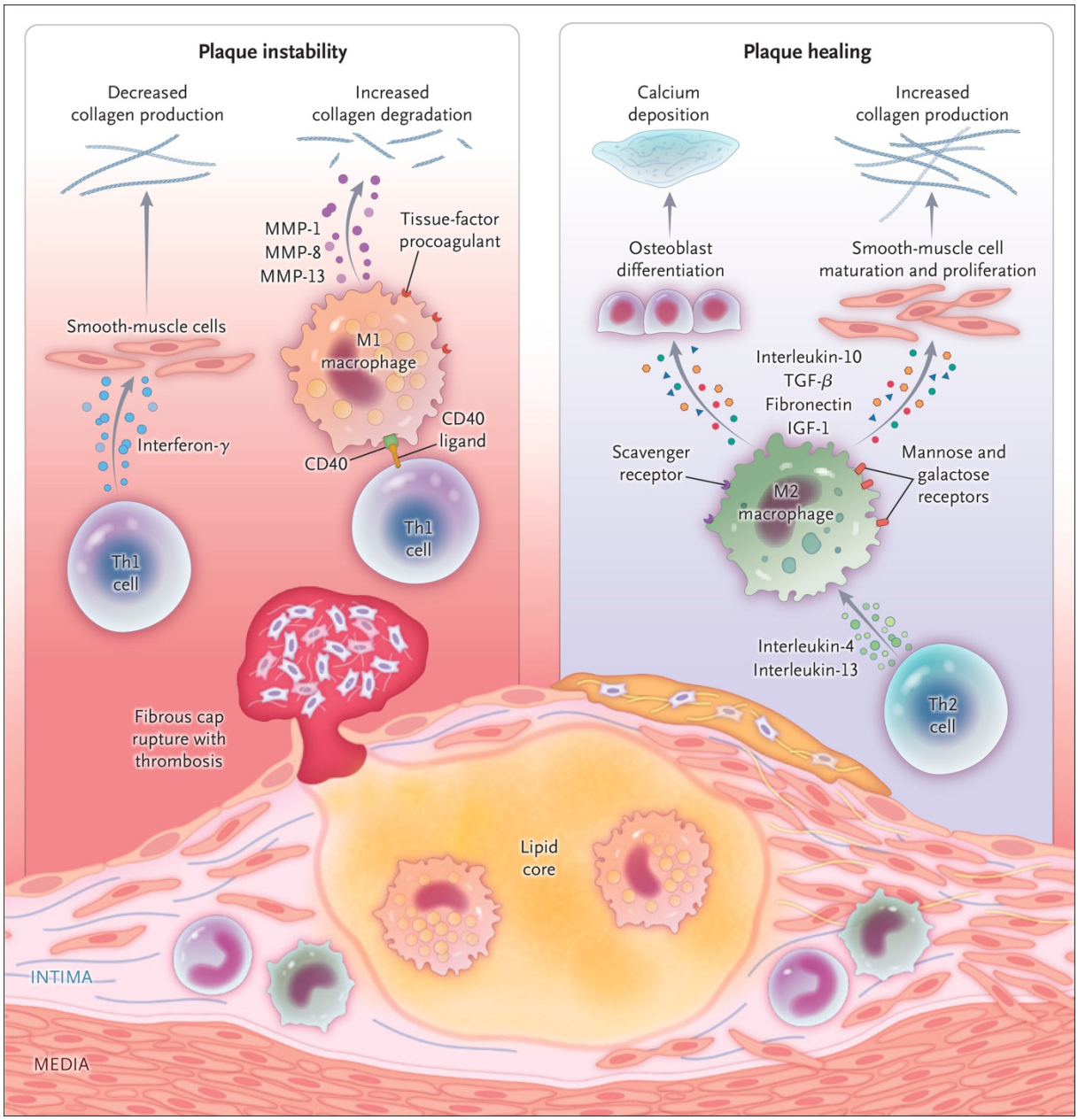


FIG 10: Inflammatory pathways involved in plaque instability and plaque healing (20)

4 IMAGING TECHNIQUES

4.1 Coronary angiography

Coronary angiography involves selective angiography of the coronary arteries, performed using a minimally invasive technique via femoral or radial arterial access.

It is the gold standard for the anatomical assessment of the coronary arteries, enabling the identification of any stenoses that impair blood flow to the myocardium, and determining their severity, location, extent and appearance.

It also represents the first step prior to any percutaneous or surgical revascularisation.

Indications for coronary angiography include situations of high coronary risk, such as unstable angina, angina refractory to medical therapy, residual angina following a heart attack or revascularisation, angina associated with heart failure, and acute coronary syndrome with or without ST-segment elevation. Furthermore, the procedure is indicated in patients with positive or equivocal functional tests, in the presence of extensive ischaemia, and in those with a clinical picture suggestive of spastic coronary artery disease or Prinzmetal's angina, typically young people and smokers. Coronary angiography is also indicated in cases of severe left ventricular dysfunction of undetermined origin, with an ejection fraction of less than 40%, and as a further investigation in the presence of valvular disease when there is a discrepancy between symptoms and the severity detected by non-invasive tests. Finally, it is an essential tool in the preoperative assessment of patients over the age of forty prior to valve surgery (55-57).

4.1.1 AHA classification

The classification system introduced by the American Heart Association (AHA) and the American College of Cardiology (ACC) was designed to estimate the likelihood of success of coronary angioplasty and the associated procedural risk. Specifically, lesions are divided into three main categories: type A, type B and type C lesions (58).

Type A lesions are simple, circumscribed, concentric lesions that are easily accessible, located in a non-angulated segment (< 45 degrees), with a regular contour, no significant calcifications, no total occlusion, non-ostial location, no involvement of the main branches and no thrombus. In this type of lesion, the predicted success rate is greater than 85% and the risk of sudden vessel occlusion is low (58).

Type B lesions are generally characterised by a tubular shape, eccentricity, accessibility affected by moderate tortuosity of the proximal segment, location in a moderately angled segment (between 45 and 90 degrees), irregular contours, the presence of moderate or severe calcifications, the presence of a thrombus, ostial location, bifurcation lesions requiring the use of two guidewires, and total occlusions that have occurred within the previous 3 months. In this type of lesion, the expected success rate is between 60% and 80%, and the risk of sudden vessel occlusion is moderate.

These lesions are further classified as B1 or B2 depending on whether they exhibit one unfavourable characteristic or two or more, respectively (58).

Type C lesions may present any of the following characteristics: extensive lesion length (>2 cm), excessive tortuosity of the proximal segments, location in an extremely angulated segment (90 degrees), total occlusion that has been present for more than three months, inability to protect the main collateral branches, or degeneration of old venous grafts with friable lesions. In these lesions, the success rate falls below 60%, or the risk of sudden vessel occlusion is high; for this reason, they are associated with a higher risk of complications during PCI (58).

4.1.2 Ambrose Classification

The Ambrose classification was proposed to characterise the morphology of coronary lesions observed on angiography and to identify those most strongly associated with acute coronary events.

Lesions are divided into two categories: type I is characterised by a concentric, regular and smooth stenosis and is associated with a low risk of acute coronary events; Type II, on the other hand, is characterised by an eccentric, irregular stenosis with irregular edges and is associated with a high risk of developing acute coronary events (59).

Type II is further subdivided into Type IIA, characterised by an eccentric lesion with an irregular surface, and Type IIB, characterised by a lesion with visible ulceration or thrombosis (59).

4.2 Optical coherence tomography (OCT)

4.2.1 Physical principle

Optical coherence tomography (OCT) is a high-resolution intravascular imaging modality widely used in clinical practice for the study of coronary atherosclerosis, offering high reliability in the in vivo identification and classification of atherosclerotic plaques (60-63). There is a wide range of clinical applications for this technique, as it is a powerful technology that provides real-time visualisation of tissue microstructure (64).

It consists of an imaging technology used to assess the microstructure of arteries with an axial resolution of approximately 10–15 micrometres, thereby providing a detailed characterisation of the superficial structures of the vascular wall. This is achieved by the use of infrared light, specifically by measuring its depth of penetration within the vascular wall. Once the catheter has been advanced over the guidewire into the distal segment of the coronary artery to be studied, and nitroglycerin has generally been administered to reduce the vasospasm induced by the catheter, image acquisition proceeds by performing a pullback at a constant speed whilst injecting the contrast medium.

There are three modes of OCT image visualisation: cross-sectional (perpendicular to the vessel axis), longitudinal, and three-dimensional reconstruction; in more modern systems, angiographic recording may also be incorporated so that cross-sectional OCT images can be linked to their position on the angiogram (61-63). More specifically, OCT performs cross-sectional and volumetric imaging by measuring the amplitude and time delay of the light backscattered by the tissues (64).

As also stated by Kraler et al. (33), the use of intravascular imaging improves the long-term outcomes of revascularisation procedures: “as demonstrated by a recent RCT in patients with ACS and by a network meta-analysis which showed a 29% reduction in the risk of target lesion failure when using intracoronary imaging compared with a revascularisation strategy guided solely by coronary angiography during PCI”.

4.2.2 Standard measurements

Araki (61), describes the fundamental measurements performed on OCT images are defined as follows:

Arc: Arc measured using the centre of the lumen as the vertex;
Depth: The distance between the luminal border and the abluminal surface of the plaque feature;
Thickness: The thickest distance between the inner and outer border of the plaque component (valid only if the deep boundary can be identified);
Area: The cross-sectional area (CSA) of the plaque component (valid only if the deep boundary can be identified);
Volume: The sum of areas of each cross-section multiplied by the slice thickness over the segment of interest (Simpson's rule);
Cap thickness: The thickness of a cap present over calcium or lipid. Minimum fibrous cap thickness is conventionally measured 3 times at the thinnest point in magnified views, and the average value is calculated.
Lesion length: The distance between the proximal and distal reference (61, 65, 66).

4.2.3 Plaque characterization

The wall of the arteries consists of three layers: the intima, the media and the adventitia; in OCT images, the media layer in a physiological state appears as a band with a lower signal intensity compared to the other two, giving a three-layered appearance (light-dark-light), as shown in Figure 11A (61).
Can also be observed the so-called intimal thickening: in the early stages of atherosclerosis, thickening of the intima can be observed, appearing as a thick, homogeneous band with high signal intensity (figure 11B) (61).

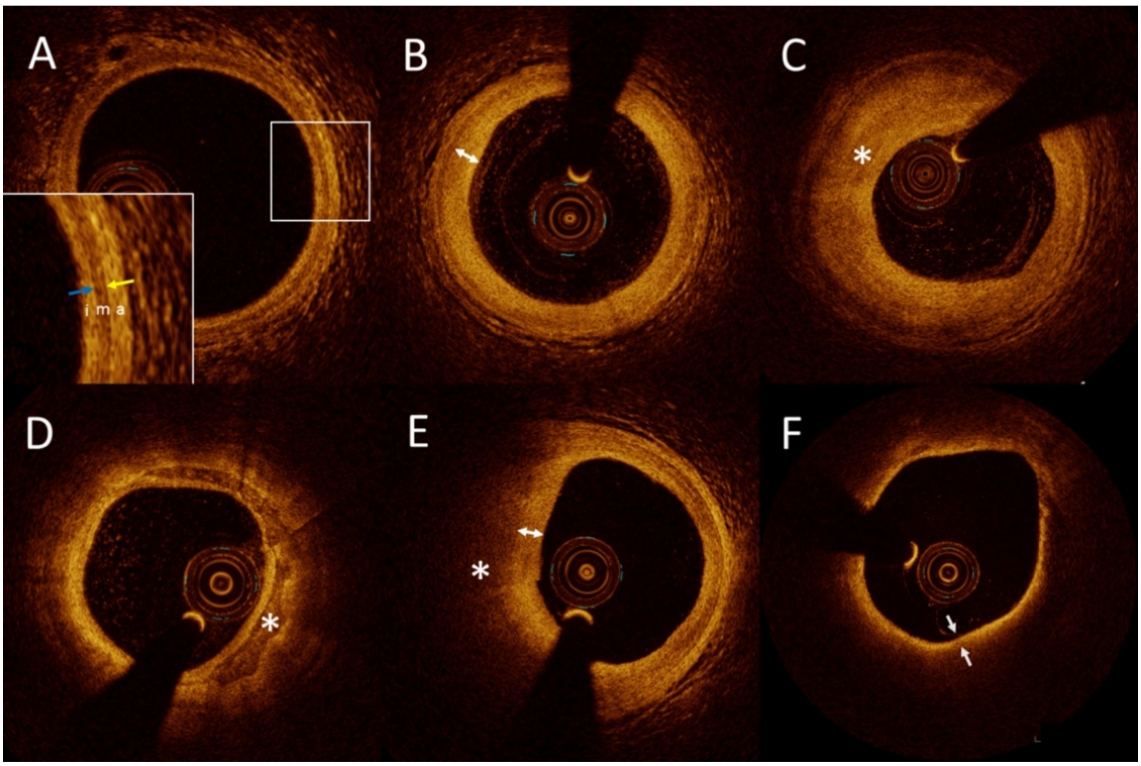


FIG 11: Normal vessel and plaques (61)

Atherosclerotic plaque is recognised on OCT images as a focal lesion of the vascular wall that appears thickened or as an area where the vessel's layered structure is lost; depending on its characteristics, it will then exhibit distinctive features (61).

Fibrous plaque, in fact, shows homogeneous regions of high signal intensity (Figure 11C); calcified plaque appears as low-signal regions with well-defined edges and limited shadows (Fig. 11D) (67, 68); finally, lipid plaque shows low-signal regions with blurred edges (lipid pool) covered by bands of high signal intensity (fibrous capsule), accompanied by high signal attenuation (Fig. 11E).

Furthermore, the circumferential arc is used to semi-quantify lipids and lipid-rich plaque is defined as a lipid plaque that has a lipid arc> 90 degrees; lipid length is measured on the longitudinal view; lipid index is calculated as the product of mean lipid arc and lipid length. Figure 11F also shows the thin cap fibroatheroma which, as previously defined, is the lipid plaque characterised by a fibrous cap thickness of <65 μm and a lipid core >90° of the circumference (61, 69,70).

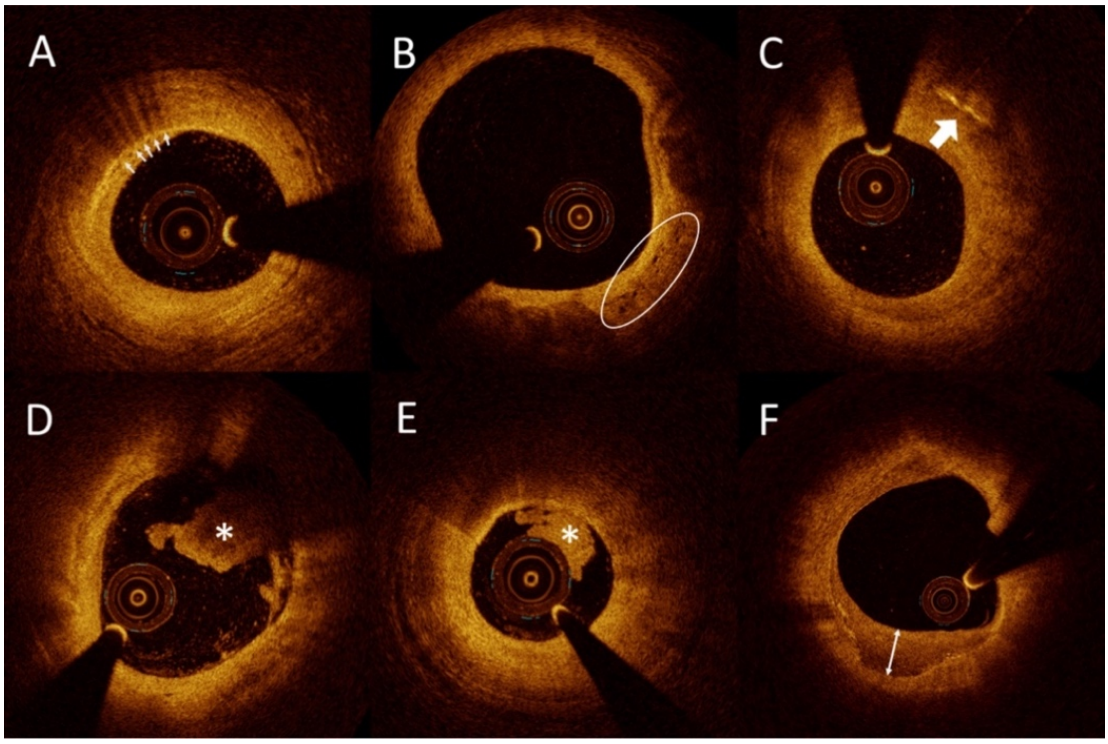


FIG 12: Qualitative findings (61)

In non-physiological conditions, various features may be observed on OCT, such as macrophages (particularly within lipid plaques), microvessels and cholesterol crystals.

Macrophages (Figure 12A) appear as distinct or confluent punctate regions of high signal intensity, exceeding that of the surrounding background. Due to their high backscatter and attenuation characteristics, they cast a dark shadow behind their aggregates (61, 71, 72).

As the plaque size increases, microvessels also appear; these are nutrient vessels that facilitate the infiltration of lipids, inflammatory cells or red blood cells into coronary plaques. They appear on OCT as signal-poor spaces, well-defined and traceable across several consecutive frames, as seen in Figure 12B (61, 73).

Cholesterol crystals can also be observed, appearing as thin, high-intensity linear regions, usually in the vicinity of a lipid plaque (Figure 12C) (61, 74).

Once the plaque becomes unstable, one may also find plaques associated with thrombi (red or white), layered plaques, or culprit plaques causing acute coronary syndromes.

The thrombus is visible on OCT as a protruding mass attached to the luminal surface or floating within the lumen; red thrombi, rich in erythrocytes, highly reflective and with strong attenuation (Figure 12D), can be distinguished from white thrombi, rich in platelets, less reflective, lighter and more homogeneous (Figure 12E) (61, 75,76).

Layered plaque, on the other hand, appears as a plaque with one or more layers of differing optical density and with a clear demarcation from the underlying components (Figure 12F, Figure 13 and Figure 14). During the healing process, in fact, type III collagen is gradually replaced by type I collagen, which appears as a band with high backscatter on OCT (61, 77). Healed plaques therefore appear as heterogeneous, signal-rich layers with an optical signal intensity different from that of the underlying plaque, creating a characteristic onion-skin appearance, either without disruption of the old fibrous cap or with a disruption suggesting a previous rupture (20).

At the end of the healing process, the inner surface is completely re-reendothelialised and the resulting plaque consists of smooth muscle cells and an extracellular matrix rich in proteoglycans that contains lipid components.

The presence of multiple layers of fibrous tissue and a necrotic core indicates successive episodes of thrombosis and healing over time, which contribute to the progression of the lesion with an increase in plaque burden; the vessel lumen narrows progressively as adequate compensation through positive remodelling is compromised by the presence of severely diseased arterial tissue (64).

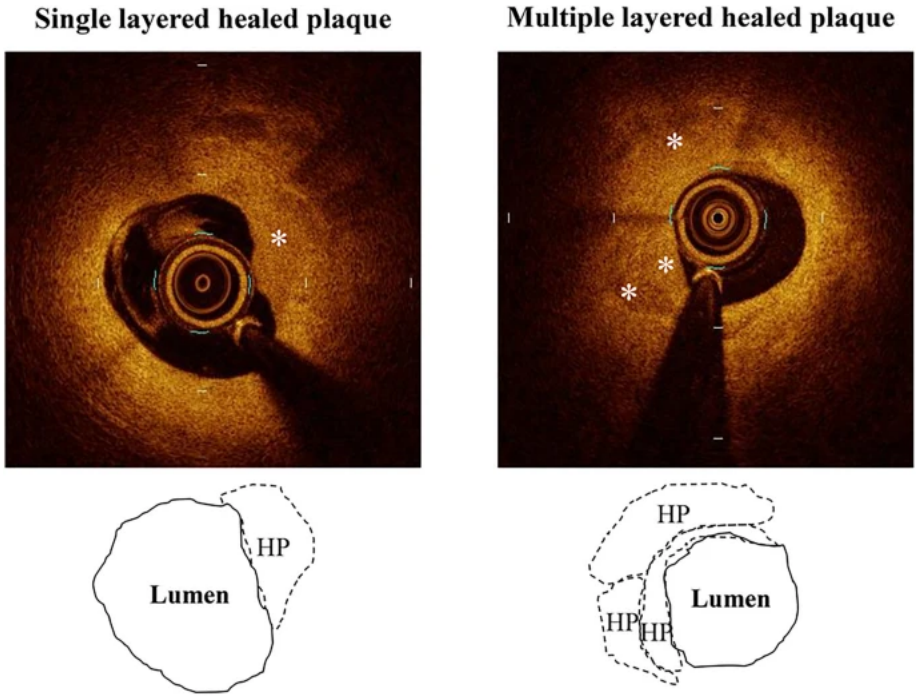


FIG 13: Optical coherence tomography and coronary angioscopy assessment of healed coronary plaque (60)

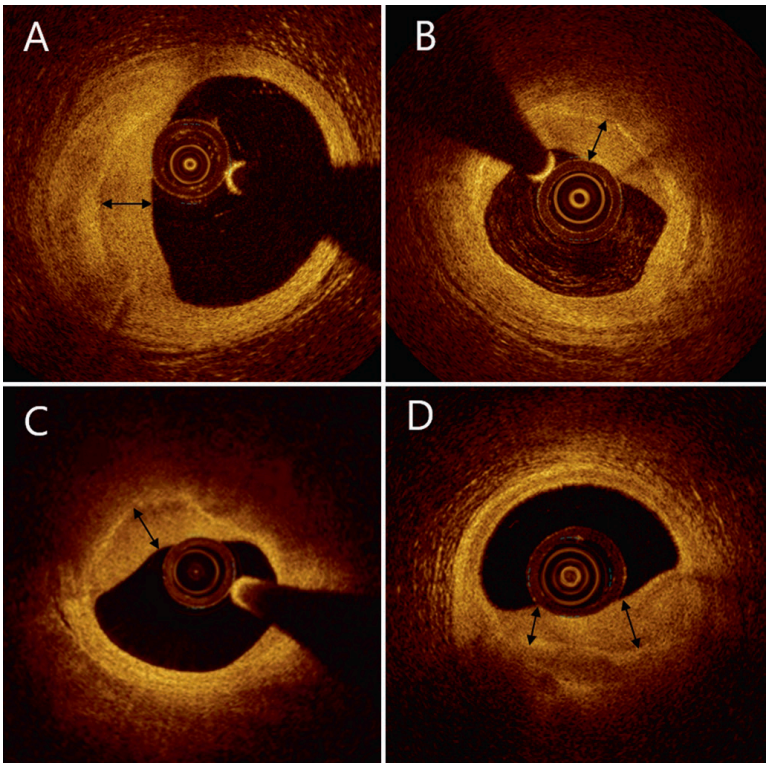


FIG 14: Healed plaque in patients with stable coronary artery disease (64)

Turning instead to the phenomena that clinically cause acute coronary syndromes, Figure 15 shows plaque rupture (15A), plaque erosion (15B) and a calcified nodule (15D).

Plaque rupture is characterised by the presence of a discontinuity in the fibrous cap with the formation of a cavity within the plaque.

Plaque erosion is characterised by the presence of an attached thrombus overlying an intact and visualised plaque.

Finally, the calcified nodule appears on OCT as a single or multiple regions of calcium protruding into the lumen with destruction of the fibrous cap, frequently forming sharp, protruding edges, and the presence of substantial calcium proximal and/or distal to the lesion (61).

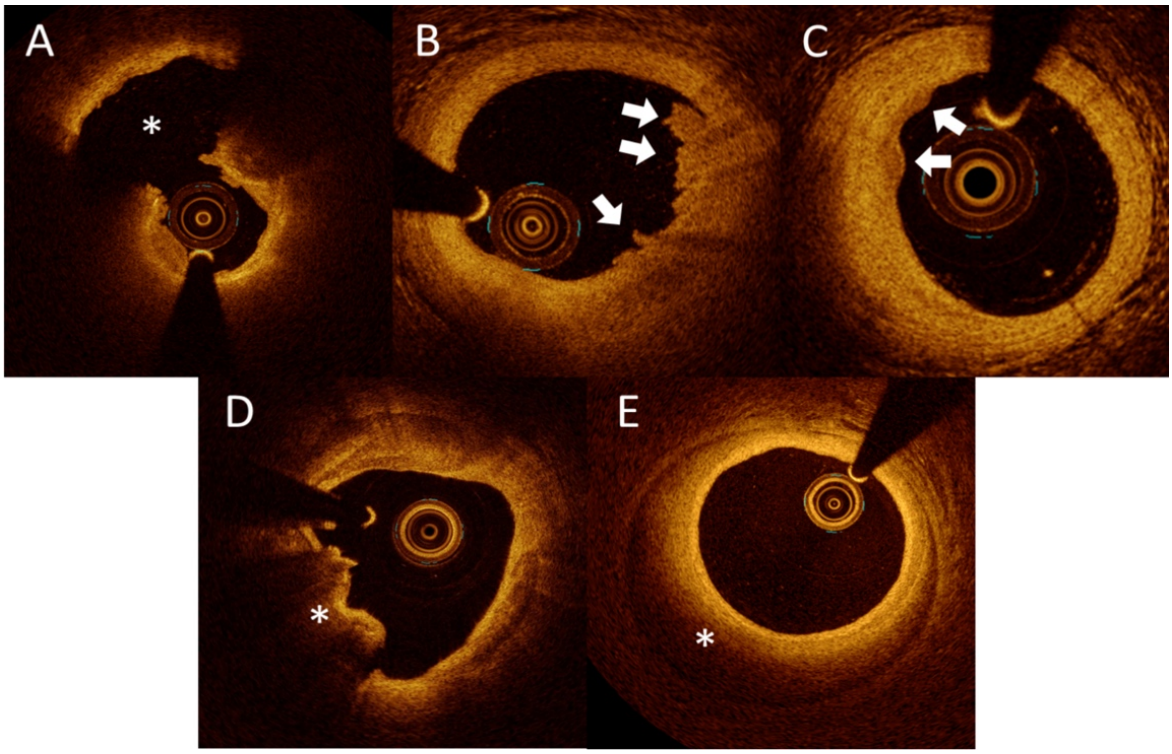


FIG 15: Culprit lesions in ACS patients (61)

4.2.4 OCT Artefacts

It is essential be aware of the limitations of OCT imaging technology and the artefacts it can produce, in order to correctly interpret plaque vulnerability, disease burden and prognosis before and after stent implantation. Furthermore, for some artefacts, if recognised, it is possible to make corrections to obtain a better interpretation of the images.

Among the causes that can give rise to artefacts is the propagation of the light within the catheter, the lumen or the vessel wall: this is centred at approximately 1300 nanometres and is capable of penetrating through most of the elements constituting the arterial wall to a depth of 1-2 mm; however, there are certain constituents of the vessel wall and external structures that attenuate it.

Artifacts may also result from the position or movement of the catheter: the appearance of the OCT image can in fact be altered both by the centred or off-centre position of the catheter within the vessel lumen, and by the rotation of the catheter and the speed of the pullback.

Finally, artefacts may be associated with the presence of a stent: metal stents strongly back-scatter light and are visible on OCT as small bright segments (64).

Guide Wire Shadow

All current images produced using OCT technology contain an artefact caused by the guide wire. The guide wire is used to guide the catheter along the coronary artery being examined and creates a shadow cone that completely obscures the features of the underlying tissue, as indicated by the asterisk shown in figure 16 (64).

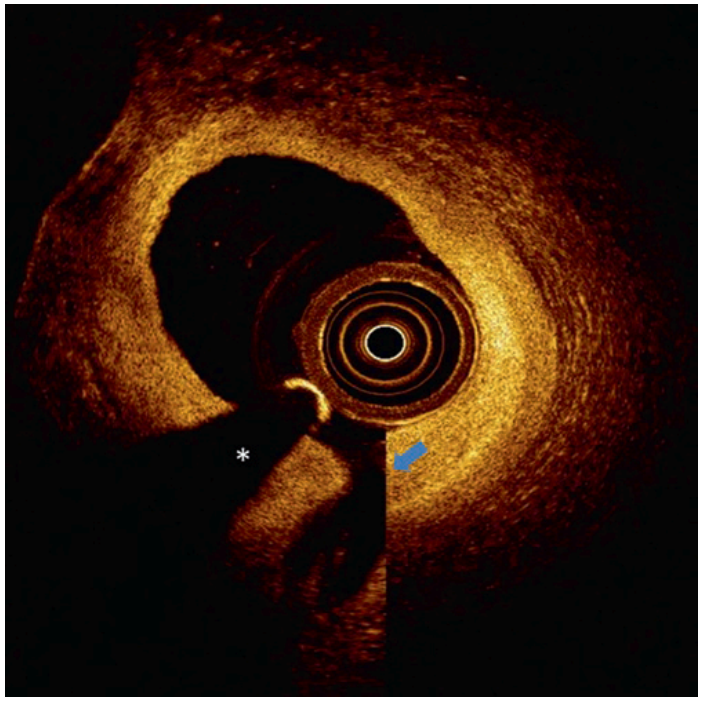


FIG 16: Guide wire shadow (64)

Ghost Lines

Ghost lines are circular structures that should not be regarded as representative of the vessel wall. A ghost line is caused by the reflection of light from at least two interfaces within the interferometer, which may include the catheter (figure 17) (64).

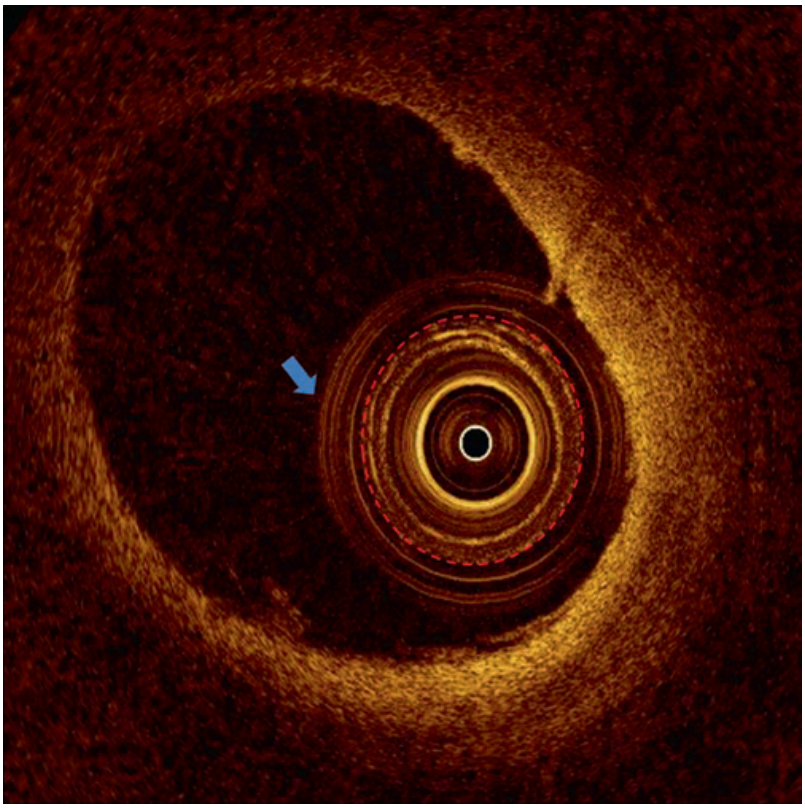


FIG 17: OCT image with ghost lines (blue arrow) around the catheter sheath (red dotted line) (64)

Residual blood from incomplete lumen flushing

When blood is not completely cleared from the lumen during OCT imaging, artefacts may arise due to light scattered by red blood cells. Such artefacts may appear as areas of hight signal intensity (in contrast to the standard image, which features a transparent lumen completely devoid of signal), and this can cause shadowing that reduces the OCT signal intensity of the arterial wall, making it difficult to interpret its structure (figure 18) (64).

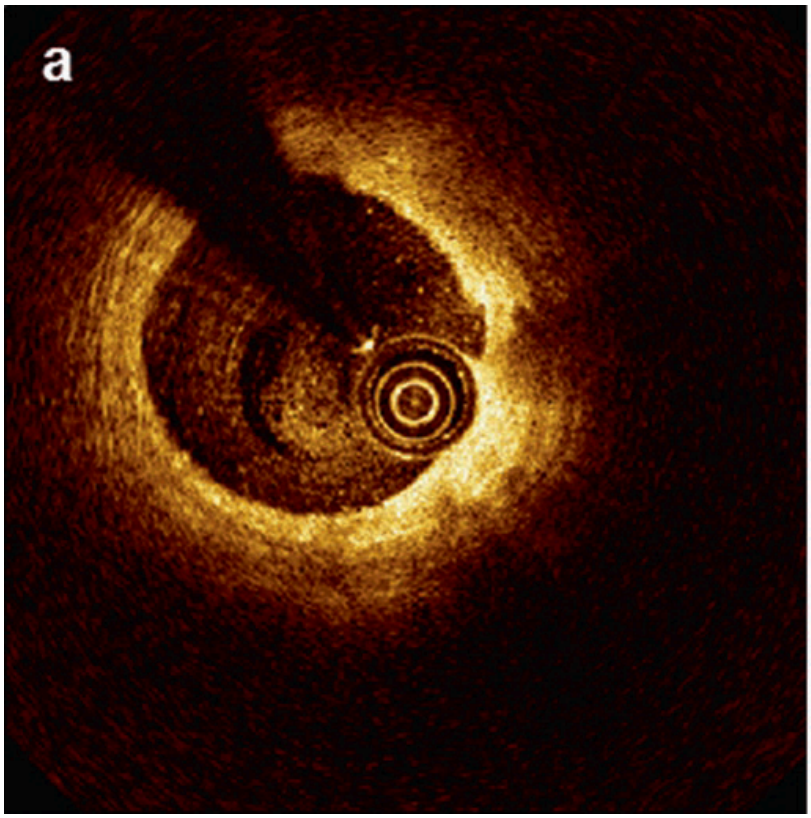


FIG 18: Coronary artery with "spotty" luminal blood due to poor clearance (64)

Thrombus

Thrombi can also cause shadowing artefacts; they can form on the surface of the arterial wall, on the stent struts or on the catheter, and when they are positioned close to the catheter, the shadow cone generated is larger.

Red clots, formed from red blood cells, produce a shadow that reduces the signal intensity from the arterial wall and also obscured the back side of the clot furthest from the light source (figure 19A).

On the other hand, white clots attenuate the signal with less intensity (figure 19B) (64).

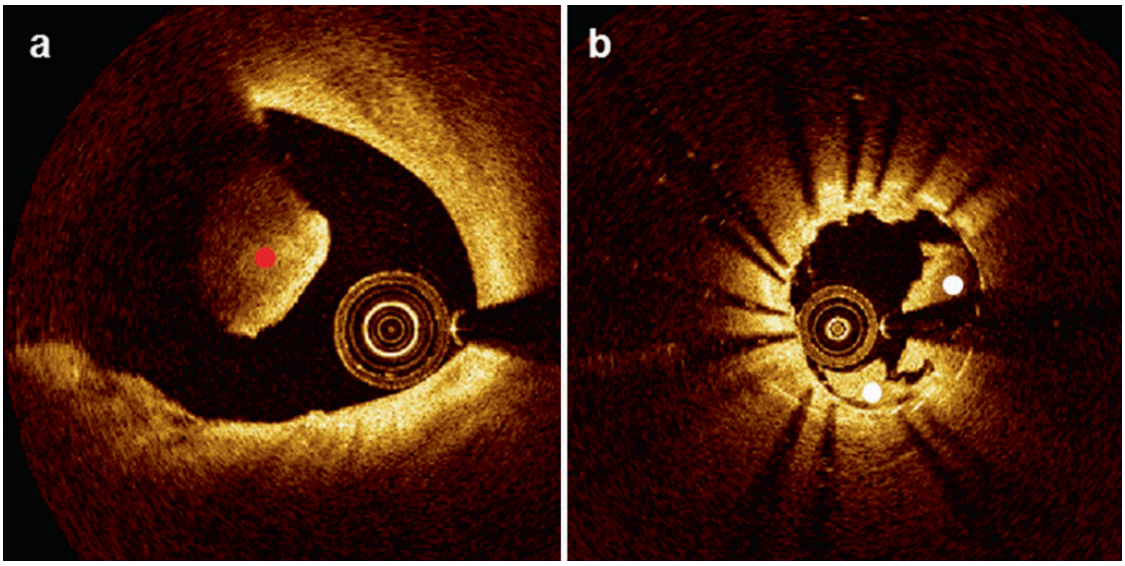


FIG 19: a) Red blood clot (denoted by red dot) causing complete attenuation of the OCT beam. (**b**) White blood clot (denoted by white dots) within a stented vessel causing partial attenuation of the OCT beam

Superficial shadowing by macrophages

As mentioned in the previous paragraph, macrophages appear as hight-intensity punctate regions accompanied by a shadow cone behind them due to their high backscatter characteristics.

Cluster of macrophages can therefore cast shadows that may be mistaken for an underlying lipid pool or a necrotic core. This shadowing is primarily caused by the fact that macrophages are rich in lipids (foam cells) and therefore exhibit attenuation characteristics due to their low refractive index. Furthermore, such clusters of macrophages are often associated with compact structures with a high refractive index, such as microcalcifications and cholesterol crystals (figure 20) (64).

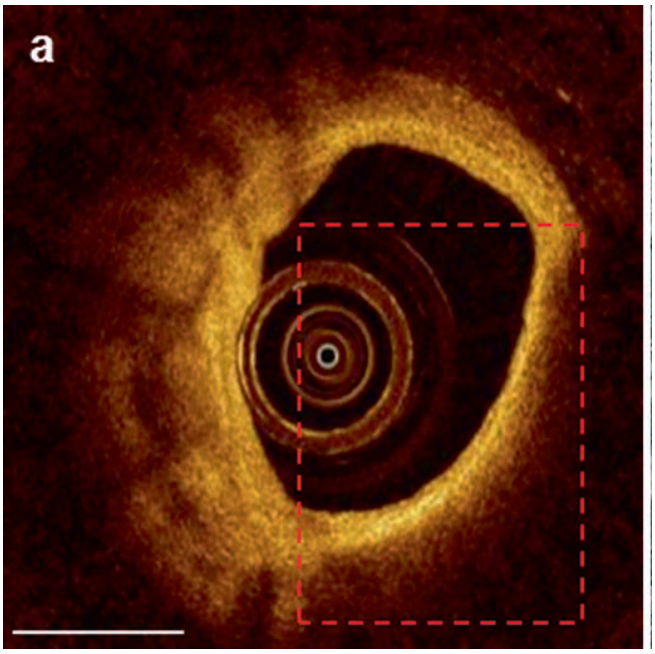


FIG 20: Superficial macrophages infiltration causes appearance of false TCFA (64)

Metallic stents

Metal stents block incident OCT light and therefore cast shadows behind each strut. This can significantly complicate the characterisation of the underlying tissue structure, as a substantial portion of the arterial cross-section is obscured by these shadows (figure 21) (64).

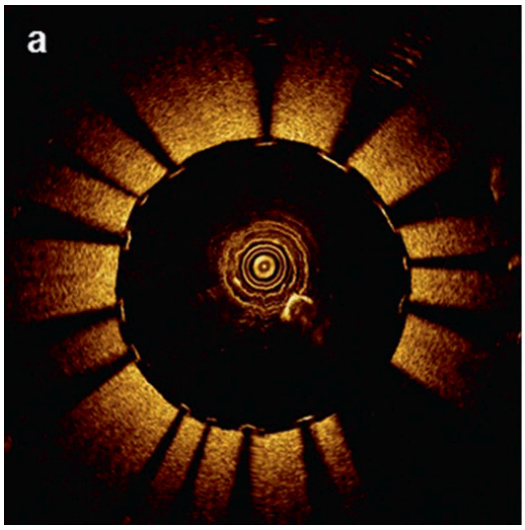


FIG 21: Stented vessel

5 DIABETES MELLITUS

5.1 Epidemiology

The number of people with diabetes worldwide was estimated to be between 589 million and 828 million during 2022 to 2024; moreover globally, 32.2% of people with type 2 diabetes have cardiovascular disease (78).

5.2 Definition and classification

Diabetes mellitus is a group of disorders of carbohydrate metabolism characterised by hyperglycaemia: this condition is caused by impaired insulin secretion by pancreatic β-cells and/or reduced sensitivity of target tissues to the action of insulin (insulin resistance). This imbalance leads to inefficient utilisation of glucose as an energy substrate and to its excessive endogenous production via inappropriate gluconeogenesis and glycogenolysis. Within this condition, several clinical categories are distinguished; the main ones are type 1 diabetes, type 2 diabetes, gestational diabetes and genetic forms of diabetes.

This classification is important to set up an appropriate treatment plan; however, at the time of diagnosis, the various forms are not always clearly distinguishable, as they may present with subtle clinical features (78, 79).

5.2.1 Type 1 diabetes

Type 1 diabetes mellitus accounts for 5–10% of all cases of diabetes and is the most common form of diabetes in childhood and adolescence, although it can occur at any age.

In most cases, it is caused by the autoimmune destruction of pancreatic beta cells, leading to a progressive deficiency of insulin until production ceases entirely (as demonstrated by low or undetectable levels of C-peptide in plasma).

The autoantibodies found in this type of diabetes are directed against both the cells of the islets of Langerhans and against insulin, glutamate decarboxylase (GAD), tyrosine phosphatase, pancreatic islet antigen 2 and the zinc transporter. Furthermore, these antibodies may appear very early in a person's life, making them useful for the early identification of the condition, even before it manifests clinically.

The causes triggering this autoimmune process include both genetic and environmental factors, although these remain poorly understood: from a genetic perspective, type 1 diabetes

is strongly associated with specific variants of the HLA system, particularly the DQB1 and DRB1 genes; among environmental factors, however, certain viral infections appear to play a role, such as those caused by enteroviruses (e.g. Coxsackie B) and the SARS-CoV-2 virus. Clinical symptoms do not occur until more than 80% of the pancreatic islets have been destroyed, and the rate at which the disease progresses is highly variable, often rapid in children and adolescents, whilst in adults the process may be slower. Frequently, in fact, type 1 diabetes in young people is diagnosed when symptoms are already evident and blood glucose levels are very high, and in a significant proportion of cases (up to 50%) the diagnosis is made in the presence of diabetic ketoacidosis (DKA).

Furthermore, type 1 diabetes is frequently associated with other autoimmune diseases, such as Hashimoto's thyroiditis, Graves' disease, coeliac disease, Addison's disease, vitiligo and autoimmune hepatitis. In some rarer cases, diabetes may form part of complex genetic autoimmune syndromes (79).

5.2.2 Type 2 diabetes

Type 2 diabetes is the most common form of diabetes, accounting for around 90–95% of all cases. Unlike type 1 diabetes, it is not caused by an autoimmune process: the pancreatic β-cells are not destroyed, but do not function properly. In particular, two main phenomena coexist: on the one hand, a reduced response of tissues to the action of insulin (insulin resistance), and on the other, a deficiency in insulin production, which becomes increasingly evident over time. At the onset of the disease, in fact, insulin levels may be normal or even elevated, but insufficient to compensate for insulin resistance; over time, the ability of β-cells to respond adequately to glucose is progressively reduced.

The causes of type 2 diabetes are numerous and not yet fully understood, but they certainly include genetic predisposition, epigenetic changes, inflammation and metabolic stress. It has been observed that type 2 diabetes is more common among first-degree relatives of affected individuals and that, in most cases, the condition is associated with being overweight or obese, conditions that directly contribute to the development of insulin resistance.

The risk of developing type 2 diabetes also increases with age, a sedentary lifestyle, in individuals with high blood glucose levels (prediabetes), in women with a previous diagnosis of gestational diabetes, and in individuals with polycystic ovary syndrome (79).

5.3 Diagnosis

A key element in the management of type 2 diabetes is early screening, particularly as the condition has a long asymptomatic phase. Identifying prediabetes or early-stage diabetes is crucial, as it allows for timely intervention and helps reduce long-term complications.

According to the American Diabetes Association's (ADA) 'Standards of Medical Care in Diabetes' (79), diabetes and prediabetes can be diagnosed based on plasma glucose criteria or HbA1c criteria: with regard to plasma glucose, one can assess the fasting plasma glucose (FPG) level, the glucose level 2 hours after a 75 g oral glucose tolerance test (OGTT), or an abnormal glucose level accompanied by the classic symptoms of hyperglycaemia (polyuria, polydipsia and unexplained weight loss). Furthermore, in the absence of unequivocal hyperglycaemia (hyperglycaemic episode), diagnosis requires two abnormal results (from the same sample or in two separate tests).

Table 2.1—Criteria for the diagnosis of diabetes in nonpregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results obtained at the same time (e.g., A1C and FPG) or at two different time points.

FIG 22: Criteria for the diagnosis in non-pregnant individuals (79)

In addition, the term 'prediabetes' refers to an intermediate stage characterised by a high risk of progression to full-blown diabetes and cardiovascular disease. The term IFG (Impaired Fasting Glucose) is used when fasting blood glucose levels are abnormal, while IGT (Impaired Glucose Tolerance) refers to a reduced tolerance to glucose identified via an OGTT.

Table 2.2—Criteria defining prediabetes in nonpregnant individuals
A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

FIG 23: Criteria defining prediabetes in non-pregnant individuals (79)

Finally, diabetes screening is recommended on the basis of risk factors or using risk assessment tools, such as questionnaires developed by diabetes associations. These tools take various factors into account, including age, gender, family history, blood pressure, level of physical activity and body weight, to estimate the likelihood of developing diabetes (79).

5.4 Clinical manifestations

Classic symptoms of diabetes include polyuria, leading to polydipsia and dehydration, and polyphagia with unexplained weight loss; these symptoms are typical of type 1 diabetes, which often has an acute onset, and rarely of type 2 diabetes, except in cases of very severe hyperglycaemia. More non-specific symptoms may also be present, such as fatigue, restlessness, growth disturbances and increased susceptibility to infections.

The acute complications with which diabetes may present are diabetic ketoacidosis, typical of type 1 diabetes, and hyperosmolar coma, typical of type 2 diabetes; both have a rapid onset and are potentially fatal. Diabetic ketoacidosis is rare in type 2 diabetes and, when it does occur, is generally linked to specific situations, such as infections, heart attacks, the use of drugs or specific medications (e.g. glucocorticoids or certain antipsychotics), or inadequate management of insulin therapy.

Furthermore, as type 2 diabetes has a slower and more compensated onset, it can often remain asymptomatic for many years and then present itself in the form of a complication (78, 79).

5.5 Complications

As both are characterised by hyperglycaemia, both type 1 and type 2 diabetes carry a similar risk of developing long-term complications.

Chronic complications usually develop after many years (10–20) and are divided into two main types: microvascular complications, such as nephropathy, retinopathy and neuropathy, and macrovascular complications, which include cardiovascular disease, cerebrovascular disease and peripheral artery disease (80, 81).

While the precise mechanisms of hyperglycaemia-induced vascular damage are both complex and not fully understood, it is thought that high levels of intracellular glucose increase the production of reactive oxygen species, altering a series of critical downstream pathways, including polyol pathway flux, advanced glycation end product formation and activation, protein kinase C activation, and hexosamine pathway flux (80).

5.5.1 Microvascular complications

Diabetic nephropathy

Diabetic nephropathy is the most common cause of end-stage kidney disease (ESKD) and is a progressive disorder affecting the blood vessels that make up the renal glomerulus, characterised primarily by two clinical markers: a reduction in glomerular filtration rate and the presence of albuminuria.

Particularly in individuals with type 2 diabetes, it is possible that kidney disease is not directly attributable to hyperglycaemia, but rather to factors independent of or indirectly related to diabetes, such as hypertension, obesity or dyslipidaemia. The temporal relationship between the diagnosis of diabetes and the onset of kidney damage can help distinguish between the two conditions.

Several studies on diabetic nephropathy have also highlighted a strong familial clustering in both T1D and T2D.

Treatment of this condition involves managing blood glucose levels, proteinuria and progressive kidney damage up to the advanced stages of renal failure, when dialysis or kidney transplantation is generally necessary for survival (81).

Diabetic retinopathy

Diabetic retinopathy is the most common complication of diabetes, with an overall prevalence in people with diabetes of around 35%, with wide variation between ethnic groups and populations globally; furthermore, it is the leading cause of blindness in adults in the United States and England.

Hyperglycaemia causes progressive damage to the retinal blood vessels, which can lead to haemorrhage, retinal detachment and blindness.

Diabetic retinopathy can be classified into an early, more common, non-proliferative form (NPDR), characterised by weakened blood vessels, and a more severe, late-stage form (PDR), characterised by the growth of new, fragile and permeable blood vessels throughout the retina and in the vitreous body of the eye. A distinct form, however, involves direct damage to the macula, defined as clinically significant macular oedema.

The severity of diabetic retinopathy is associated with the duration of diabetes, age at diagnosis, HbA1c levels, blood pressure, insulin use and the presence of proteinuria (81).

Diabetic neuropathy

Diabetic neuropathy affects around 30% of people with diabetes and over 50% of those with diabetes aged over 50.

Like other vascular complications of diabetes, it is a multifactorial condition associated with various risk factors, such as HbA1c levels, high blood pressure, smoking and BMI, and also has a genetic component.

Diabetic neuropathy mainly affects the peripheral nerves in the lower limbs, due to their greater length, and can be divided into several subtypes: symmetrical distal polyneuropathy (the most common form), autonomic neuropathies and atypical neuropathies.

From a clinical perspective, in addition to pain and a reduced quality of life, nerve damage increases the lifetime risk of foot ulcers in diabetic patients by 15–25% and the risk of lower limb amputation by 15 times compared with individuals without diabetes. (80, 81).

5.5.2 Macrovascular complications

Macrovascular complications affect large blood vessels and occur in approximately 20–30% of people with diabetes, contributing significantly to the morbidity and mortality rates associated with type 2 diabetes.

Hyperglycaemia, obesity and insulin resistance lead to increased production of reactive oxygen species and a reduction in the vasodilatory action of nitric oxide, thereby causing endothelial dysfunction and subsequent atherosclerotic changes (81).

Cardiovascular disease

Cardiovascular disease is the leading cause of death among patients with type 2 diabetes and accounts for over 70% of deaths.

Globally, coronary heart disease affects approximately 32.2% of all individuals with type 2 diabetes. Furthermore, diabetes mellitus is strongly associated with an increased risk of ischaemic heart disease, such that diabetic patients have a significantly higher 7-year risk of myocardial infarction compared with non-diabetic individuals, regardless of a previous history of myocardial infarction (81).

Cerebrovascular disease

Cerebrovascular disease affects between 20% and 40% of people with type 2 diabetes and is also one of the leading causes of mortality and morbidity in this population.

This condition manifests itself primarily in the form of two clinical entities, namely ischaemic stroke and haemorrhagic stroke: the mechanisms through which diabetes (along with other risk factors such as hypertension, dyslipidaemia, smoking and age) influences the onset of cerebrovascular disease are different and not yet fully understood; however, the common factor is accelerated atherosclerosis, which promotes endothelial dysfunction (81).

Peripheral arterial disease

Peripheral arterial disease results from atherosclerotic occlusion of the arteries supplying the lower limbs.

The most common symptom characterising this condition is intermittent claudication, that is the sensation of cramps and pain in the leg, thigh or buttock that occurs after a certain period of time whilst the person is walking.

Diabetes mellitus is associated with a higher risk of peripheral arterial disease, with a 2- to 4-fold increase compared to the risk of cardiovascular or cerebrovascular disease. The pathogenic mechanism associated with diabetes is similar to that of other macrovascular complications and involves alterations in the vascular wall through the promotion of vascular inflammation, endothelial cell dysfunction, blood cell abnormalities and factors affecting haemostasis.

Several factors have also been identified that increase the risk of developing peripheral arterial disease in diabetic patients, and these include smoking, obesity, hypertension, hypercholesterolaemia, duration of diabetes, degree of hyperglycaemia, advanced age, male sex, elevated serum lipoprotein levels, insulin resistance, elevated serum fibrinogen levels, microalbuminuria and increased levels of intercellular adhesion molecules (81).

6 ATHEROSCLEROSIS AND DIABETES

There are numerous pathological pathways linking diabetes to atherosclerotic disease: hyperglycaemia, insulin resistance, dyslipidaemia, chronic inflammation, oxidative stress, endothelial dysfunction and pathological neovascularisation play a crucial role both in plaque formation and in its progression, as we will see, frequently towards an unstable phenotype (82).

6.1 Accelerated atherosclerosis in diabetic patients

It is well known that patients with diabetes mellitus have a high prevalence of multivascular atherosclerotic disease and an accelerated progression of plaque associated with glucose levels. (83).

It has been demonstrated that these patients have a two- to four-fold higher risk of death and cardiovascular events compared to the general population (84).

As mentioned, there are numerous factors that make diabetes an accelerator in the development of atherosclerotic disease, as also demonstrated by studies reporting early-onset atherosclerosis in adolescents and children with type 1 diabetes.

Hyperglycaemia certainly plays an important role in this process: in particular, prolonged states of hyperglycaemia lead to the production of AGEs (advanced glycation end-products), which influence endothelial activation and the surface expression of adhesion molecules, thereby promoting the entry of monocytes/macrophages into the subendothelial space. AGEs can also induce an increase in cytokine release by these cells, fuelling the pro-inflammatory environment within the plaque.

Another process that may occur is the glycation of LDL particles, a modification that can be considered atherogenic and which may therefore promote the accumulation of LDL in the subendothelial space.

It is also known that both diabetes and atherosclerosis are associated with a state of chronic inflammation: one of the direct links between atherosclerosis and diabetes identified within the inflammatory pathways is the activation of neutrophil extracellular traps (NETs), which can be exacerbated by hyperglycaemic conditions.

Finally, diabetes is associated with increased production of reactive oxygen species (ROS) and reduced activity of antioxidant systems, another factor that undoubtedly promotes endothelial dysfunction and the development of atherosclerosis (82).

6.2 Impaired healing in diabetic patients

As we have mentioned, hyperglycaemia, insulin resistance and dyslipidaemia promote the release of pro-inflammatory factors and increase the inflammatory activity of macrophages, leading to a chronic inflammatory state that accelerates the processes of atherosclerosis, vascular inflammation and endothelial dysfunction (85).

We saw in the previous chapter that healthy endothelium possesses anticoagulant, antiplatelet and fibrinolytic properties; consequently, the term 'endothelial dysfunction' encompasses various pathological conditions, including alterations in the anticoagulant and anti-inflammatory properties of the endothelium, impaired modulation of vascular growth and dysregulation of vascular remodelling with abnormal neoangiogenesis.

It has been observed that patients with type 2 diabetes mellitus and poor glycaemic control exhibit reduced FMD (flow-mediated dilation), a non-invasive method for assessing endothelial function, associated with greater severity of coronary artery disease compared to those with adequate glycaemic control. This dysfunction is primarily characterised by reduced nitric oxide (NO) bioavailability and excessive production of reactive oxygen species (ROS), factors that negatively influence plaque stability.

In the same context, endothelial progenitor cells (EPCs), a cellular subgroup of myeloid origin, play a fundamental role in vascular repair, thanks to their ability to replace damaged endothelial cells and differentiate into functional endothelial cells. In patients with metabolic abnormalities, such as compensatory hyperinsulinemia, impaired fasting glucose, glucose intolerance and diabetes, a reduction in both the number and function of EPCs has been demonstrated. Cardiovascular risk factors indeed interfere with the differentiation, function and recruitment of these cells (86).

Chronic exposure to hyperglycaemia leads to a loss of endothelial cell integrity, progression towards senescence and apoptosis. The resulting cell detachment and release into the circulation leads to endothelial denudation, triggering a cascade of pro-atherosclerotic events, including platelet adhesion and aggregation, inflammation, proliferation and migration of smooth muscle cells, and extracellular matrix deposition.

In individuals with impaired glucose metabolism, reduced levels of circulating EPCs are observed, attributable to impaired mobilisation, reduced proliferation and decreased survival; several mechanisms contribute to these alterations, including reduced NO availability, defects in intracellular signalling, inflammation, the role of adipokines, increased ROS, and the direct effects of insulin and IGF-1. Furthermore, even after

mobilisation, fundamental processes such as homing to sites of vascular damage, adhesion, integration into the endothelium, proliferation and differentiation are compromised, reducing overall regenerative capacity.

Systemic inflammation contributes to atherosclerotic pathology by stimulating pro-atherogenic adhesion molecules in mature endothelial cells and also interferes with EPC-mediated regeneration: inflammatory factors, in fact, compromise their survival, differentiation and function.

Adipocytes also contribute to impaired vascular repair in diabetic patients by producing pro-inflammatory cytokines, including TNF-α, which reduces EPC proliferation. Reactive oxygen species (ROS), which are elevated in diabetes, play a key role in endothelial damage and EPC dysfunction: they exert direct cytotoxic effects, reduce the bioavailability of NO by reacting with it, and generate peroxynitrite, a potent oxidant. Although EPCs from healthy individuals show relative resistance to oxidative stress, in diabetic patients ROS significantly compromise their function and survival (86).

In conclusion, all these findings observed in diabetic patients suggest that these individuals may have a reduced capacity of healing.

Indeed, several studies have shown that atherosclerotic plaques in diabetic patients tend to be predominantly lipid-rich and macrophage-rich, exhibiting a larger lipid arc, a thinner fibrous cap and a higher prevalence of TCFA in non-culprit plaques of the vessel responsible for acute coronary syndrome (87).

Furthermore, the study conducted by Yuzhu Chen et al (88) demonstrated that the prevalence of non-culprit plaques with high-risk morphological characteristics is higher in patients with poorly controlled diabetes mellitus compared to patients with good glycaemic control, and that the prevalence of high-risk non-culprit plaques tends to increase with higher levels of glycated haemoglobin.

7 CLINICAL TRIAL

7.1 The purpose of the study

Numerous pathological and in vivo studies have shown that there are three main pathological pathways that lead to acute coronary syndrome: plaque rupture, which accounts for approximately 60% of cases; plaque erosion, which accounts for approximately 30-40% of cases; and calcific nodules, responsible for 2-8% of cases (29, 32).

Moreover, pathological studies have shown that many plaques become unstable without giving rise to an acute clinical event: symptomatic coronary syndrome occurs, indeed, when plaque rupture or erosion takes place in a pro-thrombotic environment, leading to occlusive or sub-occlusive thrombosis. If, on the other hand, anti-thrombotic factors prevail, thrombus formation is limited and the phenomenon known as plaque healing occurs (20,45).
Healed plaque appears as a plaque with one or more layers of differing optical density, heterogeneous, and with a clear demarcation from the underlying components. This creates a characteristic onion-skin appearance, either without disruption of the old fibrous cap or with a disruption suggesting a previous rupture (20).
Recent evidence suggests also that healed coronary plaques are rarely observed in patients with a history of recurrent acute coronary syndromes, whereas they are much more common in patients with long-standing stable coronary artery disease or a history of a single acute myocardial infarction (47).

At the same time, it is well known that patients with diabetes mellitus have a high prevalence of multivascular atherosclerotic disease and an accelerated progression of plaque associated with glucose levels. This condition is supported by multiple pathogenic mechanisms, including hyperglycemia, chronic inflammation, oxidative stress and endothelial dysfunction, which promote plaque formation and instability (83).

The aim of this study is to use Optical Coherence Tomography and angiographic analysis to assess the presence and characteristics of plaques in diabetic patients and compare them with those of non-diabetic patients, in order to identify specific characteristics and patterns.

7.2 Materials and methods

7.2.1 Study Participants

In this single-centre observational study, patients with acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) who underwent Optical Coherence Tomography (OCT) imaging at Ospedale Policlinico San Martino - Istituto di Ricovero e Cura a Carattere Scientifico (IRCSS), were included.

A total of 74 patients undergoing OCT evaluation (1272 coronary segments) were included in the analysis, of whom 47 patients had no diabetes (853 segments) and 27 patients had diabetes mellitus (419 segments).

7.2.2 Clinical and bioumoral data

Through the Information System of Policlinico San Martino Hospital - Istituto di Ricovero e Cura a Carattere Scientifico (IRCSS), a series of bio-humoral and clinical data were collected for each patient.

The blood analyses include: Hemoglobin (g/dL), Platelts (n/μL), White Blood Cells (n/μL), Creatinine (mg/dL), eGFR (CG), Low-density lipoprotein (mg/dL), High density lipoprotein (mg/dL), Triglycerides (mg/dL), aPTT (sec), INR, D-dimer (μg/L), Glucose (mg/dL), HbA1c (%), TnI (ng/mL), PCR (mg/L).

We also recorded patients' therapies at admission and discharge, checking the following drugs: B-block, ACE-i, Sartans, ARNI, Statins, Ezetimibe, PCSK9-i, Inclisiran, Bempedoic Acid, ASA, Clopidogrel, Prasugrel, Ticagrelor, Heparin, Fondaparinux, NAO, VKA, Ca-channel blocke, SGLT2-i, oral hypoglycemic drugs, and Insulin.

7.2.3 OCT Analysis

OCT analysis was performed offline using registered software (LightLab Imaging) by 2 independent investigators who were unaware of the clinical and laboratory data reported by the patients. In case of disagreement between observers, consensus was sought with a third investigator.

Pullbacks were obtained after intravascular administration of 200 μg nitroglycerin using an FD-OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN). Automatic pullbacks were acquired simultaneously with contrast injection according to blood clearance. Analysis was performed by dividing the vessels into 3-mm segments.

Atherosclerotic plaque appears on OCT as a region with loss of the typical three-layer structure (intima, media, and adventitia) that normally characterizes the vessel wall or as a mass-forming lesion.

The lipid plaque is defined as a region with blurred edges and low signal intensity superimposed on a layer of intense signal corresponding to the fibrous cap. The lipid arc was calculated for each mm, and the lipid length was calculated as the distance between the first and last section where lipids were visible in the context of the 3-mm segment. The lipid index was calculated as the product of lipid arc and lipid length. A lipid plaque with a lipid arc > 90° was considered lipid-rich. The thickness of the fibrous cap was measured three times at the thinnest point and the average of the three measurements was calculated. If the calculated fibrous cap thickness is < 65 μm, the lipid-rich plaque is defined as TCFA (thin-cap fibroatheroma).

Fibrous plaque is defined as a region of intense and homogeneous signal at least 600 μm thick. Pathologic intimal thickening (PIT) is defined as an intimal thickening of at least 300 μm.

Healed plaque is defined as a plaque with at least one signal-intensive heterogeneous layer with different optical properties adjacent to the luminal surface and clearly demarcated from the underlying tissue.

Calcifications are areas of hypointense or heterogeneous signal demarcated by well-defined borders. Calcifications that subtend an arc < 90° and are less than 4 mm in length are classified as "patchy calcifications".

Macrophage accumulation is defined as the presence of bright punctate signals (bright spots), either distinct or confluent, of intense signal that exceeds background signal intensity and creates a shadow posteriorly.

Neovascularization is defined as the presence of microchannels (diameter 50-330 μm) appearing as small circular or ovoid structures (small black holes), of low signal intensity, located in the intima and without connection to the vessel lumen, present in at least 3 consecutive image segments.

7.2.4 Statistical Analysis

Categorical variables were reported as counts (percentages) and compared using either the Chi-square test or Fisher's exact test. Following assessment of data distribution with the Kolmogorov-Smirnov test, continuous variables were expressed as mean ± standard

deviation or median (interquartile range), and comparisons were performed using the independent samples Student's t test or the Mann-Whitney U test, as appropriate.

Segment-based comparisons were conducted using generalized estimating equations (GEE) to consider potential cluster effects of multiple segments in a single patient. Multivariate logistic regression analysis was performed to assess the independent clinical predictors of healed plaques. All statistical tests were two-sided. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS v.21.0 (SPSS, Inc., Chicago, IL, USA).

7.3 Results

7.3.1 Baseline clinical characteristics

A total of 74 patients undergoing OCT evaluation were included in the analysis, of whom 47 patients had no diabetes and 27 patients had diabetes mellitus. Baseline clinical characteristics according to diabetes status are summarized in Table 1.

Patients with diabetes were significantly older compared with those without diabetes (71.0 ± 10.0 vs. 64.7 ± 10.7 years; p=0.013), whereas sex distribution was similar between groups (male sex: 77.8% vs. 76.6%; p=0.907). No significant differences were observed in BMI, prevalence of hypertension, current smoking, or dyslipidemia. Family history of coronary artery disease (CAD) tended to be more frequent in patients with diabetes, although it did not reach statistical significance. Clinical presentation was also comparable, with ACS being the indication for OCT evaluation in 63.0% of patients with diabetes and 57.4% of those without diabetes (p=0.642).

Regarding previous cardiovascular history, patients with diabetes showed numerically higher rates of prior ACS (40.7% vs. 25.5%; p=0.174), prior PCI (48.1% vs. 27.7%; p=0.076), and prior CABG (7.4% vs. 2.1%; p=0.268), without reaching statistical significance. As expected, glucose levels (160.2 ± 55.6 vs. 108.4 ± 20.4 mg/dl; p<0.001) and HbA1c values (7.6 ± 1.4% vs. 5.6 ± 0.6%; p<0.001) were significantly higher among patients with diabetes.

Patients with diabetes were more frequently treated with statins (66.7% vs. 36.2%; p=0.011), ACE inhibitors/ARBs (66.7% vs. 42.6%; p=0.046), oral antidiabetic drugs (66.7% vs. 0%; p<0.001), insulin (40.7% vs. 0%; p<0.001), and SGLT2 inhibitors (22.2% vs. 2.1%;

p=0.004).

Table 1. Patient baseline characteristics

	No Diabetes (n=47)	Diabetes (n=27)	P value
Age, years	64.7 ± 10.7	71.0 ± 10.0	0.013
Male sex	36 (76.6%)	21 (77.8%)	0.907
BMI, kg/m^2	27.4 ± 5.0	26.8 ± 4.3	0.667
Hypertension	32 (68.1%)	23 (85.2%)	0.105
Current smoking	14 (29.8%)	7 (25.9%)	0.723
Dyslipidemia	22 (46.8%)	16 (59.3%)	0.302
Family history of CAD	17 (36.2%)	4 (14.8%)	0.050
Clinical presentation			
CCS	20 (42.6%)	10 (37.0%)	0.642
ACS	27 (57.4%)	17 (63.0%)	
Prior ACS	12 (25.5%)	11 (40.7%)	0.174
Prior stroke	0 (0.0%)	2 (7.4%)	0.059
Prior PCI	13 (27.7%)	13 (48.1%)	0.076
Prior CABG	1 (2.1%)	2 (7.4%)	0.268
Creatinine, mg/dl	1.1 ± 0.9	1.4 ± 1.3	0.200
Glucose, mg/dl	108.4 ± 20.4	160.2 ± 55.6	<0.001
HbA1c, %	5.6 ± 0.6	7.6 ± 1.4	<0.001
Medications on admission			
Aspirin	17 (36.2%)	15 (55.6%)	0.105
P2Y12i	10 (21.3%)	7 (25.9%)	0.647
Statin	17 (36.2%)	18 (66.7%)	0.011
Beta-blocker	18 (38.3%)	16 (59.3%)	0.082
ACEi/ARBs	20 (42.6%)	18 (66.7%)	0.046
Oral antidiabetic drugs	0 (0.0%)	18 (66.7%)	<0.001
Insulin	0 (0.0%)	11 (40.7%)	<0.001
SGLT2i	1 (2.1%)	6 (22.2%)	0.004

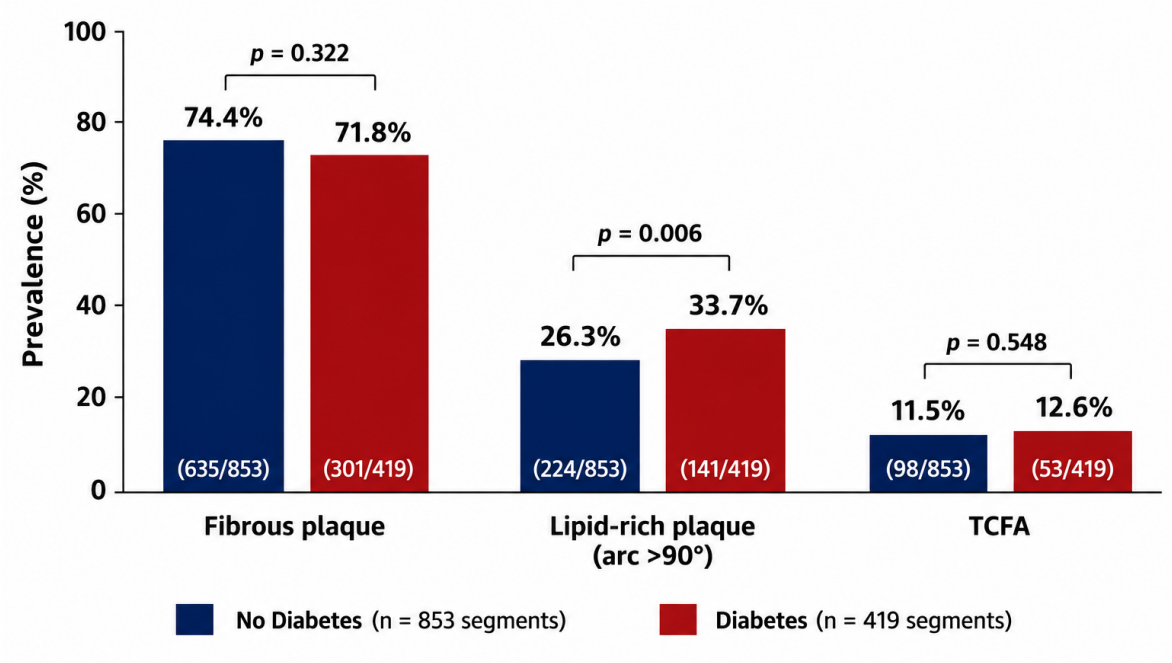
Data are reported as mean ± standard deviation or number (percentages).
ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; HbA1c, glycated hemoglobin; PCI, percutaneous coronary intervention; P2Y12i, P2Y12 receptor inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

7.3.2 OCT-derived plaque characteristics according to diabetes status

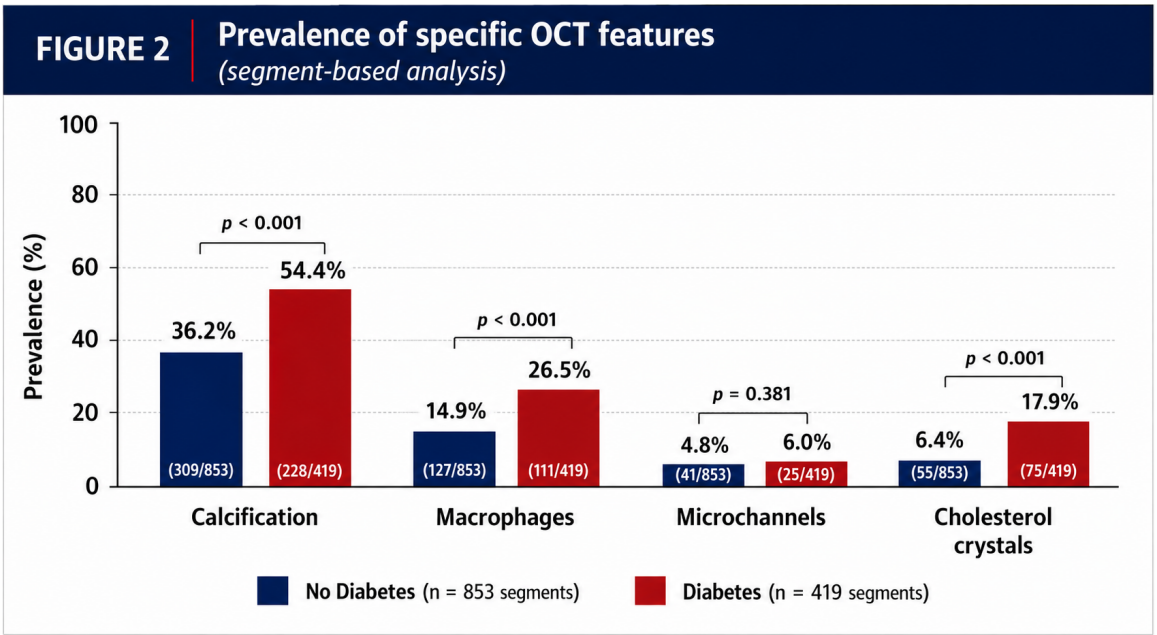
Segment-based OCT analysis included 1272 coronary segments, including 853 segments from patients without diabetes and 419 segments from patients with diabetes.

The prevalence of fibrous plaques was similar between patients without and with diabetes (74.4% vs. 71.8%; p=0.322). Conversely, lipid-rich plaques were significantly more frequent in patients with diabetes (33.7% vs. 26.3%; p=0.006). The prevalence of thin-cap fibroatheroma (TCFA) did not differ significantly between groups (12.6% vs. 11.5%; p=0.548) (Figure 1).

FIGURE 1 **Prevalence of main plaque phenotype** *(segment-based analysis)*



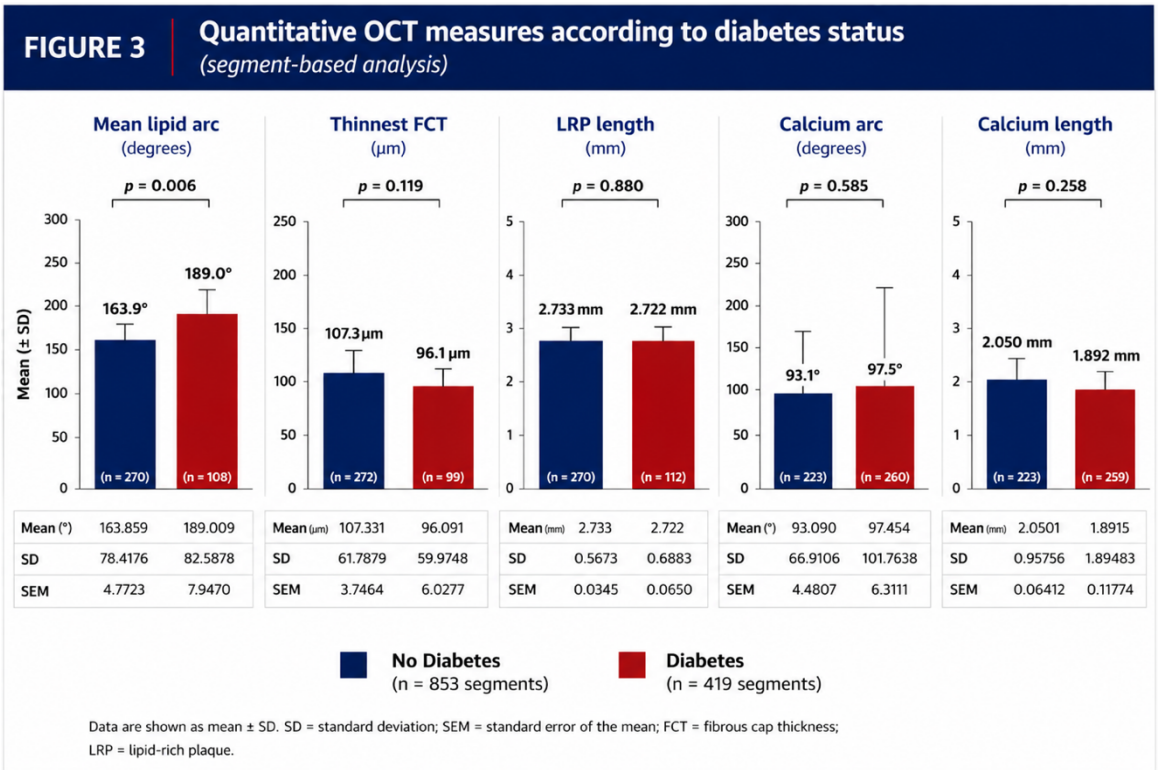
Additional OCT high-risk plaque features were more commonly observed in patients with diabetes. In particular, compared with patients without diabetes, diabetic patients showed a higher prevalence of calcification (54.4% vs. 36.2%; p<0.001), macrophage accumulation (26.5% vs. 14.9%; p<0.001), and cholesterol crystals (17.9% vs. 6.4%; p<0.001). No significant difference was observed in microchannels (6.0% vs. 4.8%; p=0.381) (Figure 2).



7.3.3 Quantitative OCT plaque assessment

Quantitative OCT analysis demonstrated that patients with diabetes had significantly larger lipid burden, reflected by greater mean lipid arc compared with patients without diabetes (189.0° vs. 163.9°; p=0.006).

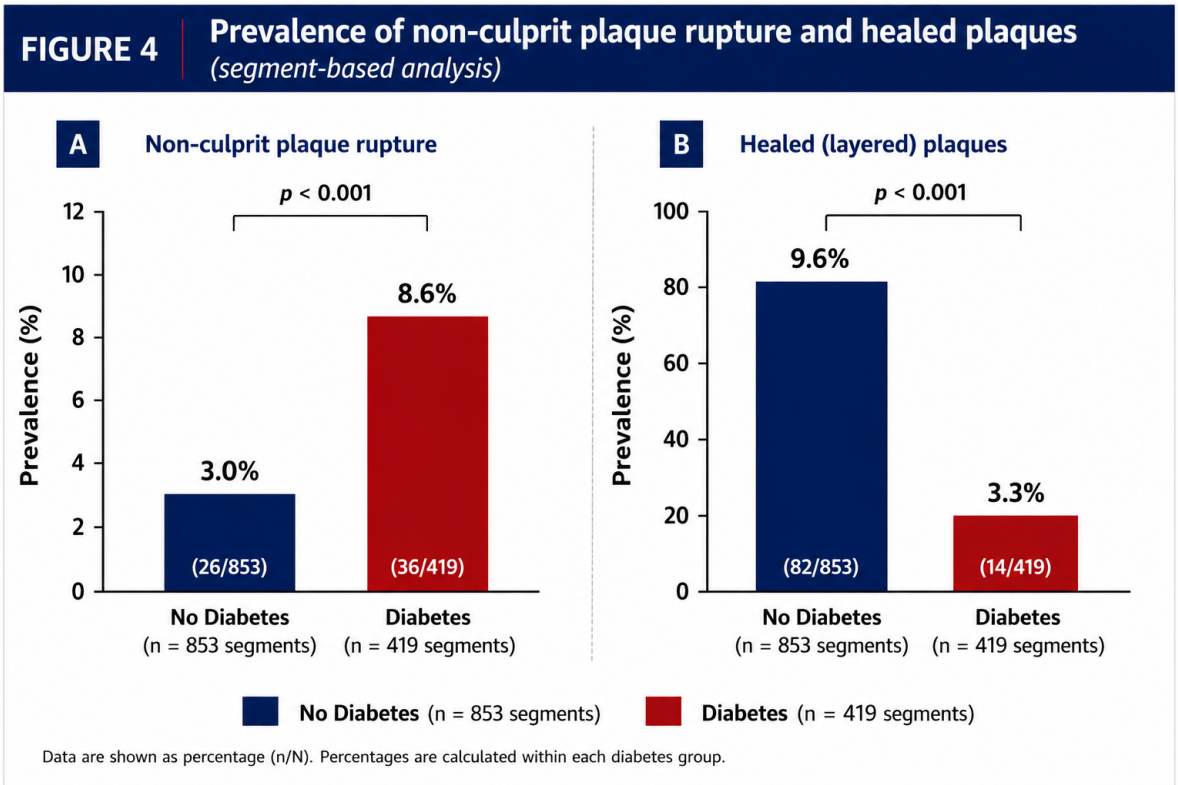
No significant differences were observed in other quantitative OCT measurements, including thinnest fibrous cap thickness (96.1 vs. 107.3 µm; p=0.119), lipid-rich plaque length (2.72 vs. 2.73 mm; p=0.880), calcium arc (97.5° vs. 93.1°; p=0.585), and calcium length (1.89 vs. 2.05 mm; p=0.258) (Figure 3).



7.3.4 Plaque rupture and plaque healing according to diabetes status

The prevalence of non-culprit plaque rupture was significantly higher among patients with diabetes compared with those without diabetes (8.6% [36/419] vs. 3.0% [26/853]; p<0.001).

Conversely, healed layered plaques were significantly less frequently observed in patients with diabetes (3.3% [14/419]) compared with patients without diabetes (9.6% [82/853]; p<0.001), suggesting impaired plaque healing response in the presence of diabetes (Figure 4).



7.3.4 Impact of glycemic control on plaque healing

Among patients with available HbA1c assessment, plaque healing was evaluated according to glycemic control status. Patients with HbA1c ≥6.5% showed a significantly lower prevalence of healed layered plaques compared with patients with HbA1c <6.5% (21.4% [6/28] vs. 58.7% [27/46]; p=0.002) (Figure 5).

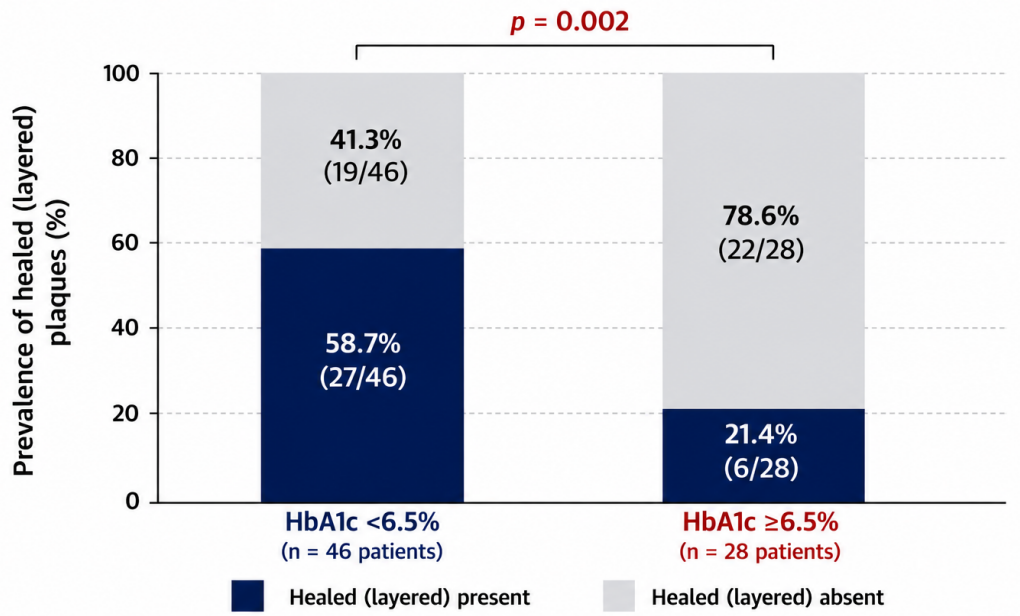
7.3.5 Independent predictors of plaque healing

Multivariable logistic regression analysis was performed to identify independent predictors of healed plaque presence (Table 2).

After adjustment for clinical characteristics, cardiovascular risk factors, clinical presentation, HbA1c levels, and medical therapy, diabetes mellitus remained independently associated with a markedly lower likelihood of plaque healing (OR 0.05, 95% CI 0.01–0.39; p=0.005).

Other independent predictors included family history of CAD (OR 0.41, 95% CI 0.19–0.88; p=0.022) and presentation with CCS (OR 2.10, 95% CI 1.07–4.13; p=0.031).

FIGURE 5 | **Prevalence of plaque healing according to HbA1c values** *(patient-based analysis)*



Data are shown as percentage (n/N). Percentages are calculated within each HbA1c group.

Table 2. Multivariate logistic regression analysis

	Odds ratio	95% CI	P value
Age, years	0.99	0.96 – 1.02	0.532
Male sex	1.07	0.57 – 2.02	0.830
Hypertension	0.79	0.38 – 1.62	0.518
Dyslipidemia	1.31	0.72 – 2.37	0.373
Current smoking	0.90	0.48 – 1.67	0.739
Diabetes mellitus	**0.05**	**0.01 – 0.39**	**0.005**
Family history of CAD	0.41	0.19 – 0.88	0.022
Presentation with CCS	2.10	1.07 – 4.13	0.031
HbA1c, %	1.00	0.99 – 1.00	0.160
Aspirin	0.57	0.26 – 1.26	0.164
Statin	2.13	0.90 – 5.01	0.084
Beta-blocker	1.46	0.82 – 2.62	0.199
ACEi/ARBs	0.90	0.45 – 1.81	0.768
Oral antidiabetic drugs	2.04	0.29 – 14.48	0.478
Insulin	4.13	0.78 – 21.78	0.095
SGLT2i	1.64	0.50 – 5.46	0.418

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCS, chronic coronary syndrome; CI, confidence interval; HbA1c, glycated hemoglobin; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

7.4 Discussion and conclusions

Numerous pathological and in vivo studies have shown that plaque rupture is the most common substrate for acute coronary syndromes and sudden cardiac death (33, 34).

However, pathological studies have shown that many plaques become unstable without giving rise to an acute clinical event: symptomatic coronary syndrome occurs, indeed, when plaque rupture or erosion takes place in a pro-thrombotic environment, leading to occlusive or sub-occlusive thrombosis. If, on the other hand, anti-thrombotic factors prevail, thrombus formation is limited and the phenomenon known as plaque healing occurs (20,45).

Recent evidence suggests also that healed coronary plaques are rarely observed in patients with a history of recurrent acute coronary syndromes, whereas they are much more common in patients with long-standing stable coronary artery disease or a history of a single acute myocardial infarction (47).

The analysis of the baseline clinical characteristics of the present study population revealed that patients with diabetes were significantly older compared with those without diabetes, whereas sex distribution was similar between groups. No significant differences were observed in BMI, prevalence of hypertension, current smoking, or dyslipidemia. Family history of coronary artery disease (CAD) tended to be more frequent in patients with diabetes, although it did not reach statistical significance. Clinical presentation was also comparable, with ACS being the indication for OCT evaluation in 63.0% of patients with diabetes and 57.4% of those without diabetes. Regarding previous cardiovascular history, patients with diabetes showed numerically higher rates of prior ACS, prior PCI, and prior CABG, without reaching statistical significance. As expected, glucose levels and HbA1c values were significantly higher among patients with diabetes. Finally, patients with diabetes were more frequently treated with statins, ACE inhibitors/ARBs, oral antidiabetic drugs, insulin and SGLT2 inhibitors.

The segment-based OCT analysis showed that lipid-rich plaques were significantly more frequent in patients with diabetes. Conversely the prevalence of fibrous plaques and of thin-cap fibroateroma (TCFA) was similar between groups. Additional OCT high-risk plaque features were more commonly observed in patients with diabetes. In particular, compared with patients without diabetes, diabetic patients showed a higher prevalence of calcification, macrophage accumulation, and cholesterol crystals. No significant difference was observed in microchannels.

Quantitative OCT analysis demonstrated that patients with diabetes had significantly larger lipid burden, reflected by greater mean lipid arc compared with patients without diabetes. No significant differences were observed in other quantitative OCT measurements, including thinnest fibrous cap thickness, lipid-rich plaque length, calcium arc, and calcium length.

The prevalence of non-culprit plaque rupture was significantly higher among patients with diabetes compared with those without diabetes. Conversely, healed layered plaques were significantly less frequently observed in patients with diabetes compared with patients without diabetes suggesting impaired plaque healing response in the presence of diabetes.

The patient-based analysis showed that among patients with available HbA1c assessment, plaque healing was evaluated according to glycemic control status. Patients with HbA1c ≥6.5% showed a significantly lower prevalence of healed layered plaques compared with patients with HbA1c <6.5%

Furthermore, on multivariate analysis, cardiovascular risk factors, clinical presentation, HbA1c levels, and medical therapy, diabetes mellitus remained independently associated with a markedly lower likelihood of plaque healing. Other independent predictors included family history of CAD and presentation with CCS.

Our data confirm the relationship between atherosclerosis and diabetes. These findings suggest that diabetes is independently associated with a distinct OCT plaque phenotype characterized by greater lipid burden, increased inflammatory and calcific features, higher prevalence of plaque rupture, and impaired plaque healing response.
In conclusion, the balance between destabilizing factors (such as inflammation, oxidative stress and macrophagic M1 phenotype) and stabilizing mechanisms (such as healing and macrophagic M2 phenotype), play a key role in the complex pathophysiology of atherosclerosis. In patients whit diabetes, this relationship appears to be unbalanced, with an increase in destabilizing factors accompanied by impaired healing responses. Such alterations may contribute to a higher risk of acute coronary syndromes and, consequently, to a worse clinical outcome.

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