UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE MEDICINA

TESIS DOCTORAL

Evaluación con tomografía de coherencia óptica de las lesiones no culpables en pacientes con síndrome coronario con elevación del segmento ST

Evaluation of non-culprit lesions in patients with ST-segment Elevation Myocardial Infarction with Optical Coherence Tomography

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

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Madrid

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To my family, mentors, friends, and supporters

For believing in my tenacity and unconditional love for my profession

1 Table of Contents

1. SUMMARY

Primary percutaneous coronary intervention (PCI) is the preferred method of reperfusion for patients with ST-segment elevation myocardial infarction (STEMI) (1-4). These patients often have multivessel coronary artery disease, with additional angiographically significant lesions in locations separate from that of the culprit lesion that caused the acute event (5). Whether to routinely revascularize these non-culprit lesions or to manage them conservatively with guideline based medical therapy alone is a common dilemma (6-8). Non-culprit lesions, which are usually discovered incidentally at the time of primary PCI, may represent stable coronary artery plaques, for which additional revascularization may not offer additional benefit (9). However, if non-culprit lesions have morphologic features consistent with unstable plaques, which confer an increased risk of future cardiovascular events, there may be a benefit of routine non-culprit-lesion PCI (10, 11).

Observational studies have suggested a possible reduction in clinical events with staged non-culprit lesion PCI, but these studies are limited by selection bias and confounding (12, 13). Early randomized trials showed reduction in the risk of composite outcomes with non-culprit lesion PCI, with results driven predominantly by the decreased risk of subsequent revascularization (14-17). Meta-analyses have suggested a reduction in the risk of death from cardiovascular causes or myocardial infarction with non-culprit lesion PCI, but previous individual trials have not had the power to examine this clinically important outcome (18-20).

The Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial was designed to address this evidence gap. The COMPLETE trial was a multinational, randomized trial among patients with STEMI and multivessel coronary artery disease who had undergone successful culprit lesion PCI that evaluated a strategy of staged complete revascularization (consisting of PCI of all suitable non-culprit lesions) as compared with a strategy of no further revascularization (21, 22). The COMPLETE trial demonstrated that routine angiography-guided PCI of obstructive non-culprit lesions as a staged procedure reduced the composite of cardiovascular death or new myocardial infarction by about 26% (p=0.004) (22).

Among patients with STEMI, approximately 30-50% have multivessel coronary artery disease with additional angiographically significant non-culprit lesions remote from the culprit lesion (10, 11, 23). Whether the benefit of routine non-culprit lesions PCI might be associated with vulnerable plaque morphology, ischemia or a combination of both mechanisms is unknown.

Although angiographic identification of non-culprit stenoses used in the COMPLETE trial is practical and feasible in every patient, intravascular imaging is required to identify whether plaques have vulnerable features. Optical coherence tomography (OCT) is an intracoronary imaging modality that can identify thin cap fibroatheroma (TCFA), the primary morphology of the vulnerable plaque (24).

This thesis is meant to define the plaque morphology of the non-culprit lesions in patients presenting with STEMI and hypothesize its relationship with the benefit of routine staged non-culprit lesion PCI. The COMPLETE OCT sub-study of the COMPLETE trial is an investigator initiative to evaluate prospectively the prevalence of TCFA by OCT in obstructive and non-obstructive non-culprit lesions among patients randomized to non-culprit PCI in the COMPLETE trial (25).

This thesis compendium is divided in 7 sessions:

1. Introduction to atherosclerosis and lesion progression; vulnerable plaque and clinical significance; and contrast of different methods to assess non-culprit lesions intervention criteria, ischemia-driven vs. imaging-guided.
2. State of knowledge for the research performed in this thesis.
3. Thesis: background, methodology, analysis, results, discussion, and conclusions.
4. A compendium of original OCT images from the COMPLETE-OCT substudy (COMPLETE OCT Atlas), showing a variety of vulnerable plaque features documented in vivo.
5. Additional original research on the evaluation of non-culprit lesions in patients in STEMI and multivessel disease.
6. Final remarks and future directions.
7. List of academic contributions around the thesis including presentations, workshops, and collaborations.

2 RESUMEN

La angioplastia primaria es el método preferido de reperfusión para pacientes con sindrome coronario agudo con elevación del segmento ST (1-4). Estos pacientes usualmente tienen enfermedad coronaria multivaso, con lesiones angiográficamente significativas en segmentos lejanos a la lesión culpable que causo el evento primario (5). Existe un dilema acerca de si tratar estas lesiones no culpables con revascularización rutinaria o manejarlas conservadoramente solo con terapia medica óptima (6-8). Las lesiones no culpables que se descubren incidentalmente al momento de la angioplastia primaria, pueden representar placas coronarias estables para las cuales revascularización adicional no ofrece beneficio (9). Sin embargo, si las lesiones no culpables tienen características morfológicas consistentes con placas inestables que confieren un riesgo incrementado de eventos cardiovasculares futuros; puede haber un beneficio considerando intervencionismo rutinario (10, 11).

Estudios observacionales han sugerido una posible reducción de eventos clínicos con el intervencionismo rutinario de las lesiones no culpables, pero estos estudios son limitados por sesgos de selección y criterios de inclusión e intervencionismo confusos (12, 13). Estudios randomizados iniciales mostraron una reducción del riesgo de resultados compuesto con el intervencionismo de lesiones no culpables, con resultados dependientes predominantemente de reducción de revascularización subsecuente (14-17). Meta análisis han sugerido una reducción del riesgo de muerte por causas cardiovasculares o infarto de miocardio con el

intervencionismo de lesiones no culpables; pero estudios previos individuales no tuvieron el poder estadístico para evaluar estos importantes desenlaces clínicos (18-20).

El estudio COMPLETE, revascularización completa versus revascularización de solo el vaso culpable de infarto para tratar enfermedad multivaso después de angioplastia primaria en pacientes con sindrome coronario agudo con elevación del segmento ST, se diseñó para abordar esta brecha en la evidencia clínica. COMPLETE es un estudio randomizado, multinacional en pacientes con sindrome coronario agudo con elevación del segmento ST y enfermedad multivaso que han tenido angioplastia primaria satisfactoria del vaso culpable, que comparó una estrategia de revascularización completa diferida (intervencionismo de todas las lesiones no culpables aptas) con una estrategia de solo tratar el vaso culpable con intervencionismo y el resto de las lesiones solo con tratamiento médico óptimo (21, 22). El estudio COMPLETE demostró que intervenir rutinariamente las lesiones no culpables con guía angiográfica en un procedimiento diferido, redujo el compuesto de muerte cardiovascular o nuevo infarto de miocardio en cerca del 26% (p=0.004) (22).

Entre los pacientes con sindrome coronario agudo con elevación del segmento ST, aproximadamente el 30-50% tienen enfermedad multivaso con lesiones en sitios remotos en comparación con la lesión culpable (10, 11, 23). Es incierto si el beneficio de revascularización rutinaria de lesiones no culpables esta relacionado con placa morfológica vulnerable, isquemia o una combinación de ambas.

Aunque la identificación angiográfica de lesiones no culpables en el estudio COMPLETE es práctico y factible en todos los pacientes, imagen intravascular es necesaria si se quiere analizar características vulnerables de las placas coronarias. La tomografía de coherencia óptica es una modalidad de imagen intracoronaria que puede identificar fibroateroma con capa fibrosa fina que es la característica principal de las placas vulnerables (24).

Esta tesis esta dedicada a definir la placa morfológica de las lesiones no culpables e hipotetizar su relación con el beneficio de la revascularización rutinaria de estas lesiones coronarias en el contexto de sindrome coronario agudo con elevación del segmento ST. El sub-estudio COMPLETE OCT del estudio COMPLETE es una iniciativa del investigador para evaluar de forma prospectiva la prevalencia de fibroateromas de capa fibrosa fina por tomografía de coherencia óptica en lesiones obstructivas y no obstructivas en pacientes randomizados a revascularización completa en el estudio COMPLETE (25).

El compendio de esta tesis se divide en 7 secciones:

1. Introducción a la aterosclerosis y la progresión de las lesiones coronarias; placa vulnerable y su significando clínico; y contraste de diferentes métodos para evaluar criterios de intervención en lesiones no culpables, demostración de isquemia vs. guiadas por imagen intracoronaria.
2. Estado del conocimiento acerca de la investigación que se desarrolló en esta tesis.
3. Tesis: antecedentes, metodología, análisis, resultados, discusión y conclusiones.

4. Compendio de imágenes originales de tomografía de coherencia óptica del subestudio COMPLETE-OCT (COMPLETE-OCT Atlas), incluyendo variedad de características de placa vulnerable documentadas en vivo.
5. Manuscritos originales adicionales en la evaluación de lesiones no-culpables de infarto en pacientes con sindrome coronario con elevación del segmento ST.
6. Comentarios finales y direcciones futuras.
7. Lista de contribuciones académicas incluyendo presentaciones, workshops y colaboraciones de investigación.

3 ABBREVIATIONS

ACS: Acute Coronary Syndrome

AUC: Area Under Curve

CABG: Coronary Artery Bypass Grafting

CAD: Coronary Artery Disease

CCS: Chronic Coronary Syndromes

CCTA: Coronary computed tomography angiography

CI: Confidence Interval

CV: Cardiovascular

ECM: Extracellular Matrix

FFR: Fractional Flow Reserve

HPR: Healed Plaque Rupture

HR: Hazard Ratio

iFR: Instantaneous Wave Free Ratio

IRA: Infarct Related Artery

IVUS: Intravascular Ultrasound

LRP: Lipid Rich Plaque

LCBI: Lipid Core Burden Index

MACE: Major Adverse Cardiac Events

MACCE: Major Adverse Cardiac and Cerebrovascular Events

MI: Myocardial Infarction

MLA: Minimum Lumen Area

MRI: Magnetic Resonance Imaging

MVD: Multivessel Disease

NSTEMI: Non-ST-Segment Elevation Myocardial Infarction

OCT: Optical Coherence Tomography

OMT: Optimal Medical Therapy

PCI: Percutaneous Coronary Intervention

PET: Positron Emission Tomography

QCA: Quantitative Coronary Angiography

RCT: Randomized Controlled Trials

RFR: Resting Full-Cycle Ratio

SAP: Stable Angina Pectoris

SCD: Sudden Cardiac Death

SIHD: Stable Ischemic Heart Disease

SMC: Smooth Muscle Cell

STEMI: ST-segment Elevation Myocardial Infarction

TCFA: Thin Cap Fibroatheroma

ThCFA: Thick Cap Fibroatheroma

TVF: Target Vessel Failure

UA: Unstable Angina

4 PART I. ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

4.1 CORONARY ANGIOGRAPHY TO DIAGNOSE AND PROGNOSTICATE CORONARY ARTERY DISEASE: A HISTORICAL PERSPECTIVE

Over decades, coronary angiography was the only available method to assess in vivo the presence of coronary atherosclerosis (26). The prognosis of patients was found to be inversely related to the number of coronary vessels with angiographically apparent stenosis. Furthermore, the presence of a high-grade stenosis (>80% angiographic diameter narrowing) and extensive coronary artery disease correlates with a higher risk of subsequent coronary artery occlusion producing a myocardial infarction (27). All this led to bestowing to coronary angiography the title of standard gold test for the evaluation of patients with suspected coronary artery disease.

However, it was relatively soon after its implementation in clinical practice that, based on necropsy studies, the discrepancy between the presence of luminal obstructions noted in the angiogram and the degree of underlying atherosclerotic involvement became evident. Such discrepancy was largely explained by the discovery of compensatory vessel remodelling over atherogenesis by Glagov et al (28-30). The landmark work of Stary et al (31-33) on the evolution of atherogenesis also highlighted that the structure of atheromatous plaques changes over time. Thus, angiography was found to be unable to detect coronary atheroma unless

obstructive lesions, and unable to provide qualitative information on the structure and composition of atheromatous plaques (with the notable exception of those with massive calcification), that can also be misleading by angiography in around 50%.

These findings are of key importance in discussing a key clinical question: how a diseased coronary segment likely to trigger an acute myocardial infarction in the future can be identified early to shift the natural history of the disease. Since 1970' several groups noted the high prevalence of future coronary events after an event of ACS. Contrary to the initial suggestion that stenosis severity was a predictor of future cardiac events, Little et al, concluded that there was no correlation between coronary stenosis and time of future events or predictive value for future myocardial infarction location, after reviewing 42 patients in a retrospective fashion and finding that over 60% of patients had <50% coronary stenosis in the future culprit lesion at the initial coronary angiography (34). Ambrose et al, also reported in a retrospective analysis that only 22% of patients had the subsequent event in a segment with previous >70% luminal stenosis in angiography (35).

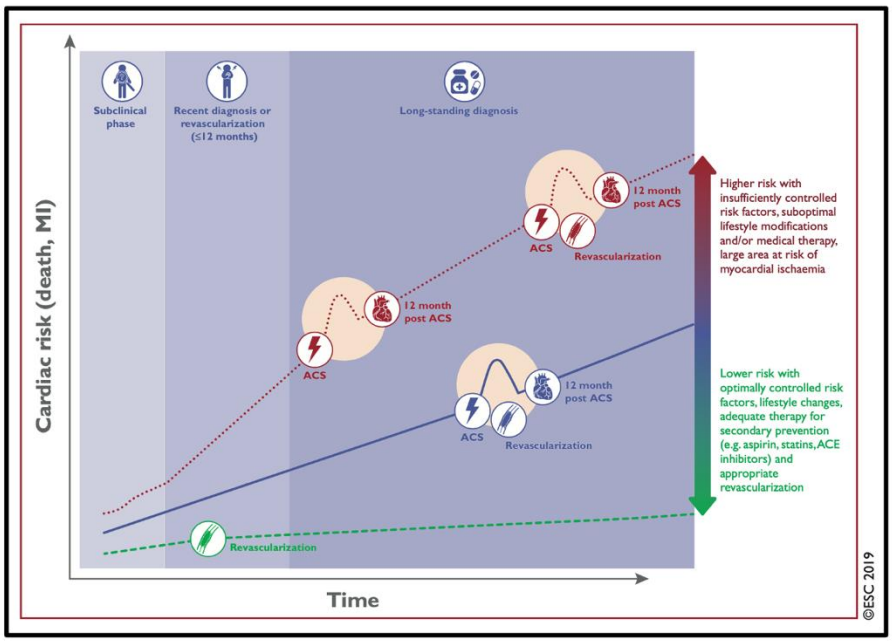
These observations opened the hypothesis that non-obstructive atherosclerosis with mild or moderate luminal stenosis might also had the powered to rupture, resulting in thrombosis formation with total or subtotal occlusion of the coronary vasculature producing myocardial infarction; and made stronger recommendation for cardiovascular risk factors modification as a

therapeutic pillar; given that available therapies for myocardial infarction at that time including thrombolysis or coronary interventions would not be able to prevent future events.

Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive. The disease can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. However, the disease is chronic, most often progressive, and hence serious, even in clinically apparently silent periods.

The dynamic nature of the CAD process results in various clinical presentations, which can be conveniently categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS). The natural history of CCS is illustrated in this Figure where the risk of acute event on chronic disease may change over time (36).

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes
Schematic illustration of the natural history of chronic coronary syndromes

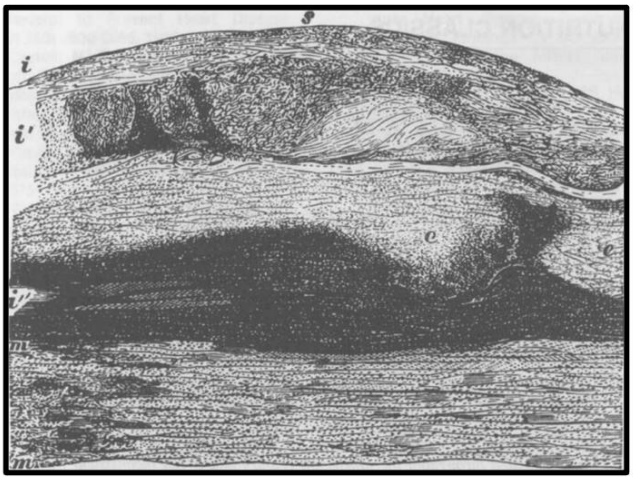


Development of an ACS may acutely destabilize each of these clinical scenarios. The risk may increase as a consequence of insufficiently controlled cardiovascular risk factors, suboptimal lifestyle modifications and/or medical therapy, or unsuccessful revascularization. Alternatively, the risk may decrease as a consequence of appropriate secondary prevention and successful revascularization. Hence, CCS are defined by the different evolutionary phases of CAD, excluding situations in which an acute coronary artery thrombosis dominates the clinical presentation which is the case of ACS.

4.2 VULNERABLE ATHEROSCLEROTIC PLAQUES

A key concept in discussing the non-lineal occurrence of cardiovascular events in CAD (i.e. the development of an ACS) is about the presence of vulnerable atherosclerotic plaques that could be present in non-obstructive coronary vessel segments and have the risk features to become the acute culprit lesion of an ACS.

Vulnerable plaque is defined as a coronary artery lesion with a high likelihood of triggering an acute coronary syndrome. Rudolf Virchow published *Cellular Pathology* lectures in 1858 (37), which laid the foundations of modern pathology and indeed of modern medical theory. In his *LECTURE XVI - Atheromatous affection of arteries*, pointed out that historically, the term "atheroma" (represented on following Figure) refers to a dermal cyst ("Grutzbalg"), a fatty mass encapsulated within a cap. Extending Virchow's argument, the fibrous cap over the lipid mass of an atherosclerotic plaque is analogous to the capsule containing an abscess, and like an abscess, the plaque can be ruptured.



Virchow, R. Nutr Rev. 1989 Jan;47(1):23-5.

Figure. Vertical section through the wall of the aorta at a sclerotic part in which atheromatous matter is already in the course of formation. Media (*m, m'*), internal coat (*i, i',il''*) and highest point of the sclerotic part where it projects into the cavity of the vessel (*s*). *i* the innermost layer of the intima running over the whole deposit, *i'* the proliferating, sclerosing layer preparing for fatty degeneration, *i''* the layer immediately adjoining the media which has already undergone fatty degeneration; and *e* is in the process of direct softening.

Rupture of the fibrous cap exposes thrombogenic plaque material to the bloodstream, initiating a platelet aggregation and coagulation process that leads to the formation of a mural thrombus. These thrombotic changes result from activation of the clotting cascade by tissue factor, and further propagation of the thrombosis results from the interaction of platelets with the active thrombogenic matrix (38). Platelet activation and thrombin formation combined with the evulsion of thrombogenic plaque contents into the lumen may result in sudden occlusion (39). The described sequence of events is supported by necropsy and clinical angiographic studies, in which the presence of surface irregularities has been interpreted as plaque rupture

(40-42). Pathological studies in patients with sudden coronary death have demonstrated evidence of plaque rupture associated with thrombosis in 73% of cases (43). Reviews of atherosclerosis have uniformly accepted plaque rupture as the most common critical event leading to coronary artery related death (38).

Several important contributions have described the atherosclerosis and mechanisms for which plaques erode or rupture causing myocardial infarction. In the late 1970s, Russell Ross highlighted the importance of smooth muscle cell (SMC) proliferation in atherosclerotic lesion formation and hypothesized that injury to the arterial wall had a major role in plaque progression (44, 45). Inflammation was later identified as the primary driving force for activation and proliferation of SMCs, processes mediated by growth factors (46). Subsequent studies from Libby and Hansson in the late 1990s indicated that atherogenesis involved a complex interaction between risk factors and inflammation; their work resulted in a move away from the idea that atherosclerosis was a bland proliferative disorder to the concept of it being a complex inflammatory disease of the vessel wall (47-49).

During the same period, Fuster and colleagues observed plaque progression as staged events: initial involvement of the endothelium, which was causally linked to the developing intima, with further injury of the underlying media in the advanced phases of development. They also recognized that deep plaque fissures and ulcerations resulted in the manifestation of complex

lesions, as a cause of luminal thrombosis and clinical presentation of acute coronary syndrome (50, 51).

Several early angiographic studies reported a surge in the incidence of coronary atherosclerosis in the months after a coronary event as well, with a worsening of not only the culprit lesion when it has not been treated by angioplasty, but also of other lesions initially deemed insignificant; this pattern appears in 20% of cases in ACS patients, compared with <5% in cases of stable coronary artery disease (52-56). It was hypothesized that such rapid development of atherosclerosis probably involved diffuse unstable atherosclerotic plaques, leading to the concept of “pancoronaritis” in ACS patients (10, 57).

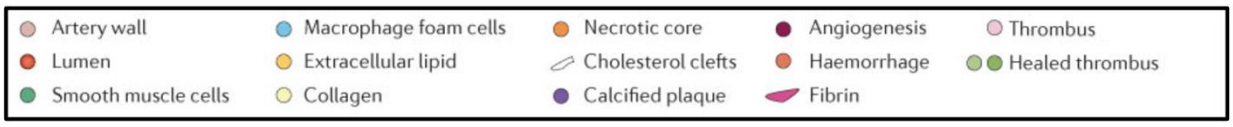
4.3 ATHEROSCLEROSIS STAGES

The atherosclerosis includes precursor, established, chronic and complicated lesions; that represent different disease stages. Patients presenting with STEMI are at high risk to have pan atherosclerosis with evidence that all these disease stages can coexist in the coronary vasculature of a single patient. COMPLETE OCT was a unique opportunity to obtain closer in-vivo insights on this phenomenon.

The following section aims to describe these different stages, contrasting the pathological definition described by Renu Virmani (58) and in-vivo cross-sectional images from the COMPLETE OCT study if detectable in each category (25).

This is the descriptive nomenclature that Dr. Virmani has used in the pathophysiology of CAD and it is used to represent findings in the following Figures.

Coronary artery vessel components and pathological tissues. Atherosclerosis.



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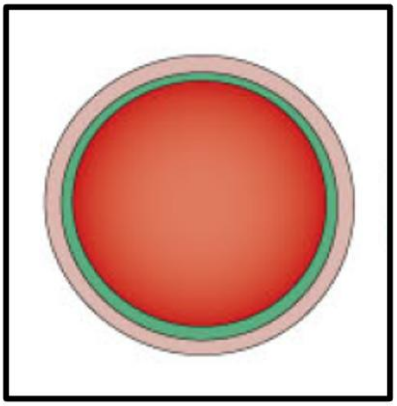
4.3.1 Nonatherosclerotic intimal lesions

4.3.1.1 Adaptive or diffuse intimal thickening

Adaptive or diffuse intimal thickening is often observed in atherosclerosis-prone arteries (59), and is considered a physiological response to blood flow rather than an atherosclerotic process. Study of young population has indicated that intimal masses that form near branch points enlarge with advancing age and might be precursors to high-risk plaques with the potential to thrombose (60, 61).

Adaptive or diffuse intimal thickening



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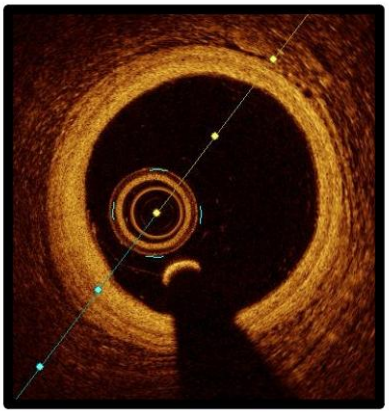

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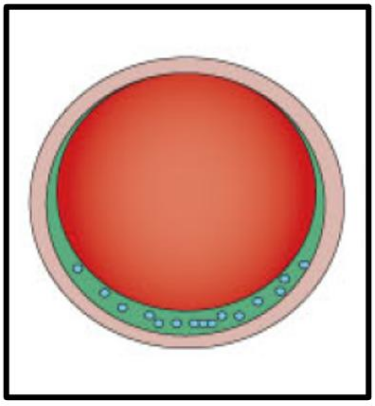
4.3.1.2 Intimal xanthomas

Intimal xanthomas, or so-called 'fatty streaks', are lesions primarily composed of infiltrating macrophage foam cells and, to a lesser extent, lipid-laden smooth muscle cells within the intima (62, 63). This type of lesion has been shown to regress, especially in the thoracic aorta and the right coronary artery in young individuals (64-66). Intimal xanthomas do not always convey the mandatory features of more-advanced atherosclerotic plaques and, therefore, are not considered progression-prone disease.

Intimal Xantomas



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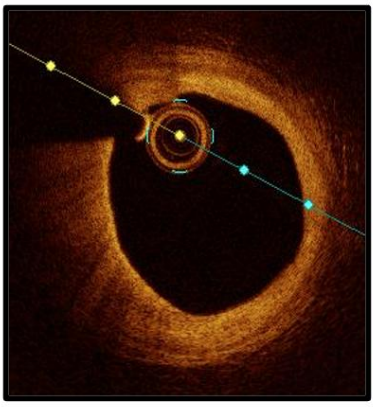

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COMPLETE-OCT

4.3.2 Progressive atherosclerotic lesions

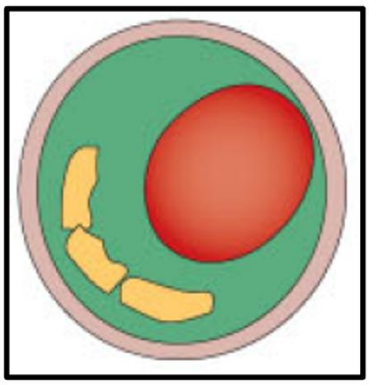
4.3.2.1 Pathological intimal thickening

Pathological intimal thickening is the earliest progressive lesion consisting of SMC remnants within an extracellular matrix (ECM) composed of proteoglycans and collagen type III with a co-existing lipid pool (67). The ECM consists primarily of hyaluronan and proteoglycans with neutral lipids and free cholesterol. Remnants of apoptotic SMCs are generally visualized by a thickened basement membrane (68), and are thought to support continued intimal growth. The lipid pools show a relative absence of viable SMCs. When present, resident macrophages in pathological intimal thickening are often seen localized to the luminal aspect of the lipid pool, which is likely to indicate a more-advanced stage of atherogenesis. Typical pathological intimal thickening, consisting of extracellular lipid under layers of macrophage-derived foam cells, is found at locations near branch points (69).

Fine crystalline structures of free cholesterol are also seen in lipid pools, but never in excess. Smith and Slater found a high percentage of unesterified cholesterol in the deep layers of the lipid pool in early plaques and concluded that most of this cholesterol was derived directly from plasma LDL (70). However, the precise origin of free cholesterol in pathological intimal thickening remains unknown but might be derived from membranes of dead SMCs (71). Pathological intimal thickening is also the earliest type of lesion exhibiting calcification; von Kossa or Alizarin demonstrates the presence of microcalcification in the lipid pools (72).

The ECM is increasingly being recognized as being important in the early steps of inflammation, particularly through its influence on macrophage phenotype. Pathogenesis studies of inflammation in atherosclerosis have shown that macrophages are recruited into the lipid pools where they eventually undergo necrosis (73).

Pathological intimal thickening. Without Macrophages



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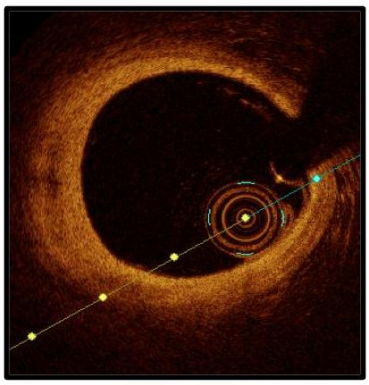

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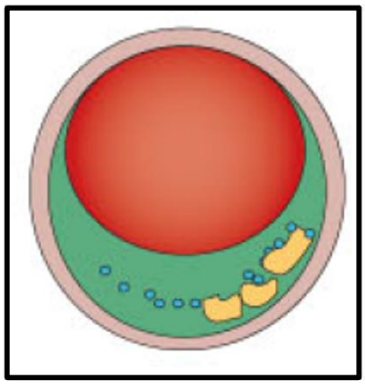
Pathological intimal thickening. With Macrophages



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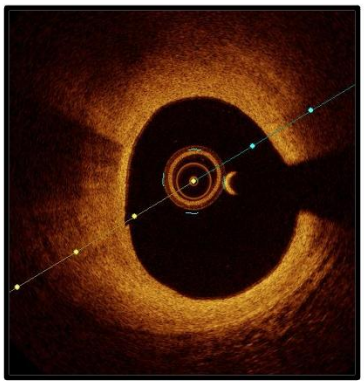

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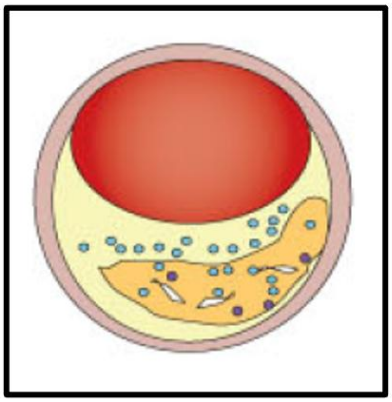
4.3.2.2 Fibroatheromas

Fibroatheromas are a progressive stage of atherosclerotic disease characterized by the presence of an acellular necrotic core generated by macrophage infiltration into lipid pools. There are two unambiguous phases of the necrotic core formation relative to 'early' or 'late' necrosis, mainly on the basis of the relative extent of matrix proteoglycans.

4.3.2.2.1 Early Fibroatheroma

Early Fibroatheromas have and early-phase necrosis (transition from lipid pool) that is associated with an appreciable decrease in the expression of proteoglycans within the lipid pool together with infiltrating macrophages, which are undergoing necrosis or apoptosis.

Early Fibroatheroma



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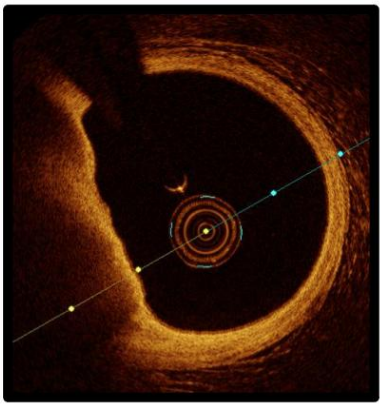

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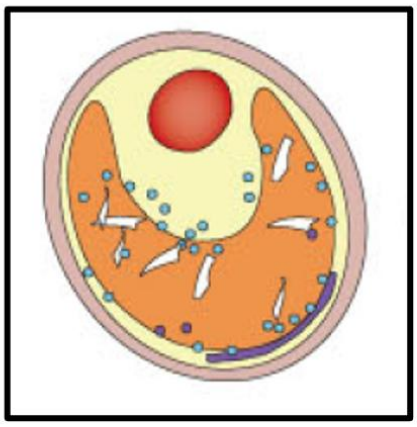
4.3.2.2.2 Late Fibroatheroma

Late Fibroatheroma has a necrotic core with noticeably deficient in ECM and more cholesterol clefts, calcification, intraplaque hemorrhage, and surrounding neoangiogenesis, than the early fibroatheroma. These ones also have thick fibrous caps composed of collagen type and proteoglycans interspersed with SMCs. The fibrous cap is the main structural element responsible for harbouring the atheromatous hemorrhagic contents of the necrotic core and is vulnerable to thinning and rupture. Although the precise mechanisms of fibrous cap thinning are not fully understood, ECM degradation facilitated by proteases secreted by an overabundance of macrophages are likely to be involved (74, 75), in addition to possible deficiencies in repair mechanisms (76).

Late Fibroatheroma



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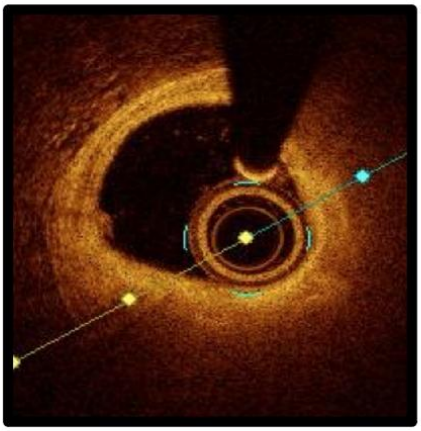

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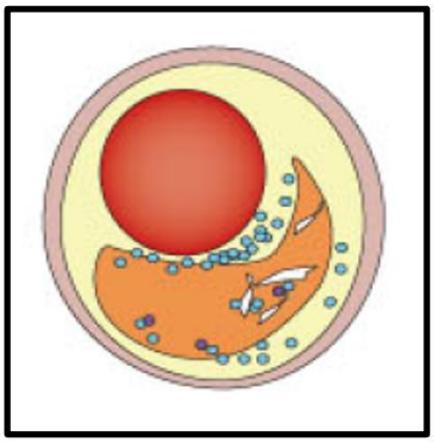
These morphological attributes provide important mechanistic insight into how necrotic cores initiate and evolve (77-79). The presence of accumulated macrophages within lipid pools coinciding with an appreciable increase in free cholesterol and breakdown of ECM essentially defines the 'early necrotic core'. Moreover, macrophage death in tandem with defective phagocytic clearance of apoptotic macrophages in animal models is another consistent feature of early necrotic core formation (80). Consistent with this observation, a systematic assessment of progressive coronary lesions shows the greatest density of apoptotic bodies in late versus early fibroatheromas, and least in pathological intimal thickening (81).

4.3.2.3 Thin-cap Fibroatheroma (TCFA)

The concept of TCFA was originally developed from observations of ruptured coronary lesions where the distinguishing morphological features relative to rupture were the absence of a luminal thrombus along with a disrupted cap. TCFAs are essentially synonymous with the more widely used term 'vulnerable plaques', referring to precursor lesions with a tendency to rupture (67).

TCFAs generally have a large 'late' necrotic core, with an overlying thin intact fibrous cap that is composed predominantly of collagen type I with varying degrees of macrophages and lymphocytes, and paucity or absence of SMCs. Fibrous cap thickness <65 um is considered a pathological indicator of lesion vulnerability based on observations of ruptured plaques in necropsy studies (82).

Thin Cap Fibroatheroma TCFA



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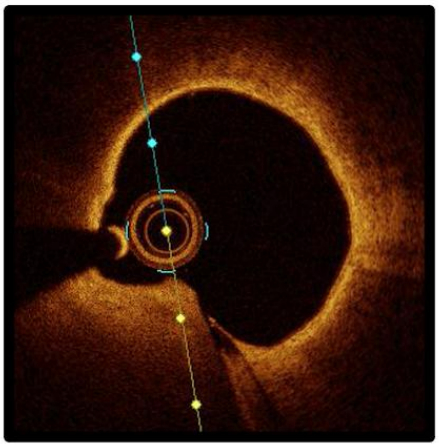

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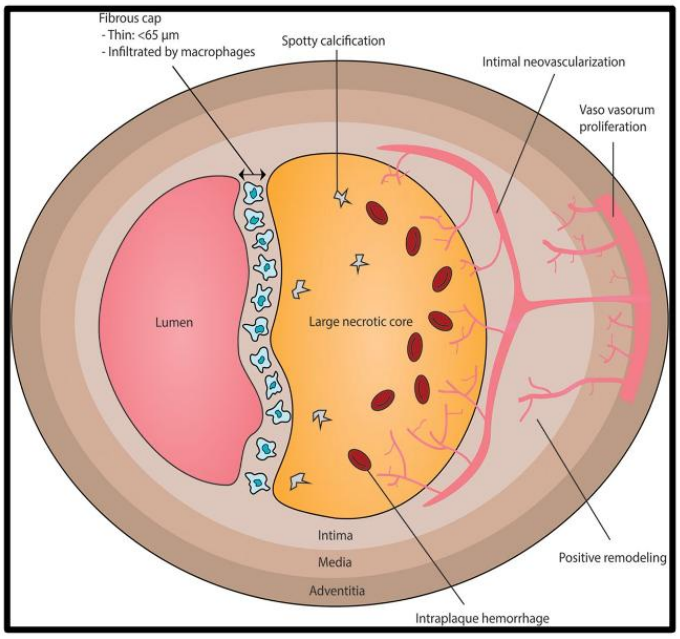
The term “vulnerable plaque” was introduced by Muller et al, in the late 1980s as a coronary plaque with a high susceptibility to rupture (83). Nowadays, the vulnerable plaque is commonly referred to as a lesion with a high likelihood of precipitating thrombosis (84). Recently, Stone et al; have introduced an alternative, more clinically relevant definition of the vulnerable plaque, that is, a plaque that places a patient at risk for future MACE (85).

Historically most pathophysiological studies on plaque morphology predisposing to ACS have focused on plaque rupture; however, a plaque with a large necrotic core and a thin fibrous cap is suspected to be rupture prone and is frequently referred to as TCFA; then, TCFA has been considered the surrogate for “vulnerable plaque”.

The following is a schematic representation of a suspected vulnerable plaque, including the morphological aspects associated with rupture (86).

Schematic representation of a suspected Vulnerable Plaque



Bom MJ et al. Circulation: Cardiovascular Imaging. 2017;10:e005973

Morphological characteristics might be valuable surrogates of lesion instability that could be assessed by invasive or non-invasive imaging technologies to improve prediction of TCFAs that are susceptible to rupture. Overall, a large necrotic core that is separated from the lumen by a thin fibrous cap (<65 µm), infiltrated by macrophages, with proliferation of the vasa vasorum that leads to intimal neovascularization are the most important characteristics of TCFAs, although the most useful is fibrous cap thickness, as it is the one characteristic that leads to the

susceptibility to rupture, which at the end is the link to rupture plaque and culprit lesion of ACS (86, 87).

Other important characteristics that increase the vulnerability definition are the immature neovessels that tend to leak red blood cells and cause intraplaque bleeding; and the positive (outward) remodeling, necrotic core, and spotty calcification (86).

TCFA is more common among individuals presenting with acute plaque rupture than among those with stable plaques or culprit lesions involving erosions (88). Also, patients with high serum total cholesterol level, smoking history, age >50 years, and elevated levels of C-reactive protein measured by high sensitivity assay have increased risk of TCFA (89).

4.3.3 Atherosclerotic Plaque Instability, Healing and Progression

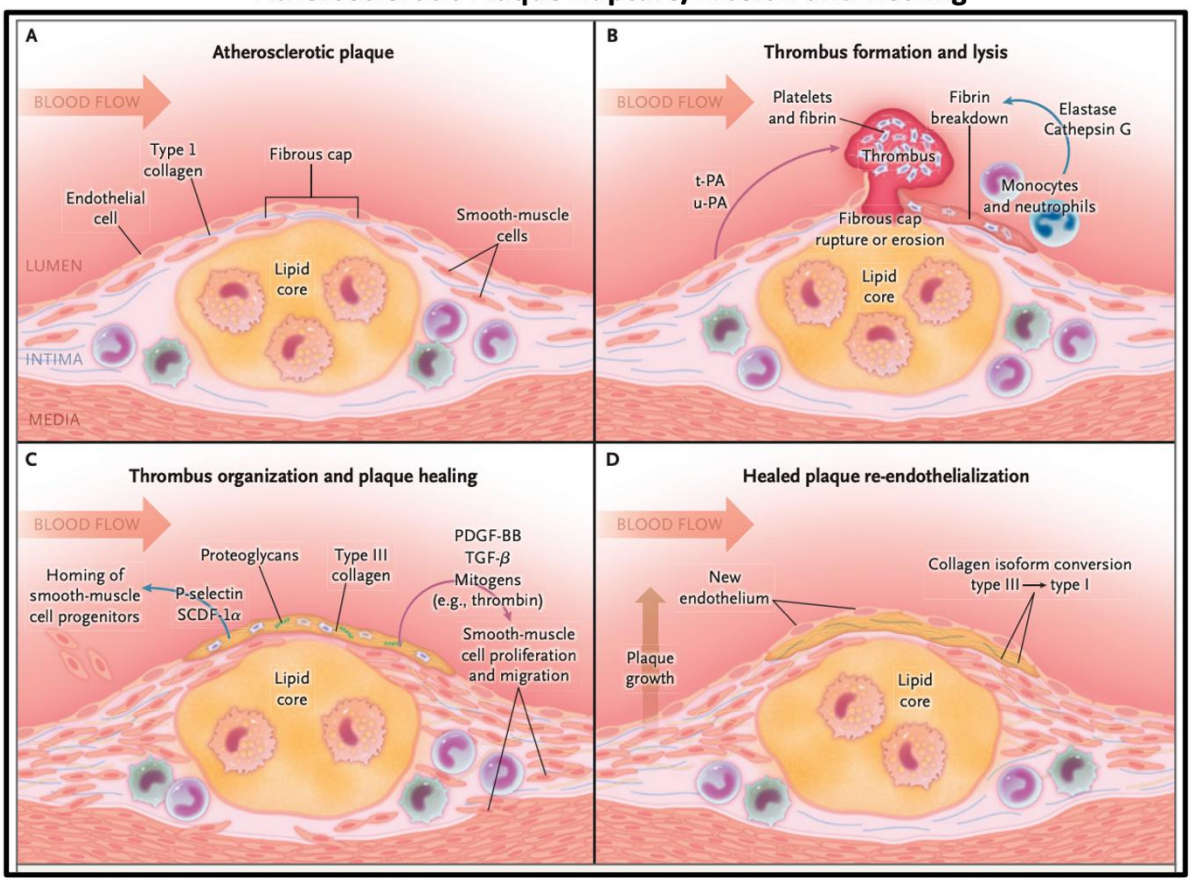
Atherosclerotic plaques typically develop over a period of years or decades. In contrast, the thrombotic complications of atherosclerotic disease occur suddenly, often without warning (90). The notion that ACSs develop from the rupture or superficial erosion of an atherosclerotic plaque is an oversimplification of a process involving plaque activity, blood thrombogenicity, and healing (91, 92). Pathological studies have shown that many atherosclerotic plaques destabilize without resulting in a clinical syndrome (93, 94).

Atherosclerotic plaque consists of extracellular lipid particles, foam cells, and debris that have accumulated in the intima of the arterial wall and formed a lipid or necrotic core. The core is surrounded by a layer of collagen-rich matrix and SMC covered by endothelial cells, known as the fibrous cap. Inflammatory cells (mainly T cells and macrophages) infiltrate the lesion and are involved in plaque progression and thrombosis, leading to an ACS (90-92).

The two most frequent causes of thrombosis are plaque rupture and superficial erosion. Plaque rupture occurs when the fibrous cap covering the necrotic core fissures, exposing the highly thrombogenic core to flowing blood. The TCFA, a plaque with a large necrotic core covered by a thin (<65-µm) fibrous cap infiltrated by activated macrophages, is considered the prototype of the rupture-prone plaque (90-92, 95). Plaque erosion is caused by endothelial damage or

denudation and overlying thrombosis in the absence of frank cap rupture. Plaques subject to erosion tend to be proteoglycan-rich and lipid-poor and usually lack prominent inflammatory infiltrates (91, 92, 95). When plaque rupture or erosion occurs in a prothrombotic milieu, sub-occlusive or occlusive thrombosis results, causing a symptomatic acute coronary event; otherwise, if thrombosis-resisting factors prevail, thrombus formation is contained, and plaque healing occurs (90, 96).

Atherosclerotic Plaque Rupture/Erosion and Healing



Vergallo R, Crea F. N Engl J Med. 2020 Aug 27;383(9):846-857.

The occurrence of an acute coronary syndrome probably depends on the disruption of a balance between instability ("activation") and healing ("passivation") of an atherosclerotic plaque. During the past 30 years, research efforts have mostly been focused on the mechanisms of plaque instability (91, 92). Yet the risk of acute MI or SCD from coronary causes remains difficult to predict, suggesting that other pathogenic mechanisms should also be investigated (97).

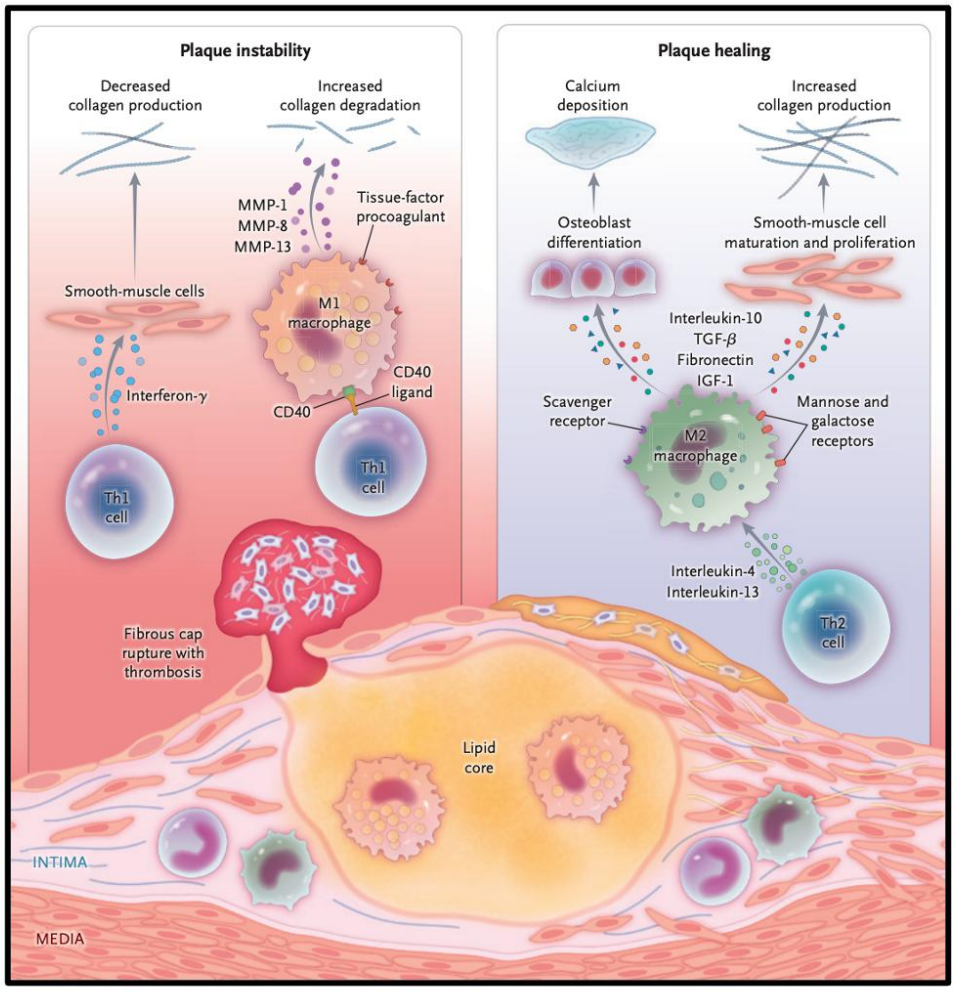
Recently, the notion that plaque healing may play a key role in the natural history of atherosclerotic disease has been gaining attention, in part because of the development of new imaging techniques, allowing in vivo study of the morphologic features of atherosclerotic plaque (98, 99).

Although the mechanisms through which inflammation can precipitate or exacerbate the thrombotic complications of atherosclerosis have been extensively investigated, the link between inflammation and plaque healing remains incompletely elucidated (90, 100).

In the plaque instability process, SMC showed that exposure to interferon-γ, secreted by activated type 1 helper T (Th1) cells, inhibits the ability of SMC to produce the interstitial collagen needed to repair the fibrous cap and maintain its integrity, even when the SMC are maximally stimulated by TGF-β (101). In addition, crosstalk between Th1 cells and macrophages (through the interaction between the T-cell–derived cytokine CD40 ligand and the

macrophage receptor CD40) boosts the production of interstitial collagenases, including matrix metalloproteinases 1, 8, and 13, which promote interstitial collagen breakdown, weakening the fibrous cap (102, 103). These phagocytes, known as M1 macrophages, are part of Th1 responses and are involved in proinflammatory activities (104).

Plaque Instability and Plaque Healing



Vergallo R, Crea F. N Engl J Med. 2020 Aug 27;383(9):846-857.

In contrast; in the plaque healing process, so-called alternative M2 macrophages are triggered by type 2 helper T (Th2) cytokines, including interleukin-4 and interleukin-13, and secrete anti-inflammatory cytokines, including interleukin-10, which counterbalance the proinflammatory activity of M1 macrophages and promote tissue repair (104, 105). M2a macrophages, traditionally recognized as wound-healing macrophages, produce profibrotic factors, which may contribute to plaque healing (104-106).

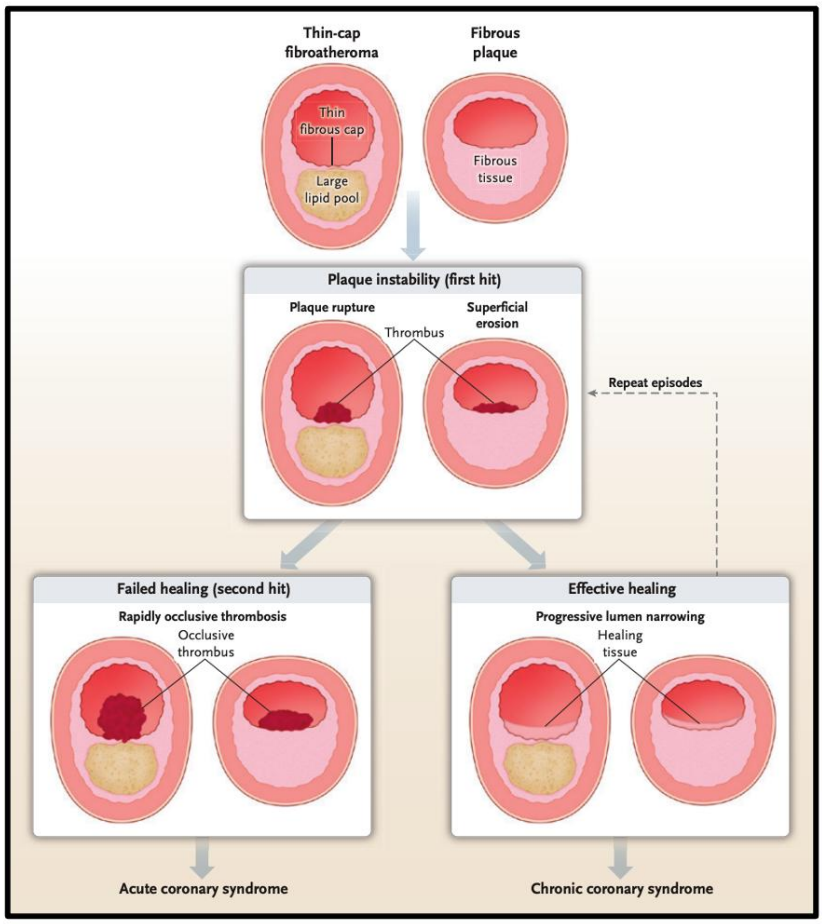
In the late phases of the healing process, M2 macrophages not only prompt the production of extracellular matrix but also may promote plaque calcification by stimulating osteoblastic differentiation (107, 108). Pathological studies have shown that maximum calcification is present in healed plaque rupture and in fibrocalcific plaques and that the calcification area steadily enlarges with progressive luminal narrowing. Healed plaques frequently contain diffuse sheets of calcification, which provide mechanical support for the healed plaque (109).

Much of the work addressing the mechanisms of ACS during the past three decades has focused on the pathogenesis of plaque instability (90-92). However, recent intracoronary imaging studies suggest that acute coronary syndromes may require a “double hit” of plaque disruption and impaired healing (99). The acute destabilization of an atherosclerotic plaque by either rupture or erosion (the first hit) leads to thrombosis and an ACS in patients with an impaired healing capacity (the second hit). In contrast, in patients with an effective

healing system, the first hit is contained, the unstable plaque is “pacified,” and the healing process promotes the development of a more fibrous, stable plaque (110).

Repeated cycles of thrombosis and healing lead to progressive encroachment on the arterial lumen, with silent, stepwise stenotic progression possibly leading to high-grade coronary occlusion in the absence of acute coronary events. In vivo, healed coronary plaques detected on OCT imaging have been consistently associated with a significantly smaller luminal area, and the prevalence of healed plaques steadily increases with a greater degree of stenosis (98, 99, 111). The clinical significance of plaque healing is still a matter of debate. Impaired healing has been associated with recurrent ACS due to silent progression of stenosis, recurrent coronary thrombosis, or vasospasm (99, 110, 112-115).

Role of Plaque Healing in the natural history of ischemic heart disease



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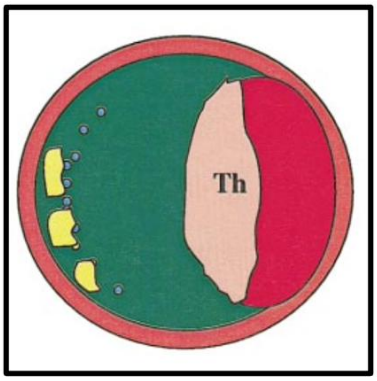
4.3.3.1 Layered luminal thrombosis

Silent luminal thrombi are usually nonocclusive, but if occlusive, chronic total occlusion occurs. Nonocclusive thrombi can result from silent plaque ruptures or erosions, and the thrombus will organize with granulation tissue and subsequent infiltration by SMCs with deposition of proteoglycans and collagen. However, the thrombus propagates proximally and distally and, when they heal, it converts into a fibrous plaque (116).

Layered Intraluminal Thrombosis



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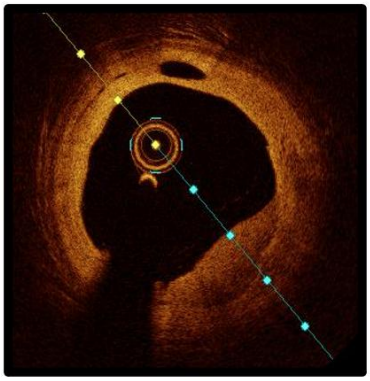

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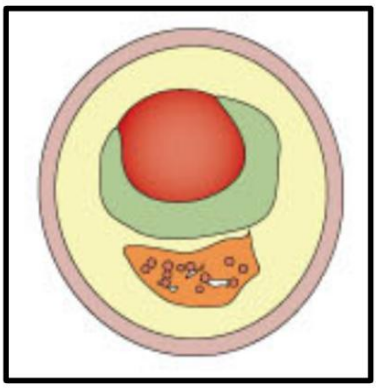
4.3.3.2 Healed rupture plaques

Episodic rupture and healing are believed to be the main mechanism of lesion progression. In the early 1990s, Mann and Davies introduced the concept of plaque progression through the identification of episodic rupture and healing in coronary arteries from patients who had died because of unstable angina or acute myocardial infarction. Microscopic analysis of Picrosirius Red staining viewed under polarized light identified healed plaque ruptures (HPRs) as breaks in the fibrous cap showing disrupted collagen type I, together with an overlying repair reaction consisting of SMCs, proteoglycans, and varying amounts of different types of collagen, dependent on the time since rupture (94).

Healed plaque rupture. Single layer



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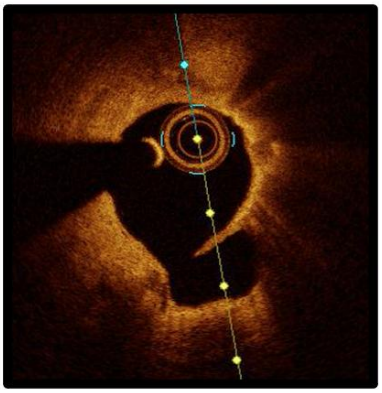

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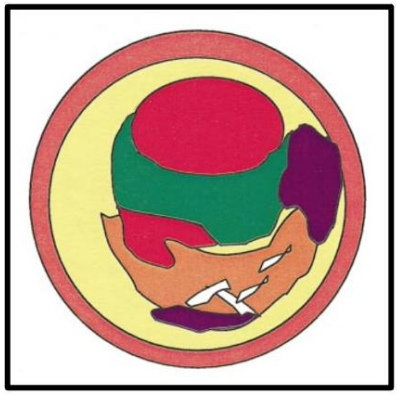
Healed plaque rupture. Multiple layers



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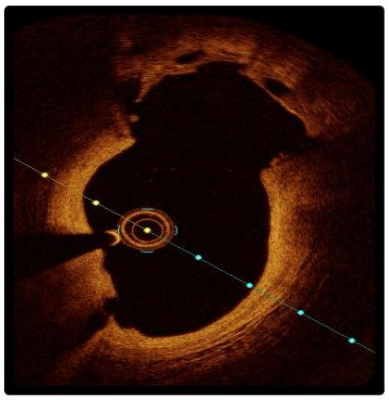

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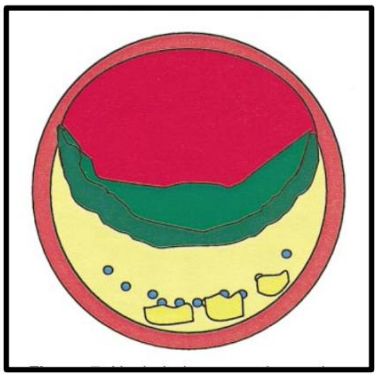
Progressive healing of silent ruptures is characterized by the initial accumulation of proteoglycans and collagen type III, which is later replaced by collagen type I. Although the prevalence of silent ruptures in the general population remains unknown, Mann and Davies

reported an incidence of HPRs of 16% (94). In a later study, 61% prevalence of subclinical ruptures in sudden cardiac death (SCD) was reported. The incidence was highest in culprit lesions of stable plaque (80%), followed by acute rupture (75%) and plaque erosion (9%). Multiple HPRs with layering were more common in proximal segments with underlying significant luminal narrowing at the site of acute rupture, suggesting that SCD with thrombosis was the culmination of the multiple previous silent events (93).

4.3.3.3 Healed erosion plaques

Plaque erosion can occur quietly without obvious clinical symptoms, forming typical healed plaque, and repeated cycles of non-culprit plaque erosion and healing may lead to culprit plaque erosion (98). Recent study revealed the formation rate of healed plaque was 55.5% at 1 month and 69.2% at 1 year, in line with previous intravascular OCT studies (115). Dai et al. showed that culprit healed plaque was observed in 40.3% of acute MI patients (117). Wang et al. observed that healed plaque accounting for 51.4% in 144 ACS patients (111). Previous pathological study focusing on sudden death victims showed that above 85% of thrombi in plaque erosion exhibiting late stages of healing (118).

Healed Plaque Erosion



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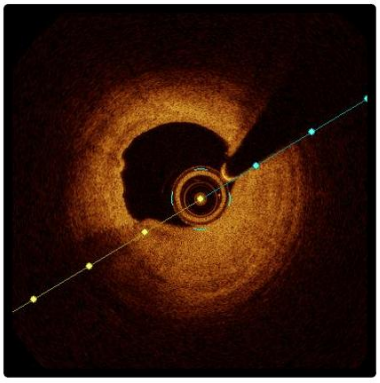

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4.3.3.4 Necrotic core expansion

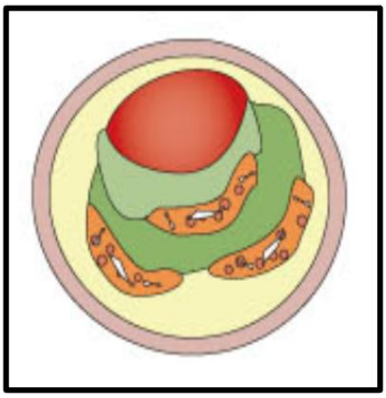
The two plaque morphologies that can led to necrotic core expansion are plaque fissure and intraplaque hemorrhage.

4.3.3.4.1 Plaque Fissure

In the 1960s, Constantinides and colleagues initially described the notion of cracks or fissures originating from the luminal surface as an entryway of blood into the lesions (119). This concept was expanded upon in the 1980s by Michael Davies, who defined the term 'plaque fissure' as an eccentric collection of blood, giving rise to fibrin deposition within the necrotic core (120). As highlighted by Davies, fissures and plaque ruptures are distinct entities; the latter are always accompanied by an appreciable luminal thrombus, whereas fissures generally have an intra-intimal thrombus consisting of fibrin and platelets with scattered erythrocytes and, if present,

luminal thrombi associated with fissures are generally very small. Rather than being an overt breech of the fibrous cap and superimposed thrombus, as seen in ruptures, a lateral or marginal tear in an eccentric plaque with underlying small necrotic core characterizes the plaque fissure. The separation line of the fissure begins in the necrotic core and extends into the lumen. The path is lined by few macrophages and red blood cells and/or fibrin.

Episodic Plaque Fissure Healing



K. Yahagi, Virmani R
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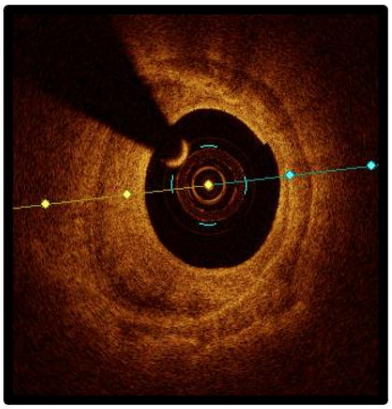

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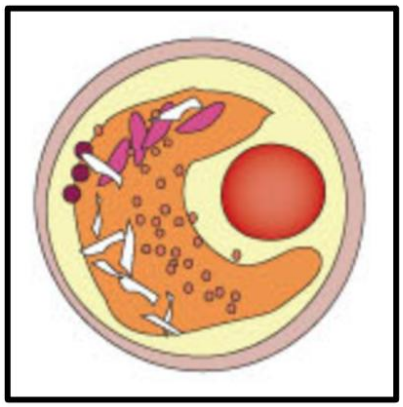
4.3.3.4.2 Intraplaque hemorrhage

The more dominant mechanism of intraplaque hemorrhage, however, occurs through intraplaque vasa vasorum, which extend into the intima from the adventitia. Kumamoto and colleagues demonstrated that intraplaque hemorrhages are 28-fold more common than plaque fissures (121). The extent of neovascularization correlated with luminal stenosis an inflammation.

Intraplaque Hemorrhage. Necrotic Core



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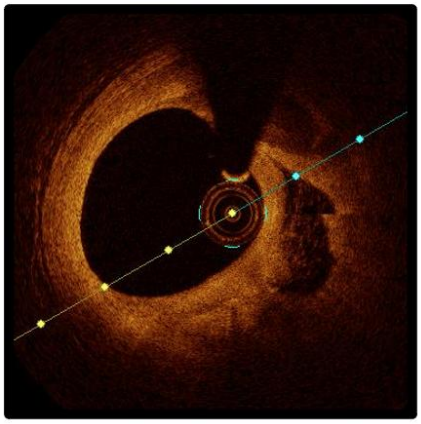

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4.4 TECHNIQUES FOR VULNERABLE PLAQUE DETECTION

4.4.1 Non-Invasive techniques

4.4.1.1 Coronary Computed Tomographic Angiography

Coronary computed tomography angiography (CCTA) allows non-invasive characterization and quantification of coronary atherosclerotic plaque (122-126). Recent clinical studies have shown that CCTA-characterized high-risk plaque morphology and CCTA-measured plaque burden provide an incremental value for predicting ACS compared to clinical risk factors and significant luminal stenosis (123, 126-130). TCFA is considered the precursor of plaque rupture and the prototype of vulnerable plaque (131, 132). Intravascular imaging has the advantage of detecting rupture prone TCFAs characterized by a large necrotic core covered by a thin FCT (<65 μm) (87, 133).

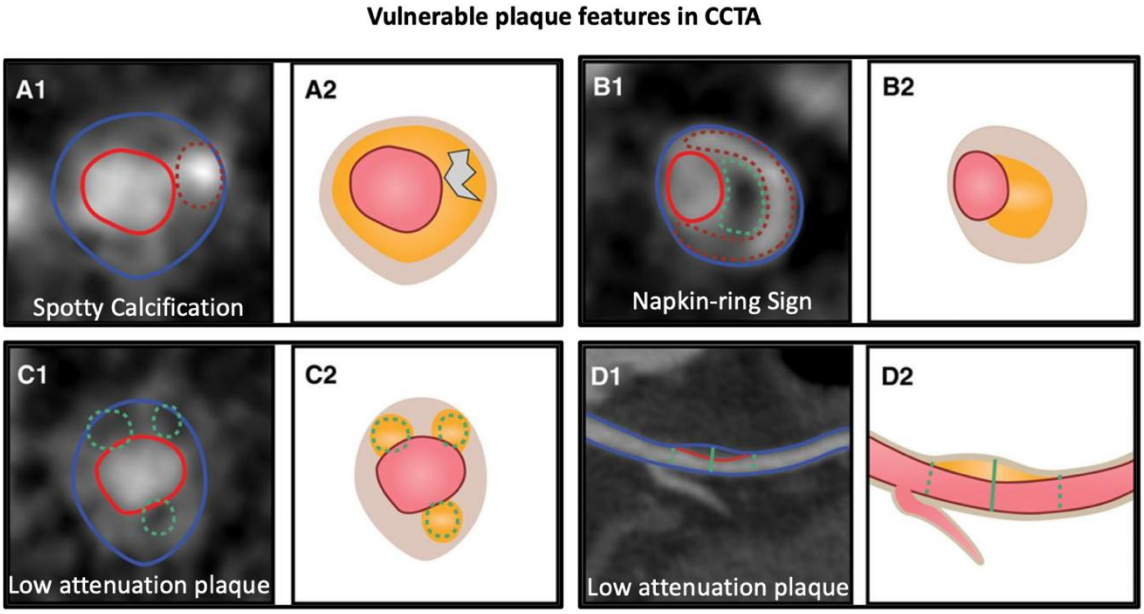
Even though the spatial resolution of CCTA imposes limitations for measuring FCT (134), recent comparative studies between CCTA and intravascular imaging modalities (IVUS and OCT) have shown some optimistic results (135-139). Coronary lesions demonstrating positive remodelling, low attenuation plaque, spotty calcification and napkin ring sign when imaged with CCTA were associated with vulnerable plaques (140).

Positive remodeling is a suspected feature of CCTA-derived plaque vulnerability (137, 139, 141, 142). In a direct comparison between CCTA and VH-IVUS, Kröner et al (137), reported that

plaques with positive remodeling had larger necrotic cores and were more frequent TCFA than plaques without positive remodeling.

CCTA uses CT attenuation, expressed in Hounsfield Units, to differentiate between calcified plaques with higher attenuation and noncalcified plaques with lower attenuation. Low-attenuation plaques have been shown to correlate with lipid-rich plaques assessed by VH-IVUS (138, 143, 144). Furthermore, studies that compare CCTA with OCT have reported that both positive remodeling and low-attenuation plaque were associated with OCT-derived TCFA and OCT-derived TCFA with macrophage infiltration (139, 141).

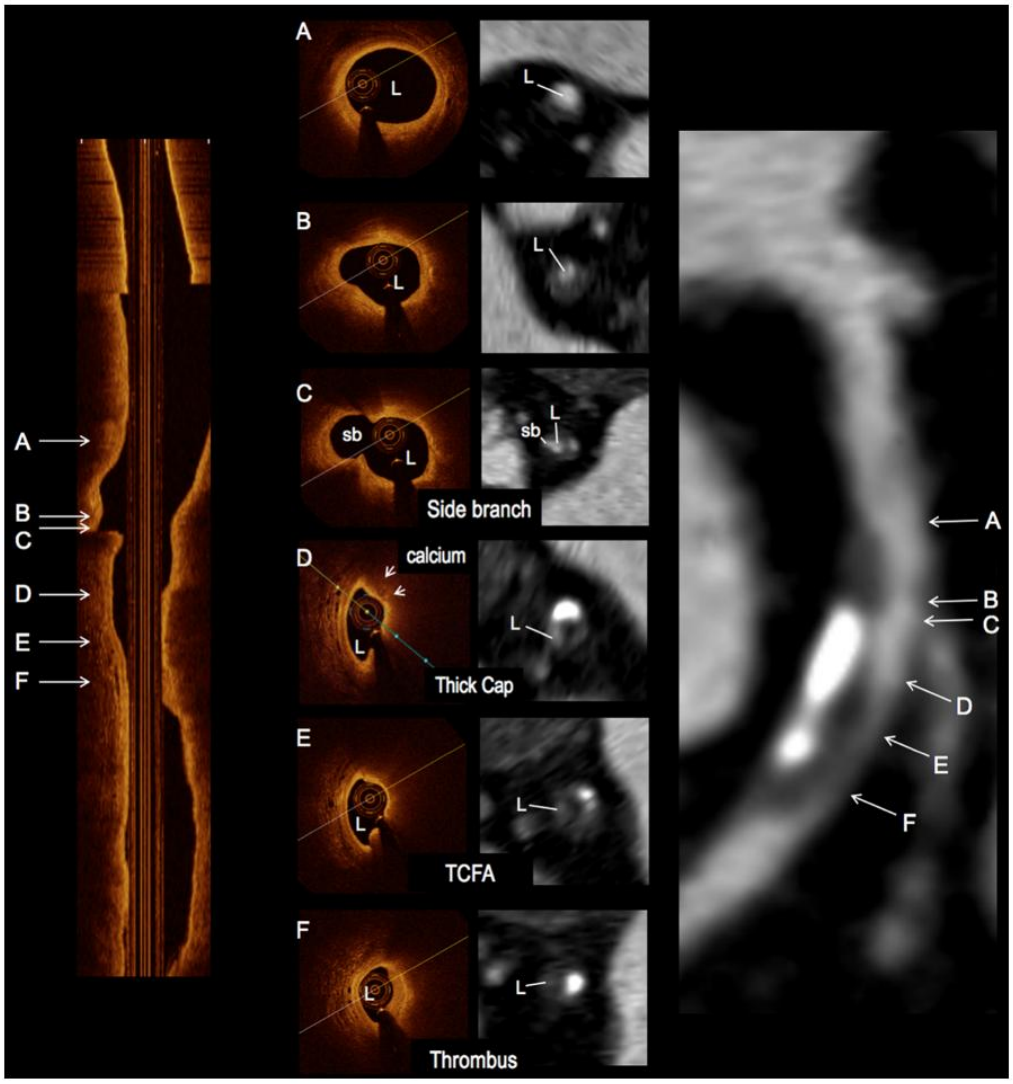
CCTA studies have suggested that plaques with spotty calcification might be considered vulnerable (125, 126, 145). The napkin-ring sign is an additional suspected CCTA feature of plaque vulnerability and represents a necrotic core with low attenuation surrounded by a ring-like area of higher attenuation (135, 136, 146, 147). Recent autopsy studies on human donor hearts confirmed the presence of a large necrotic core in plaques with a napkin-ring sign and showed excellent diagnostic accuracy of the napkin-ring sign for TCFA (147).



Bom MJ et al. Circulation: Cardiovascular Imaging. 2017;10:e005973

Plaque quantification and characterization by automated software has been proposed to increase prognostic value of CCTA in recent years, and studies have shown good correlation with VH-IVUS and OCT (138, 140, 144).

Correlation between OCT and CCTA



Yang DH, et al. Eur Radiol (2018) 28:833–843

4.4.1.2 Positron Emission Tomography

Although Positron Emission Tomography (PET) has been used widely in oncology for several decades, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and ^{18}F-sodium fluoride (^{18}F-NaF) have been proposed in the imaging of atherosclerosis. ^{18}F-FDG is a radiolabeled glucose analogue, and its uptake determined by PET imaging can be used as a surrogate for metabolic activity (148). ^{18}F-FDG uptake has been linked with increased plaque macrophage density in animal models and in human carotid arteries after endarterectomy and is considered to be a marker of plaque inflammation and vulnerability (149-151).

^{18}F-NaF is a PET tracer that detects areas of microcalcification by binding to hydroxyapatite and is not hampered by uptake in the myocardium (152). Unlike macrocalcification, which can be visualized by CT, these microcalcifications are considered an important feature of the vulnerable plaque (153). The prognostic value of ^{18}F-NaF uptake was recently confirmed in a prospective study that showed that ^{18}F-NaF uptake was higher in culprit lesions than in non-culprit lesions in patients after MI and in patients with symptomatic carotid artery disease (154). Furthermore, ^{18}F-NaF uptake showed a trend for the identification of TCFA on intravascular ultrasound (P=0.068) (154). ^{18}F-NaF PET imaging seems a promising imaging technique for the non-invasive identification of vulnerable plaques.

4.4.1.3 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) has been widely used in carotid artery disease to differentiate between plaque components and to study high-risk plaque features (155). The identification of intraplaque hemorrhage, lipid core, fibrous tissue components, and calcification can be achieved by the use of several MRI image techniques, that is, pre- and post-contrast T1-weighted, T2-weighted, proton-density, and time-of-flight imaging. The use of MRI in coronary arteries however is limited by its relatively low spatial resolution and by cardiac and respiratory motion.

Despite these limitations, the use of MRI has shown some potential in CAD. A post-mortem study on 28 plaques obtained from human donor hearts has reported an excellent correlation of ex vivo T1-weighted, T2-weighted, and ultrashort echo time MRI with histology for the identification of calcified and lipid-rich coronary plaques (156). High signal intensity on T1-weighted images is reported to be a marker for intraplaque hemorrhage and intracoronary thrombus and is shown to be associated with IVUS-derived positive remodeling (157), with low CT-attenuation and with OCT-derived intracoronary thrombus (158, 159), macrophage accumulation (160), lipid-rich plaque, plaque rupture, and TCFA (159). Further studies are needed to evaluate the role of the various MRI techniques in the visualization of the suspected vulnerable plaque.

4.4.2 Invasive techniques

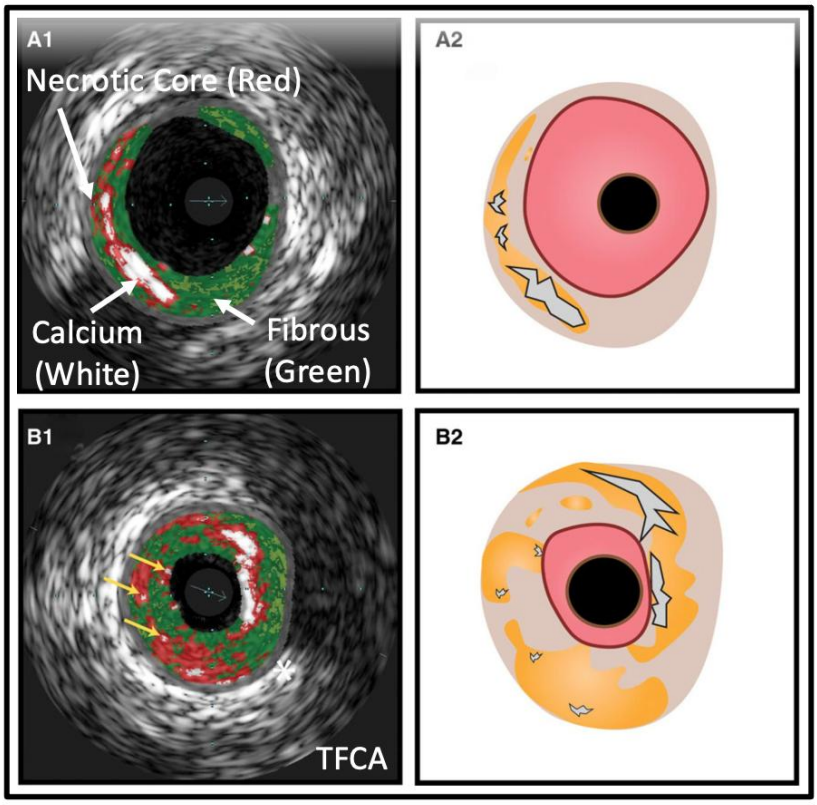
4.4.2.1 Intravascular Ultrasound

Intravascular Ultrasound (IVUS) is an intravascular imaging technique based on the reflection of emitted ultrasound waves, according to the acoustic properties of the tissue (161). Gray scale IVUS is based only on the amplitude of sound waves backscattered from tissue and results in relatively low spatial resolution that hampers detailed plaque characterization. Radiofrequency analysis IVUS has been introduced, of which virtual histology (VH-IVUS) is the most widely available. This technology uses frequency in addition to echo-intensity information to compose an intraluminal image of the coronary artery wall. VH-IVUS can visualize 4 distinct plaque components, that is, fibrous plaque, fibrofatty plaque, necrotic core, and calcium, as shown (162-164).

TCFA can be identified by VH-IVUS in fair good correlation with histology despite an axial resolution (100–200 μm) that limits the visualization of a thin FCT (≤65 μm) (133, 165, 166). VH-derived TCFA (VH-TCFA) is defined as a lesion with a confluent necrotic core (≥10%) plaque in direct contact with the lumen (97, 165, 167, 168). Three relevant studies have been published on the prognostic value of VH-TCFA. PROSPECT study (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) (97), VIVA study (Virtual Histology in Vulnerable Atherosclerosis) (167), and ATHEROREMO-IVUS study (European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound)

(168); although these studies have shown that large plaque burden is a common feature of ruptured plaques, the combined end points were mainly driven by unstable or refractory angina, instead of MI and death.

Plaque morphology with the use of VH-IVUS



Bom MJ et al. Circulation: Cardiovascular Imaging. 2017;10:e005973

Positive remodeling as defined by gray scale IVUS has been reported to be more common in patients with ACS and at sites with ruptured plaques (169-171). Lesions with positive remodeling more frequently had a large plaque burden (≥70%), when compared with lesions with intermediate or negative remodeling (97, 167, 168). IVUS studies have also identified a

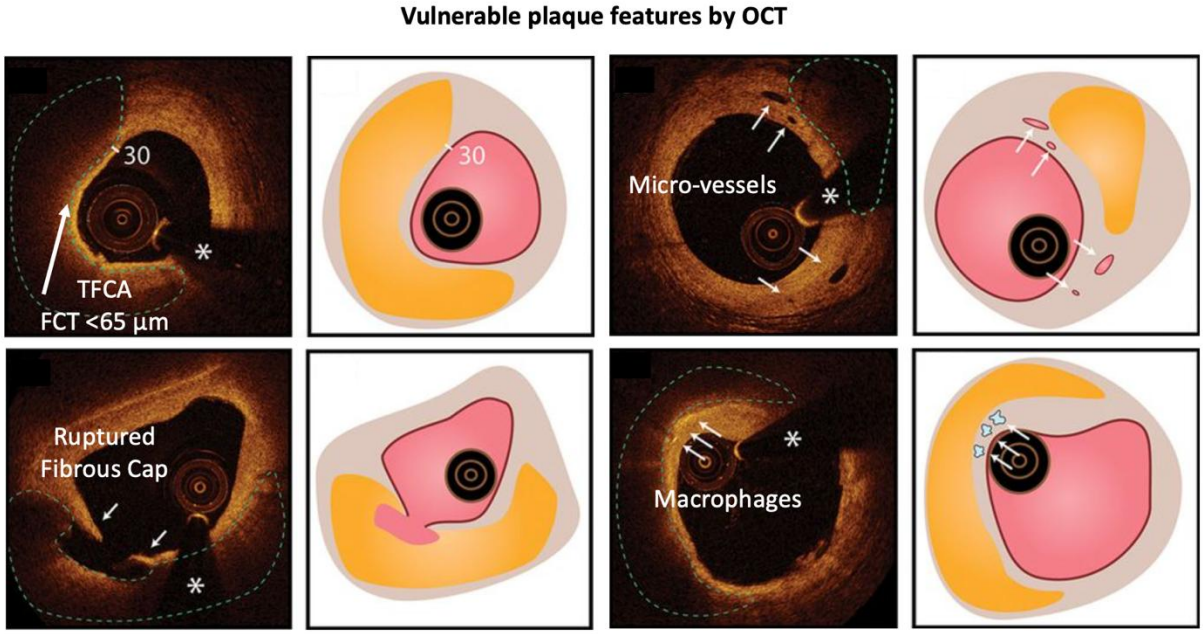
specific pattern of calcification, called spotty calcification, which is thought to be a marker of plaque vulnerability (172-175). Spotty calcification on IVUS has been associated with ACS (172), with ruptured plaques in autopsy studies (173), and with VH-TCFA and a large necrotic core.

4.4.2.2 Optical Coherence Tomography

Optical Coherence Tomography (OCT) is an intravascular imaging technique based on infrared light source directed at the vessel wall, using the backscattered light to produce an image of the tissue. The resolution of OCT surpasses that of IVUS with an axial resolution of 10 to 20 µm (versus 100–250 µm, respectively), at the cost of a limited depth penetration 0.1 to 2.0 mm (versus 7–10 mm, respectively). OCT was proposed in the beginning as an alternative to IVUS in the guidance of PCI procedures (176-178), and in the visualization of plaque morphology in vivo with good histology correlation (179). Studies that directly compare the ability of IVUS and OCT to identify histopathologic TCFA have consistently shown better performance of OCT, as OCT allows to measure the thin FCT (<65 µm) (133, 165).

There are additional parameters to define vulnerable plaque more than TCFA. The arc of the lipid pool must be large, as a surrogate for a large necrotic core, with a frequently used cut-off of ≥90° (180-182). Macrophage infiltration of the thin fibrous cap is thought to be an important feature of the vulnerable plaque (87). Macrophages appear on OCT as so-called bright spots with a high signal attenuation behind it (24). Vaso vasorum and micro vessels within coronary atherosclerotic plaques can be visualized by OCT, appearing as microchannels (183, 184).

Several reports have shown a correlation between the density of microchannels in OCT and plaque vulnerability (defined as TCFA) and increase in plaque volume (181, 182, 185, 186).



Bom MJ et al. Circulation: Cardiovascular Imaging. 2017;10:e005973

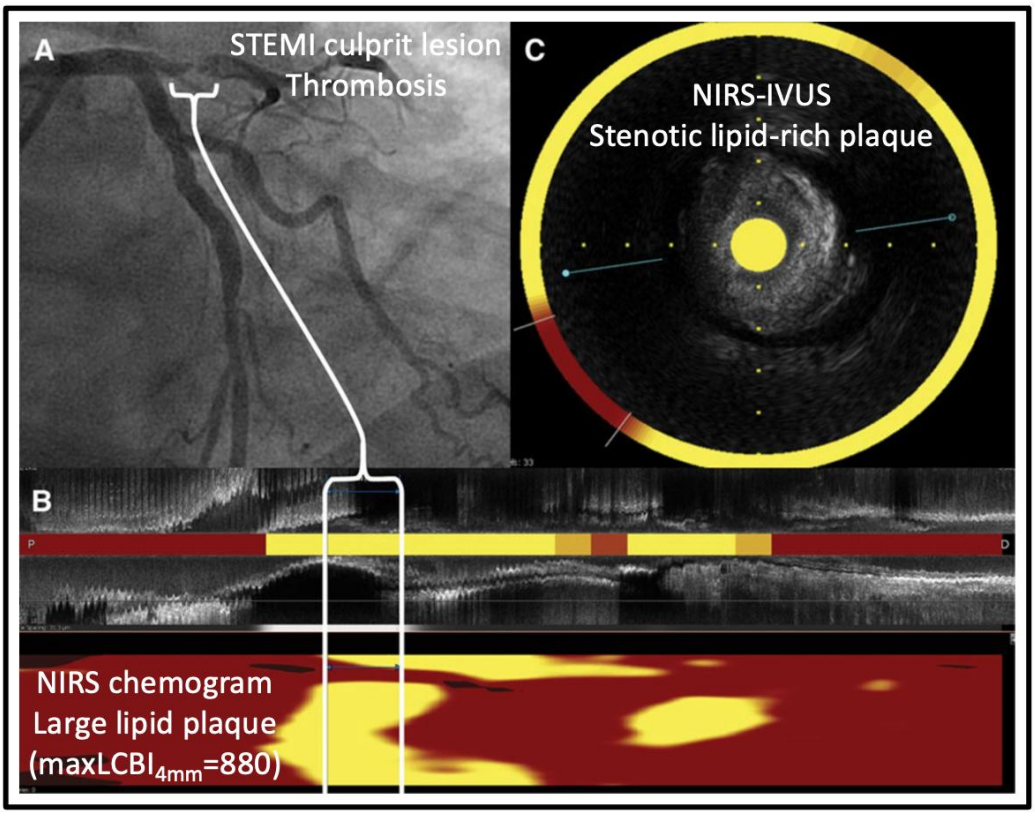
4.4.2.3 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is an intravascular imaging technique based on a scanning laser that delivers near-infrared light to the tissue of interest and the proportion of light reflected back is measured over the range of optical wavelength by a detector. Cholesterol has specific features in the wavelength region of NIRS, allowing distinct imaging of a lipid core plaque (187). The measured data are displayed as a chemogram, a 2D visualization of the probability of the presence of a lipid plaque per millimeter. NIRS data can also be used to calculate a lipid core burden index (LCBI), which is the amount of lipid in a scanned artery.

LCBI4mm is commonly used to represent the amount of lipid in a coronary segment of 4 mm length.

NIRS alone, however, is limited by its inability to provide information about the lumen and plaque depth. Therefore, NIRS is commonly combined with IVUS in a combined NIRS-IVUS catheter, in which both techniques can be acquired simultaneously. Multiple post-mortem studies have compared the ability of NIRS and gray scale IVUS alone versus combined NIRS-IVUS to identify fibroatheroma and showed that combined NIRS-IVUS was superior to NIRS or IVUS alone (188, 189). In vivo studies have shown that with NIRS-IVUS, LCBI4mm with a cut-off of >400 was able to identify culprit lesions in patients with STEMI, non-STEMI, and unstable angina (190, 191).

Vulnerable plaque features by NIRS-IVUS



Bom MJ et al. Circulation: Cardiovascular Imaging. 2017;10:e005973
Images from Ryan Madder, MD, Spectrum Health, Grand Rapids, MI, USA

4.5 VULNERABLE PLAQUE CLINICAL SIGNIFICANCE

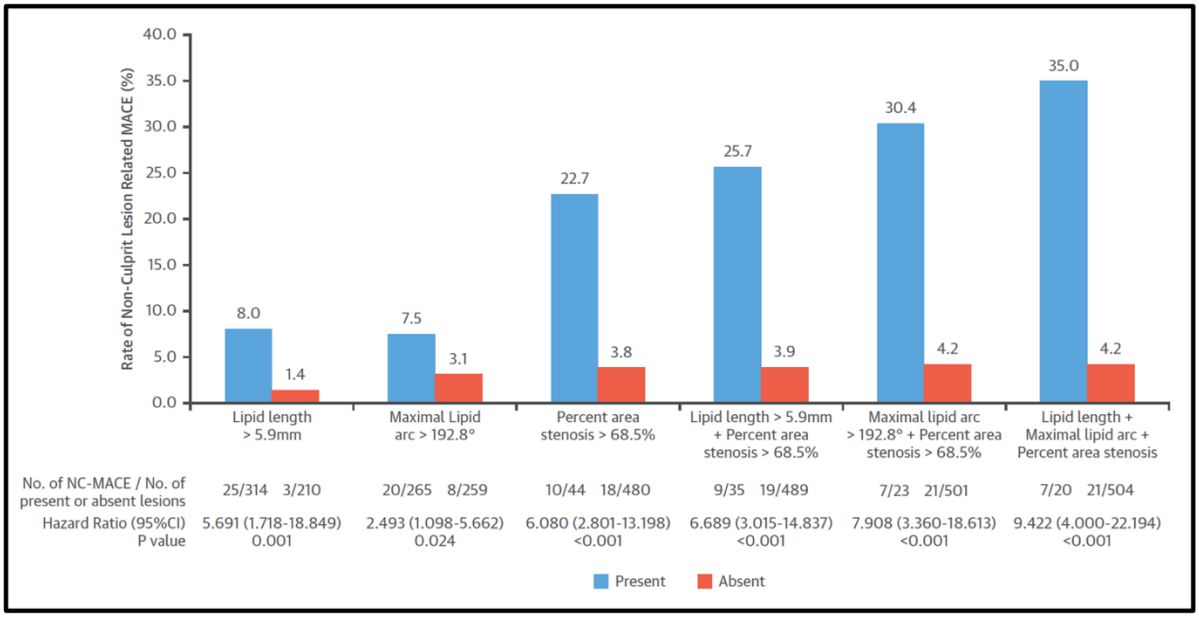
Despite advances in pharmacological therapy and PCI, recurrent major adverse cardiac events (MACE) still occur in patients with coronary artery disease (192, 193). Vulnerable plaque is thought to be responsible for most cases of MACE (89). There have been several academic efforts focused on the detection of vulnerable plaque, under the premise that local treatment could prevent future MACE. Given the high resolution, OCT did open the window for in-vivo diagnosis; however, there is ongoing research focus on other plaque and lumen criteria that can be combined with imaging-based diagnosis of vulnerable plaque to justify local intervention.

Recurrent cardiac ischemic events can be due to recurrence at the original treatment site, the presence of untreated lesions elsewhere, or lesion progression. Pathological studies have shown thrombotic coronary occlusion after rupture of a vulnerable plaque with only a thin fibrous layer of intimal tissue covering the necrotic core; TCFA, is the most common cause of myocardial infarction and SCD (89, 194, 195). Several years and pathology studies were needed to understand the pathophysiology of ACS; after understanding in detail, clinical practice faced the challenge of the in-vivo diagnosis of vulnerable plaque. The prospective identification of TCFA was not possible until high-resolution intravascular imaging techniques like IVUS and OCT were available. The new challenge is to know how to tackle vulnerable plaques in non-culprit sites or no significant luminal stenosis.

Despite of the challenges to understand how to treat vulnerable plaques, these are known to be more unstable, prone to rupture, and become highly thrombogenic when disrupted (196). A previous autopsy study in patients with fatal MI demonstrated vulnerable plaque with superimposed thrombus at most of the culprit sites (197). Studies of vulnerable plaque at culprit sites detected by OCT and other intravascular imaging modalities in ACS patients documented a close association between vulnerable plaque and cardiovascular events (198). Madder et al. (199) reported the association between large lipid-rich plaques, detected by NIRS, at non-stented sites in a target vessel and subsequent events.

Xing et al. (200) showed in a retrospective fashion that one-third of patients with ACS had a vulnerable high-risk plaque in a non-culprit region; related to a higher incidence of future cardiac events than those patients without a high-risk plaque. Vulnerable plaques related to MACE showed longer lipid length, wider lipid arc, and smaller luminal size. When analyzing OCT predictors, a curve analysis identified as best cut-off values lipid length >5.9 mm (area under curve [AUC]: 0.656; p = 0.005); maximal lipid arc of >192.8^{o} (AUC: 0.640; p = 0.012); and %AS of >68.5% (AUC: 0.656; p = 0.005). The cumulative Kaplan-Meier analysis showed MACE rate rose to 35.0% when all three criteria where combined. Presence of vulnerable plaque does not necessarily lead to MACE but it is an indicator of higher risk for future cardiac events. These findings indicated that detection of vulnerable plaque by OCT in the non-culprit regions could predict increased risk for future MACE; then OCT imaging might help to stratify the risk of patients undergoing PCI for future cardiac events.

OCT parameters alone or in combination and rate of non-culprit lesion related MACE.

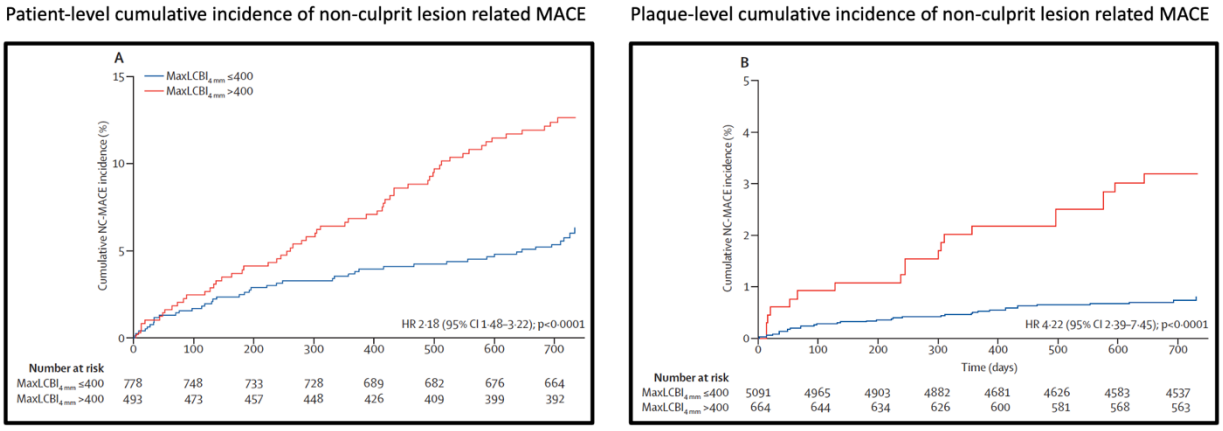


Xing, L et al. J Am Coll Cardiol 2017 Vol. 69 Issue 20 Pages 2502-2513

There have been other studies with different imaging modalities trying to understand the clinical significance of vulnerable plaque. The limited ability of IVUS to accurately identify lipid core in plaques, considered to be a primary defining feature of vulnerable plaques, led to an effort to develop NIRS, a technique with a high sensitivity for lipid plaque detection. Waksman et al. (201) conducted the Lipid-Rich Plaque study; a prospective trial that aimed to establish the relationship between lipid rich plaques detected by NIRS-IVUS imaging at unstented sites and subsequent coronary events from new culprit lesions. Patients were enrolled after successful culprit lesion PCI.

The 2-year cumulative incidence of non-culprit lesion related MACE was 9%. On a patient level, the unadjusted hazard ratio (HR) for non-culprit lesion related MACE was 1·21 (95% CI 1·09–1·35; p=0·0004) for each 100-unit increase maxLCBI4mm) and adjusted HR 1·18 (1·05–1·32; p=0·0043). In patients with a maxLCBI$_{4mm}$ more than 400, the unadjusted HR for non-culprit lesion related MACE was 2·18 (1·48–3·22; p<0·0001) and adjusted HR was 1·89 (1·26–2·83; p=0·0021). At the plaque level, the unadjusted HR was 1·45 (1·30–1·60; p<0·0001) for each 100-unit increase in maxLCBI$_{4mm}$. For segments with a maxLCBI$_{4mm}$ more than 400, the unadjusted HR for non-culprit lesion related MACE was 4·22 (2·39–7·45; p<0·0001) and adjusted HR was 3·39 (1·85–6·20; p<0·0001).

LIPID-RICH PLAQUE Study. Kaplan-Meier time-to-first event curves for NCL-related MACEs



Waksman, R et al. Lancet 2019 Vol. 394 Issue 10209 Pages 1629-1637

The largest natural history studies about atherosclerosis are the PROSPECT trials. In the first PROSPECT publication, Stone et al. (97) showed that in patients who presented with an ACS and

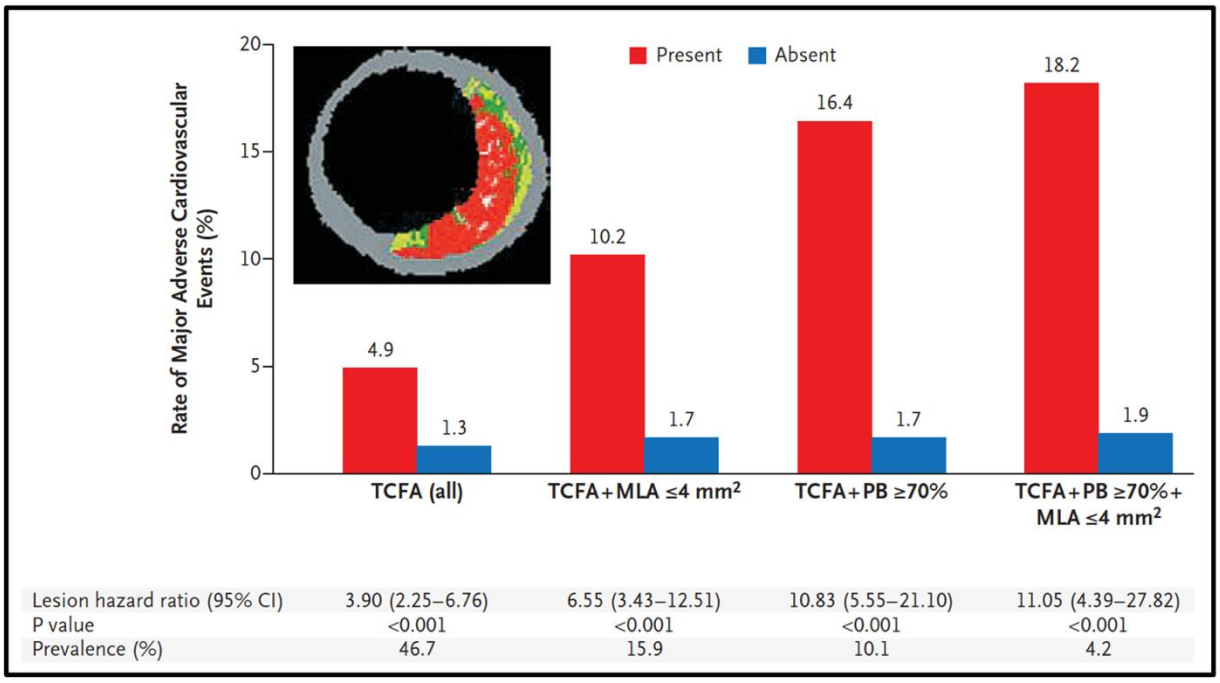
underwent PCI of culprit and flow limiting lesions, MACE occurring during follow-up were equally attributable to recurrence at the site of culprit lesions and to non-culprit lesions. Although non-culprit lesions that were responsible for unanticipated events were frequently angiographically mild, most were TCFAs or were characterized by a large plaque burden, a small luminal area, or some combination of these characteristics, as determined by IVUS. It is important to acknowledge important limitations: TCFA was defined by VH-IVUS that is a limited technique to accurately define TCFA, and that most of the MACE were target lesion revascularization, mainly due to plaque progression to obstructive lesions.

One of the most important concepts to understand the risk of future ischemic cardiac events is lesion progression; Virmani et al. (67), whereby the atherosclerotic lesion progresses from a low-risk to a high-risk phenotype before plaque ruptures. PROSPECT showed that despite undergoing successful PCI for all coronary stenoses believed to require revascularization, within 3 years after treatment 11.6% of patients had unanticipated MACE associated with untreated coronary segments. Most of these sites showed no evidence of severe stenosis on initial conventional angiography, but the prospective fashion of PROSPECT was able to identify three characteristics of lesions that were significant predictors of subsequent events: a small luminal area, a large plaque burden, and the presence of TCFA.

Estimated Kaplan-Meier events when TCFA criteria were present was 4.9%, when plaque burden of at least 70% rate was 9.6% and when minimal luminal area of 4.0 mm^2 or less, event

rate was 5.3%. When all three predictive variables were present, the event rate rose to 18.2%. This suggest that although such lesion characteristics are conducive to the occurrence of a subsequent event, they are not sufficient to predict which atheromas will undergo plaque progression in the intermediate term.

PROSPECT. MACE rate for lesions that were and were not TCFA at a median follow up of 3.4 years



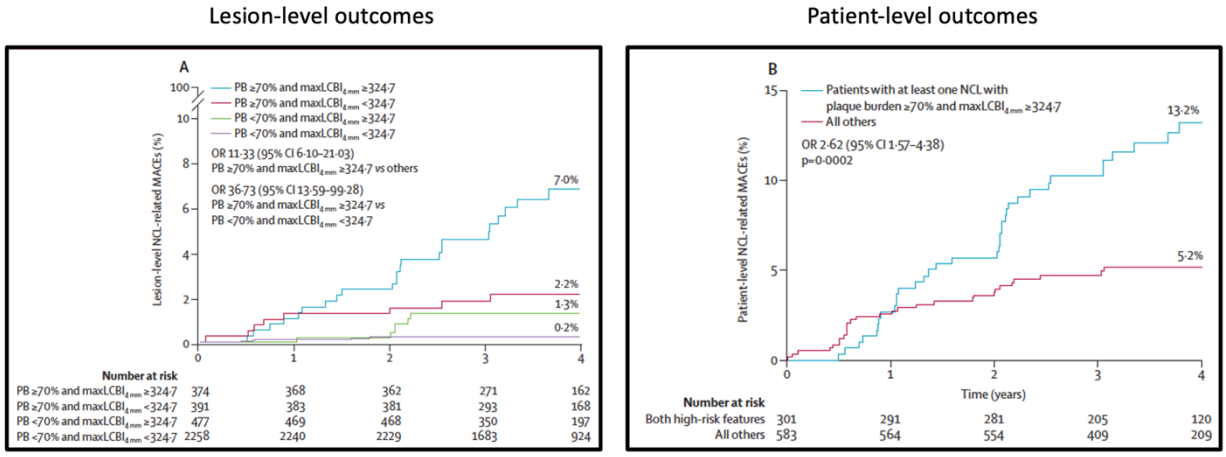
Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

Stone, GW et al. N Engl J Med 2011 Vol. 364 Issue 3 Pages 226-35

Erlinge et al. (202) conducted PROSPECT II, a prospective natural history study. Similar design that PROSPECT, patients were recruited after successful PCI of all flow limiting lesions while presenting with ACS. 3 vessel imaging was performed to detect non-culprit lesions, that were identified by intravascular ultrasound and their lipid content was assessed by NIRS. The primary outcome was the covariate-adjusted rate of MACEs (the composite of cardiac death, myocardial

infarction, unstable angina, or progressive angina) arising from untreated non-culprit lesions during 4-year follow-up.

PROSPECT II. Kaplan-Meier time-to-first event curves for NCL-related MACEs



Erlinge, D et al. Lancet 2021 Vol. 397 Issue 10278 Pages 985-995

The 4-year MACE rate arising from plaques with the combination of maxLCBI$_{4mm}$ of 324·7 or greater and plaque burden of 70% or greater was 7% (95% CI 4·0–10·0) per lesion, and patients with one or more of these high-risk plaques had a 4-year MACE rate of 13% (95% CI 9·4–17·6). This study establishes the incremental value of identifying high lipid content in lesions with a large plaque burden. Untreated lesions with both high lipid content and large plaque burden represented those at the highest risk for subsequent MACEs within 4 years.

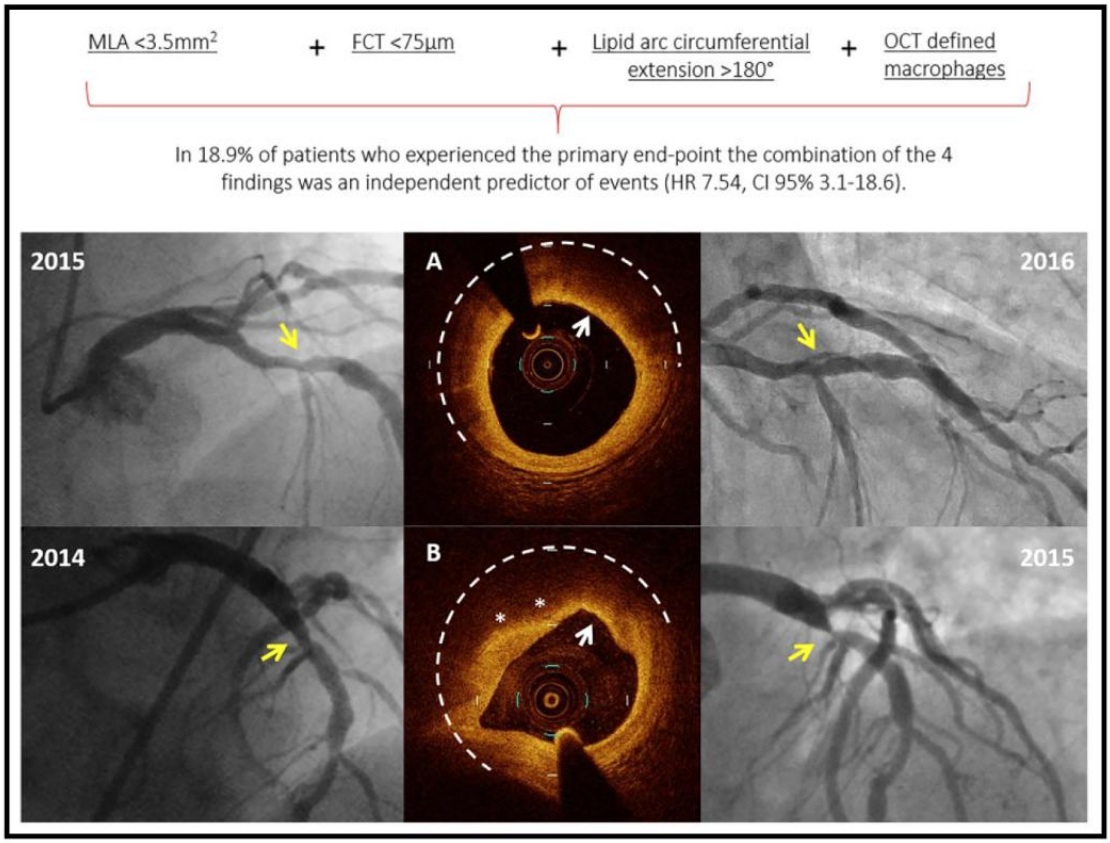
Equally informative is the negative predictive value of low-risk plaques. In the first PROSPECT study (97), no non-culprit lesion-related MACEs arose within 3 years from a lesion with plaque

burden less than 40%. In PROSPECT II study, no non-culprit lesion-related MACEs arose within 4 years from a lesion with plaque burden lower than 56%. Indeed, 65% of the non-culprit lesions had both plaque burden lower than 70% and maxLCBI4mm less than 324·7; the 4-year non-culprit lesion-related MACE rate from these lesions was only 0·2% (95% CI 0·1–0·5). Even if one of the two major predictive high-risk plaque features (large plaque burden or high lipid content) was present, the 4-year lesion-related MACE rate was only 1·3–2·2%, suggesting that high-risk features impact outcomes in a synergistic manner.

With the initial imaging studies, different modalities thresholds and specific criteria were linked to a higher risk of MACE. Most recent studies have tried to test those findings in specific populations. The CLIMA study (203) is a prospective observational, multicenter registry that recruited patients undergoing OCT assessment of the proximal left anterior descending atherosclerosis with the intent to explore the predictive value of multiple high-risk plaque features in the same coronary lesion. Composite of cardiac death and target segment myocardial infarction was the primary clinical endpoint.

Definitions and cut-offs for OCT parameters that defined high-risk plaques were MLA <3.5 mm^2 measured along the entire length of the assessed coronary segment, derived from the 4.0 mm^2 cut-off applied in the PROSPECT clinical study (97), and corrected for the relative IVUS overestimation (24, 204); minimum FCT <75 μm, lipid arc extension >180^o, and presence of macrophage clusters.

CLIMA Study. High-risk plaques and subsequent risk of cardiovascular events

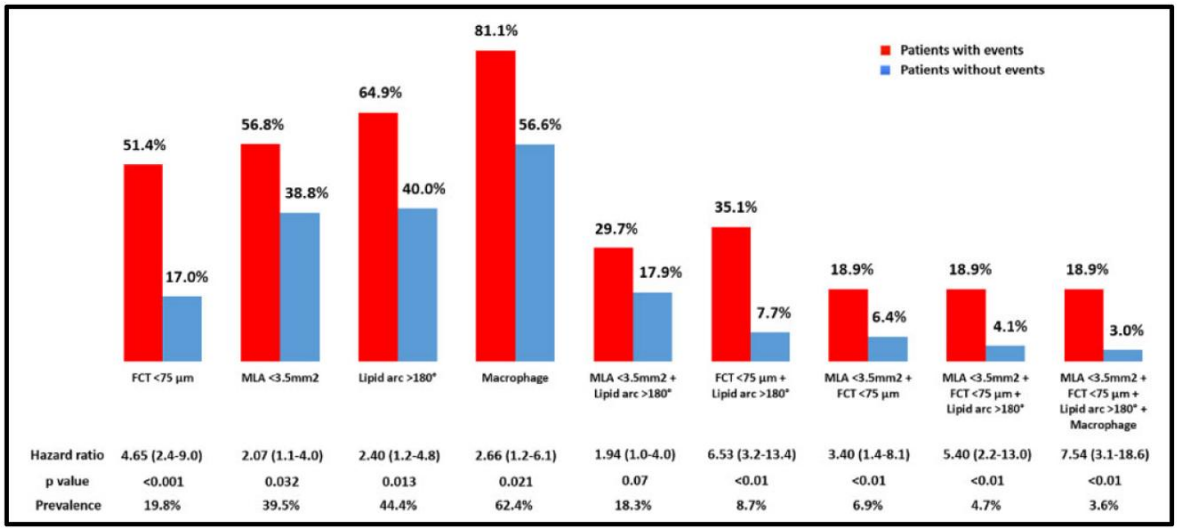


Prati, F et al. Eur Heart J 2020 Vol. 41 Issue 3 Pages 383-391

At 1-year, the primary clinical endpoint was observed 3.7% of the patients. The presence of MLA <3.5 mm^2 [HR 2.1, 95% CI 1.1–4.0, p = 0.032], FCT <75 mm (HR 4.7, 95% CI 2.4–9.0, p<0.001), lipid arc circumferential extension >180^o (HR 2.4, 95% CI 1.2–4.8, p = 0.013), and OCT-defined macrophages (HR 2.7, 95% CI 1.2–6.1, p = 0.021) were all associated with increased risk of the primary endpoint. The pre-specified combination of plaque features (simultaneous presence of the four OCT criteria in the same plaque) was observed in 18.9% of patients

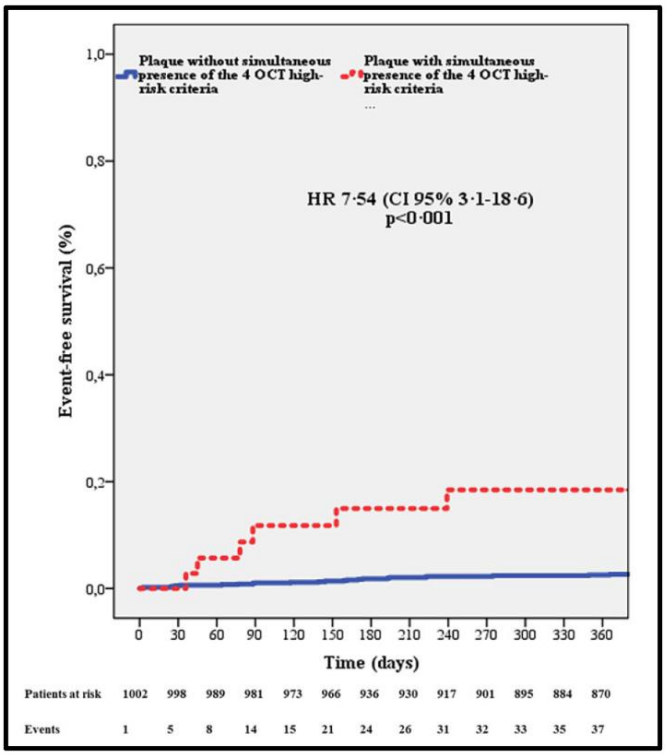
experiencing the primary endpoint and was an independent predictor of events (HR 7.54, 95% CI 3.1–18.6, p<0.001).

CLIMA Study. One-year event rates for lesions with and without OCT-defined high-risk criteria.



Prati, F et al. Eur Heart J 2020 Vol. 41 Issue 3 Pages 383-391

CLIMA. Clinical outcomes.



Prati, F et al. Eur Heart J 2020 Vol. 41 Issue 3 Pages 383-391

The CLIMA study showed the simultaneous presence of multiple OCT high-risk coronary plaque features in about 20% of patients with MACEs in the first year of follow-up. Future larger studies with longer follow-up are needed to determine if these features provide incremental value over clinical variables and to understand whether personalized medical treatment or interventional procedures can improve clinical outcome in presence of such high-risk coronary plaques.

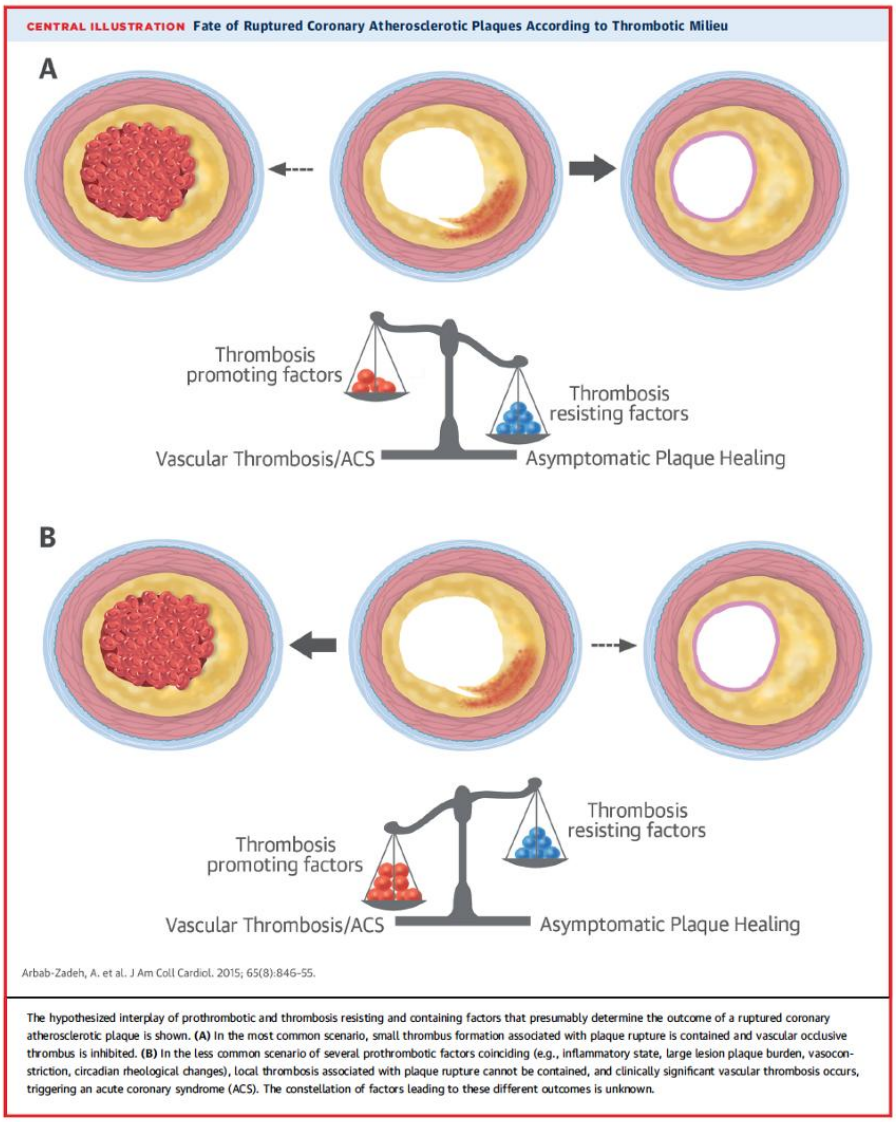
There is enough evidence that untreated non-ischemic lesions have higher rates of MACE during follow-up in patients with ACS than in chronic coronary syndromes (205). Treatment of non-culprit lesions that are angiographically severe or ischemic has been shown to reduce reinfarction rates in STEMI (22). However, whether prophylactic revascularization of angiographically non-severe high-risk lesions that are no flow limiting may be safely performed and improve patient outcomes is still under ongoing investigation. There has always been debate whether we should approach these no flow limiting lesions with physiology or imaging.

4.6 THE MYTH OF VULNERABLE PLAQUES

Over the past few decades, clinical and laboratory investigations have led to a more complex concept of the pathophysiology of acute coronary events, involving numerous processes, many with poorly understood interactions (206, 207). Although the occurrence of acute coronary events typically requires alterations of coronary atherosclerotic plaques (rupture or erosion), a thrombosis-promoting milieu is necessary to allow a clinically significant decrease in coronary blood flow and associated myocardial ischemia (206-208).

Such a setting appears to result from an unfortunate constellation of prothrombotic features, for example, in patients with increased inflammatory activity and systemic or local suppression of fibrinolytic performance, an extraordinarily large stimulus for thrombosis, vasoconstriction, and/or others (206). The respective contributions of these factors (some hereditary, some environmental) and their temporal relationships necessary to trigger clinically meaningful vascular thrombosis are unknown.

Factors favoring thrombosis need to be collectively sufficient to tilt the scale away from localized thrombus and toward extensive vascular thrombosis. Because numerous factors influence the performance of the coagulation system at any given point in time, acute coronary events may arise as result of a “perfect storm” scenario, in which plaque disruption occurs in a specific, thrombosis-promoting setting (206).



Arbab-Zadeh, A et al. J Am Coll Cardiol 2015 Vol. 65 Issue 8 Pages 846-855

The risk of an acute coronary event equals the probability of plaque rupture or erosion coinciding with vascular thrombosis-promoting conditions that cannot contain the thrombus in

the vascular wall. Frequent plaque ruptures, as with a large, metabolically active atherosclerotic disease burden, increase the chance that a plaque rupture coincides with a thrombosis conducive setting. Accordingly, the strongest predictors of adverse events are the magnitude and activity of the coronary atherosclerotic plaque burden and the number of risk factors for a prothrombotic milieu, a concept supported by many clinical studies and epidemiologic data (209-213).

Coronary artery imaging has provided insights into numerous lesion characteristics, but we have yet to identify which are useful for guiding management. Individual plaque features may have particular significance in specific settings; for example, TCFAs may have different implications in patients with or without known susceptibility to vascular thrombosis. Thus, integration of lesion characteristics with risk factors may be valuable. Currently unknown features of atherosclerotic plaque may conceivably independently herald poor outcome.

Advanced imaging techniques may elucidate such features and allow further insights into mechanisms of acute coronary event pathophysiology (214). To determine truly independent risk prediction, any plaque assessment should be measured against the predictive power of atherosclerotic burden and its metabolic activity.

Although general morphologic patterns of atherosclerotic disease influence the probability of ACS, they are clearly modified by individual characteristics. Furthermore, the patterns and

morphologic features of atherosclerotic disease appear similar among populations, suggesting that the patient's response to a thrombogenic trigger is critical for determining the probability of events. Traditional risk factors for coronary artery disease (e.g., diabetes, smoking, dyslipidemia) and genetic predisposition modify such responses. Several mutations are also associated with increased event hazard, and individualized risk characterization may soon be available (215-217).

We need a better understanding of which combination of imaging information and risk factors yields the most accurate individual risk prediction. Research is needed to investigate mechanisms influencing the coagulation system's response to various internal and external modifiers, both locally and systemically. Specifically, we need to understand and potentially to predict the response of the coagulation system to stimuli occurring with atherosclerotic plaque alterations. Variability in the coagulation system's performance depends on numerous hormonal, dietary, and environmental influences, hampering our ability to predict its function at a given time (218-220).

Thus, we must strive for comprehensive risk assessment that integrates specific information on the atherosclerotic plaque burden and systemic factors that increase the risk for disease activity and vascular thrombosis and is tailored to specific patient populations and individual patients. This would enable effective, efficient triaging of patients into treatment categories ranging from continued risk factor control to coronary arterial revascularization (221).

4.6.1 Are there *JUST* "vulnerable plaques" *OR* "vulnerable patients"?

Despite significant advances in diagnostics, ranging from blood testing to genetics, imaging, hemodynamics, and 'omics'; identification of patients and plaques at higher risk of adverse events remains limited.

The positive predictive value of detecting the high-risk plaque characteristics remains too low for clinical relevance, and it is also still unclear which individual plaque features are most useful in predicting the 'hard' clinical endpoint of death and myocardial infarction.

Nevertheless, improving imaging modalities supported by ongoing deep machine learning-based developments provide new avenues of precision medicine that are likely to translate into personalized preventive and therapeutic approaches to high-risk plaques occurring in 'vulnerable' patients. Further interdisciplinary research taking advantage of opportunities offered by both systemic and 'local' diagnostics and therapies is warranted.

Two important messages around vulnerability:

- Atherosclerosis—as a systemic disease with focal manifestations— may require systemic pharmacologic therapy and local interventional treatment of advanced lesions.

• Improving coronary plaque imaging may be instrumental in guiding pharmacotherapy, facilitating optimal allocation of novel, more aggressive, and costly treatment strategies and tailoring the treatment of ACS to a specific underlying mechanism (culprit plaque rupture, erosion, calcified nodule, or functional coronary alterations).

4.7 WHICH IS THE BEST METHOD TO GUIDE NON-CULPRIT LESION REVASCULARIZATION?

The COMPLETE trial definitively established the benefit of a complete revascularization strategy in patients with STEMI and multivessel CAD (22). COMPLETE was a multinational, randomized trial evaluating a strategy of complete revascularization, consisting of angiography-guided PCI of all suitable non-culprit-lesions versus a strategy of culprit-lesion-only PCI (optimal medical therapy alone), in 4,041 patients from 140 centres in 31 countries undergoing primary PCI for acute STEMI. Complete revascularization, defined by the angiographic core laboratory as successful treatment of all target lesions, was achieved in 99.1% of patients randomized to this arm of the trial. At a median follow-up of 3 years, complete revascularization reduced the first co-primary outcome of CV death or MI by 26% compared with the culprit-lesion only strategy (HR 0.74; 95% CI 0.60-0.91; P=0.004). The second co-primary outcome of CV death, new MI or ischemia-driven revascularization was reduced by 49% with complete revascularization (HR 0.51; 95% CI 0.43-0.61; P<0.001). The results of COMPLETE have had a far-reaching impact on global practice and is being incorporated into guideline recommendations.

However, it has also raised new questions on how to optimally manage these high-risk patients. The most critical questions are: How to select which non-culprit lesions could benefit from revascularization? All of them despite of the angiographic complexity? Only the non-culprit lesions causing ischemia assessed by physiology? Only the ones that have vulnerable features? Or a combination of ischemic and vulnerable lesions?

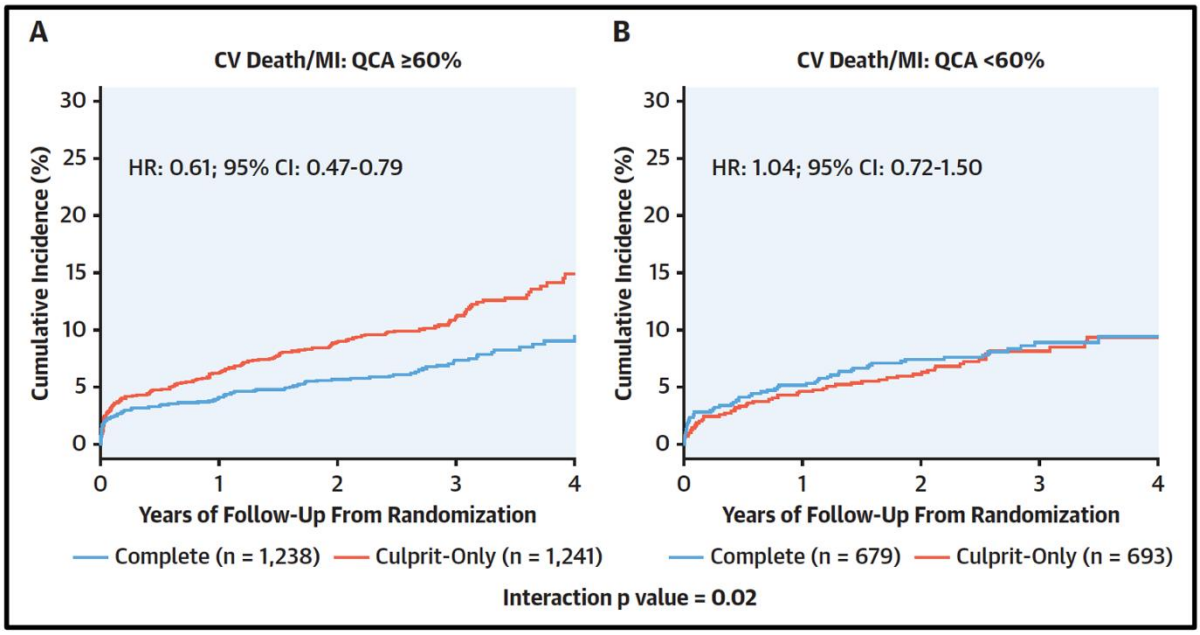
4.7.1 Angiography-Guided Non-Culprit Lesion Revascularization

Angiography-guided PCI is the most common method used to identify lesions suitable for PCI because this approach is simple to perform and has broad applicability. It was the strategy in the COMPLETE trial to identify non-culprit lesions judged to be ≥70% by visual estimation of the operator.

Despite the success of this approach in guiding non-culprit PCI, there are potential limitations of an angiography-guided strategy. First, although angiography-guided non-culprit-lesion PCI reduced hard outcomes in COMPLETE, this approach could select some patients who do not require PCI, resulting in some unnecessary procedures, costs, and PCI-related complications. Second, data from the COMPLETE angiographic core lab analysis demonstrated that the benefit of complete revascularization is dependent on the degree of stenosis (Figure 1). A Quantitative Coronary Angiography (QCA) core lab analysis evaluated 3,851 patients with 5,355 non-culprit-lesions and found that, in the 2,479 patients with > 60% QCA stenosis, the first co-primary outcome was reduced with complete revascularization (HR 0.61; 95% CI 0.47-0.79), whereas in the 1,372 patients with QCA stenosis <60%, there appeared to be no benefit (HR 1.04; 95% CI 0.72-1.50; interaction P=0.02); suggesting that approximately 1/3 of patients with less severe lesions did not seem to benefit from an angiography-guided non-culprit lesion PCI

strategy (222). Third, visual stenosis severity judged by operators correlates poorly with QCA values measured in an angiographic core lab.

COMPLETE. Kaplan-Meier Estimates of the Cumulative Incidence of CV death or MI by subgroups of stenosis severity



Mehta, SR et al. N Engl J Med 2019 Vol. 381 Issue 15 Pages 1411-1421

4.7.2 Ischemia-Driven Lesion Revascularization

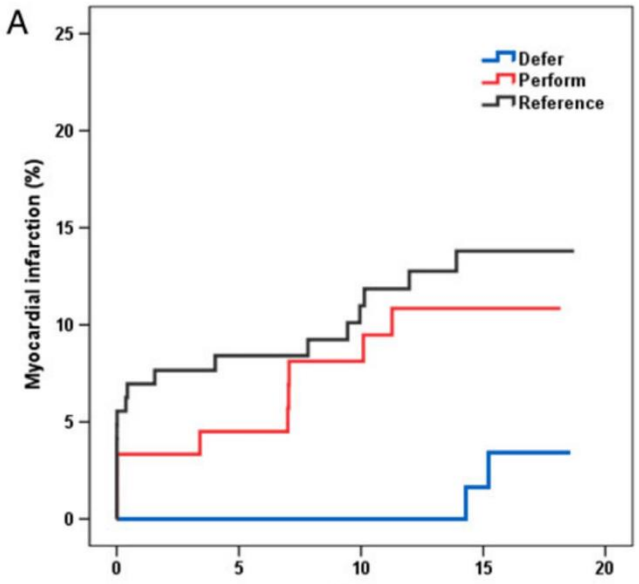
A physiology-guided approach addresses many of the limitations of an angiography-guided approach in identifying which lesions might benefit from revascularization (223). Physiology overcomes this limitation by localizing and quantifying the ischemic potential of epicardial stenoses and assessing the distal microcirculatory bed supplied by the coronary artery. In this way, only those lesions that are deemed to be functionally significant are treated with PCI; lesions that are not functionally significant do not receive PCI (they are “deferred”) and are treated with medical therapy alone.

The most used physiology-guided approach is Fractional Flow Reserve (FFR). There are also several resting indices; from which the most used and the only one with randomized clinical data is Instantaneous Wave Free Ratio (iFR). These resting indices are measured by inserting a pressure wire across a lesion and comparing the pressure distal to the stenosis with aortic pressure. FFR is measured under maximal hyperemic conditions, established by administering intravenous or intracoronary adenosine, while resting indices do not required hyperemia.

4.7.2.1 Ischemia-driven non-culprit Lesion Revascularization in SAP

An FFR-guided strategy for PCI is well established in patients with stable CAD and has been shown to be superior to an angiography-guided strategy. From the early studies that have compared FFR-guided to Angio-guided PCI; the one that has presented the longest follow-up is the DEFER study, randomized controlled trial that investigated the safety of deferring PCI in an angiographically significant, but functionally non-significant coronary stenosis as indicated by an FFR ≥ 0.75 in 325 patients. Results showed that even after 15 years of follow-up, the prognosis of functionally non-significant deferred lesions is excellent, that PCI of such stenoses has no advantage and even results in more MI when compared with medical therapy (224). These results extend from earlier findings in DEFER study at 2- and 5-year follow-up (225, 226).

DEFER. 15 years follow-up. Kaplan–Meier curves of Myocardial Infarction.



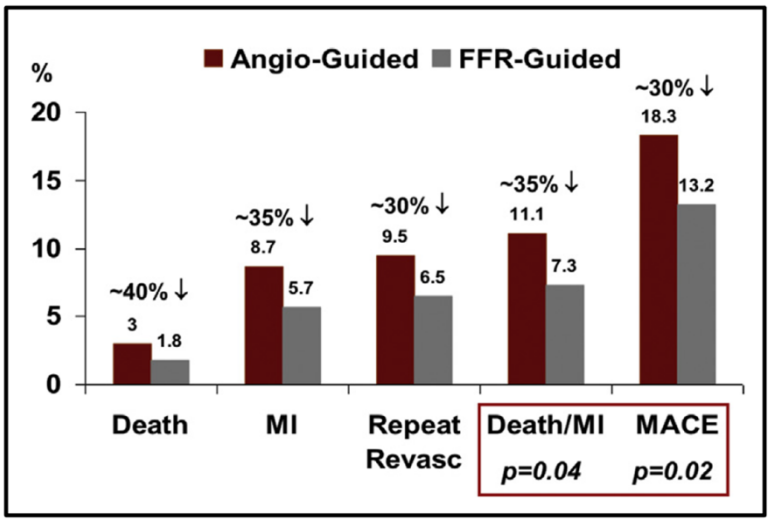
Zimmermann, FM et al. Eur Heart J 2015 Vol. 36 Issue 45 Pages 3182-8

Over the past decade, the landmark Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trials have established the clinical benefit of an FFR-directed strategy for PCI and ushered in the contemporary era of invasive coronary physiology evaluation to guide revascularization (227-229).

FAME was a multicenter, international, randomized clinical trial in 1005 patients with multivessel CAD undergoing PCI that compared an FFR-guided strategy with the standard angiography-guided strategy, published in 2009. The primary end point was the rate of MACE at 1 year, defined as a composite of death, myocardial infarction, and any repeat revascularization. The primary endpoint occurred significantly more often in the angiography-only group compared with the FFR group at 1 year (18.3% vs 13.2%, *p* 0.02). This finding was

driven by numerically lower event rates across each of the individual component endpoints. There were significantly more stents per patient placed in the angiography-only group (2.7±1.2 vs 1.9±1.3, $p<0.001$). FFR-guided PCI was associated with a 30% to 40% relative risk reduction in individual MACE endpoints, including significantly less death or MI (227).

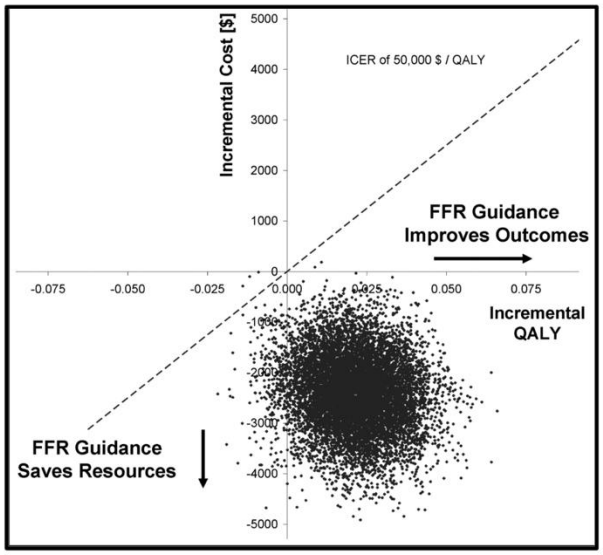
FAME Trial. Outcomes at 1 year among patients randomized to FFR-guided versus angiography-guided PCI



Tonino, PA et al. N Engl J Med 2009 Vol. 360 Issue 3 Pages 213-24

The mean cost of the index procedure was significantly higher in the angiography group than the FFR group ($6007 + $2819 vs $5332 + $3261, $p<0.001$). A dedicated cost-effectiveness analysis suggested that FFR-guided PCI in multivessel CAD was a dominant strategy; that is, it was one that not only improved clinical outcomes but also provided cost savings.

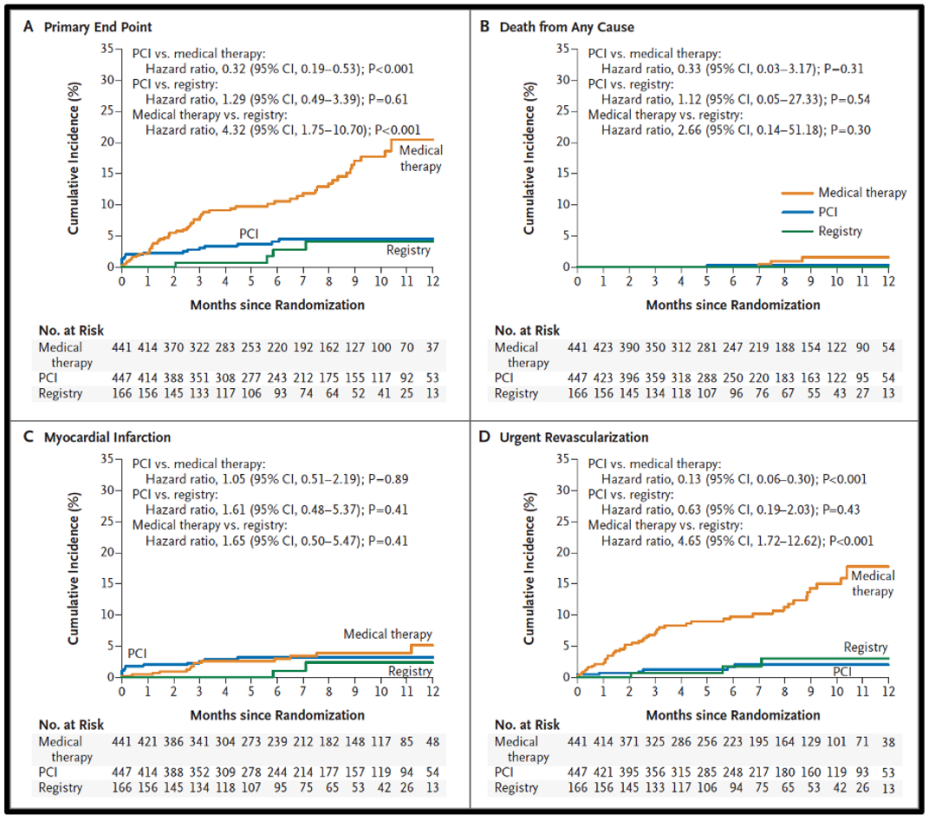
FAME Trial. Cost-effectiveness model of FFR-guided versus angiography-guided PCI.



One of the criticisms of the original FAME trial was that there was not an arm that received Optimal Medical Therapy (OMT) alone. FAME 2 sought to answer the question of whether PCI improved outcomes when compared with OMT in patients with Stable Ischemic Heart Disease (SIHD). FAME 2 was a multicenter, international, randomized clinical trial published in 2012 that compared the initial strategies of FFR-guided PCI with OMT in 1220 patients with SIHD. All patients underwent coronary angiography and FFR interrogation of all $\geq$ 50% diameter stenoses deemed by the operator to require stenting based on angiographic and clinical data. All functionally significant stenosis (FFR $\leq$ 0.80) were randomized to FFR-guided PCI versus OMT, whereas those whose stenoses all had FFR values > 0.80 were enrolled in a registry and also treated with OMT.

Patient recruitment was stopped prematurely by the independent Data and Safety Monitoring Board because of a significantly lower rate of the primary endpoint in the FFR-guided PCI group compared with the OMT group (4.3% vs 12.7%, HR: 0.32, 95%, CI: 0.19–0.53; *p*<0.001). This difference at short-term follow-up (213 ± 128 days) was driven by substantially less urgent revascularization (1.6% vs 11.1%; HR: 0.13; 95% CI: 0.06–0.30; *p*<0.001) in the FFR-guided PCI group, particularly those prompted by MI or ischemic electrocardiographic changes (228).

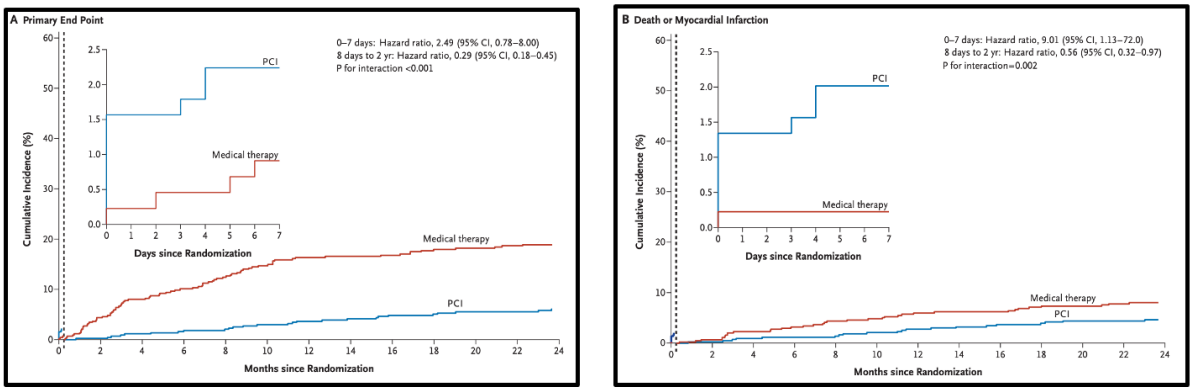
FAME 2. Kaplan–Meier curves for the cumulative incidence of MACE and individual components FFR-guided PCI vs Medical Therapy; and Registry (Stenosis ≥ 50% with FFR > 0.8)



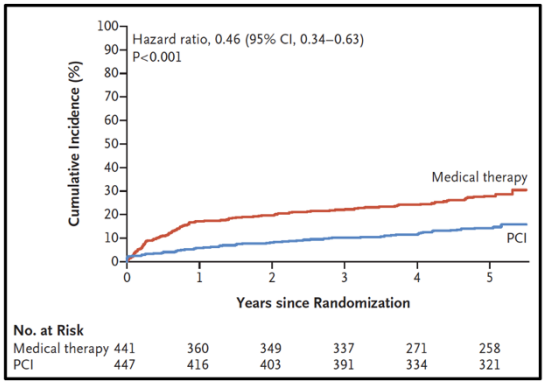
De Bruyne, B et al. N Engl J Med 2012 Vol. 367 Issue 11 Pages 991-1001

Long term data for the FAME 2 trial has been consistent with initial results. The rate of the primary endpoint remained significantly lower in the FFR-guided PCI group compared with the OMT group at 2 years (8.1% vs 19.5%, HR: 0.39, 95% CI: 0.26–0.57; *p*<0.001), and 5 years (13.9% vs 27%, HR: 0.46, 95% CI: 0.34–0.63; *p*<0.001), owing to a sustained reduction in urgent revascularizations over time. At 5 years, there remained no significant between-group differences in MI or death. However, overall, MI and spontaneous MI were both lower in the FFR-guided PCI arm compared with OMT alone (230, 231).

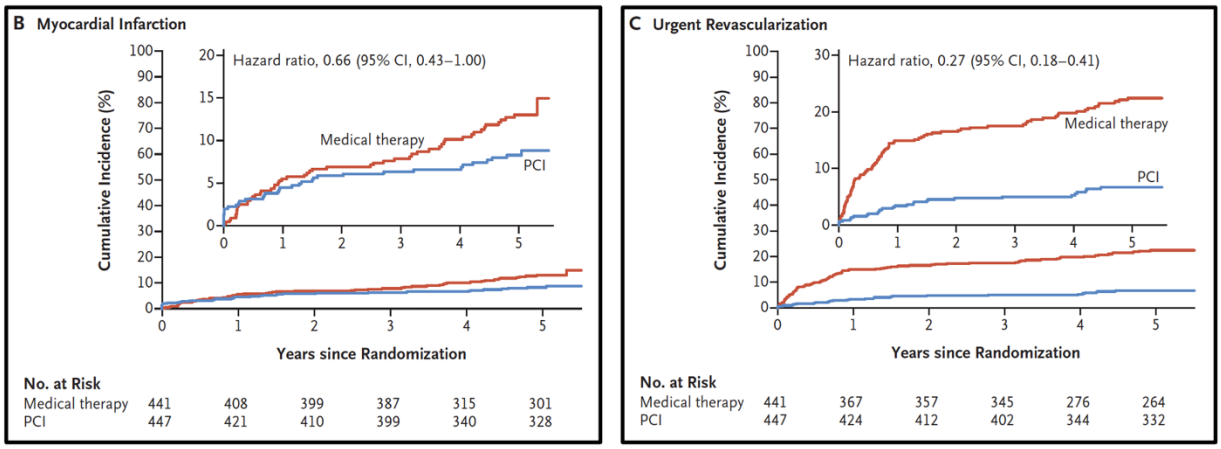
FAME 2. 2-years follow up. Kaplan–Meier curves for the Landmark Analyses.



FAME 2. 5-years follow up. Kaplan–Meier curves for the Primary Endpoint.



FAME 2. 5-years follow up. Kaplan–Meier curves for Myocardial Infarction and Urgent Revascularization.



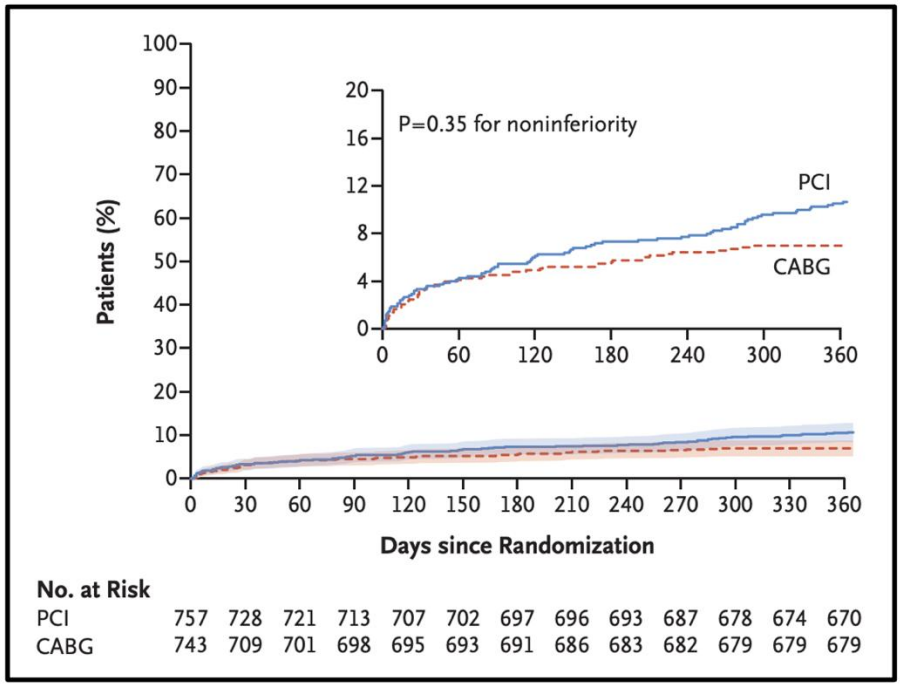
Xaplanteris, P et al. N Engl J Med 2018 Vol. 379 Issue 3 Pages 250-259

FAME 3 was a multicenter, international, noninferiority trial, in 1500 patients with three-vessel CAD that also recruited patients with ACS. These patients were randomly assigned to undergo Coronary Artery Bypass Grafting (CABG) or FFR-guided PCI with current-generation zotarolimus-eluting stents; that was recently published. The primary end point was the occurrence within 1 year of major adverse cardiac and cerebrovascular events (MACCE), defined as death from any cause, MI, stroke, or repeat revascularization. Noninferiority of FFR-guided PCI to CABG was

prespecified as an upper boundary of less than 1.65 for the 95% CI of the HR. Secondary end points included a composite of death, MI, or stroke; safety was also assessed (229).

The 1-year incidence of the composite primary end point was 10.6% among patients randomly assigned to undergo FFR-guided PCI and 6.9% among those assigned to undergo CABG (HR: 1.5; 95% CI, 1.1 to 2.2), findings that were not consistent with noninferiority of FFR-guided PCI (*p*=0.35 for noninferiority). The incidence of death, MI, or stroke was 7.3% in the FFR-guided PCI group and 5.2% in the CABG group (HR: 1.4; 95% CI, 0.9 to 2.1). In conclusion, in patients with three-vessel CAD, FFR-guided PCI was not found to be noninferior to CABG.

FAME 3. 1-year follow up. Kaplan–Meier curves for the Primary Endpoint.



Fearon, WF et al. N Engl J Med 2021

The current trial involved routine measurement of FFR to guide PCI, with the expectation that the use of FFR would lead to more judicious stenting — that is, an FFR-guided strategy would result in PCI being used to treat only functionally significant lesions, which have been shown to be associated with higher rates of adverse events when treated with medications alone, and would avoid unnecessary stenting of non–flow-limiting lesions, which respond as well to medical therapy alone as they do to PCI (and may even respond better to medical therapy alone). As anticipated, patients in FAME 3 received fewer stents than those in the SYNTAX trial (3.7 vs. 4.6), which compared PCI (without FFR guidance) with CABG, although the number of coronary lesions was similar (232). Although these trials are not directly comparable, patients assigned to undergo PCI in FAME 3 also had a lower incidence of repeat revascularization (4.9% vs. 13.5%) and lower mortality (1.6% vs. 4.4%) than those in the SYNTAX trial, despite similar patient characteristics and risk profiles in the two trials. Plausible explanations for these findings include the lower number of stents placed (with reduced risk of stent-related complications such as thrombosis or restenosis), improved stent technology, and high levels of adherence to recommended medical therapy.

Of note FAME 3 had only 12% intracoronary imaging guidance in the FFR-guided PCI group that might have influenced the higher rate of MACCE at an expense of MI and repeat revascularization compared to CABG. Intracoronary imaging in such complex population would

have helped with plaque vulnerability detection, complex plaque modification and PCI optimization.

4.7.2.2 Ischemia-driven non-culprit Lesion Revascularization in ACS

In patients with stable angina pectoris (SAP), clinical practice guidelines recommend the use of coronary physiology to decide if revascularization of intermediate-severity coronary stenosis is indicated (233, 234). In these patients, the use of FFR has been shown to be safe (224, 225, 227, 228). With the growing adoption of coronary physiology, FFR is also increasingly being used to guide revascularization in patients with ACS, particularly to assess the functional relevance of non-culprit vessels in patients with multivessel disease.

Available evidence, including RCTs (14, 16), supports the use of FFR guidance in ACS non-culprit stenoses compared with culprit-only treatment. Moreover, the use of FFR has demonstrated better outcomes with respect to angiography-only approaches in both ACS and SAP (235). Despite this, few data are available regarding the comparative performance of FFR in ACS versus SAP.

Although some studies support the reliability of FFR measurements in patients with ACS, several studies have consistently reported poorer clinical outcomes in patients with ACS in whom revascularization was deferred based on FFR measurements (14, 16, 236, 237).

The uncertainty regarding the use of a physiology-guided strategy in the setting of ACS comes from the uncertainty of the benefit of a physiology-guided strategy to guide PCI for non-culprit lesions in STEMI. A possible concern with a physiology-guided strategy is its inability to account for the impact of plaque morphology on future events. It is possible that a physiology-guided PCI strategy would lead to deferral of lesions that, despite not being physiologically significant, still harbor high-risk morphologic features (referred to as TCFA) at high risk for plaque rupture leading to future MACE. The potential benefit of an FFR-guided strategy may be attenuated by deferring intervention on such lesions.

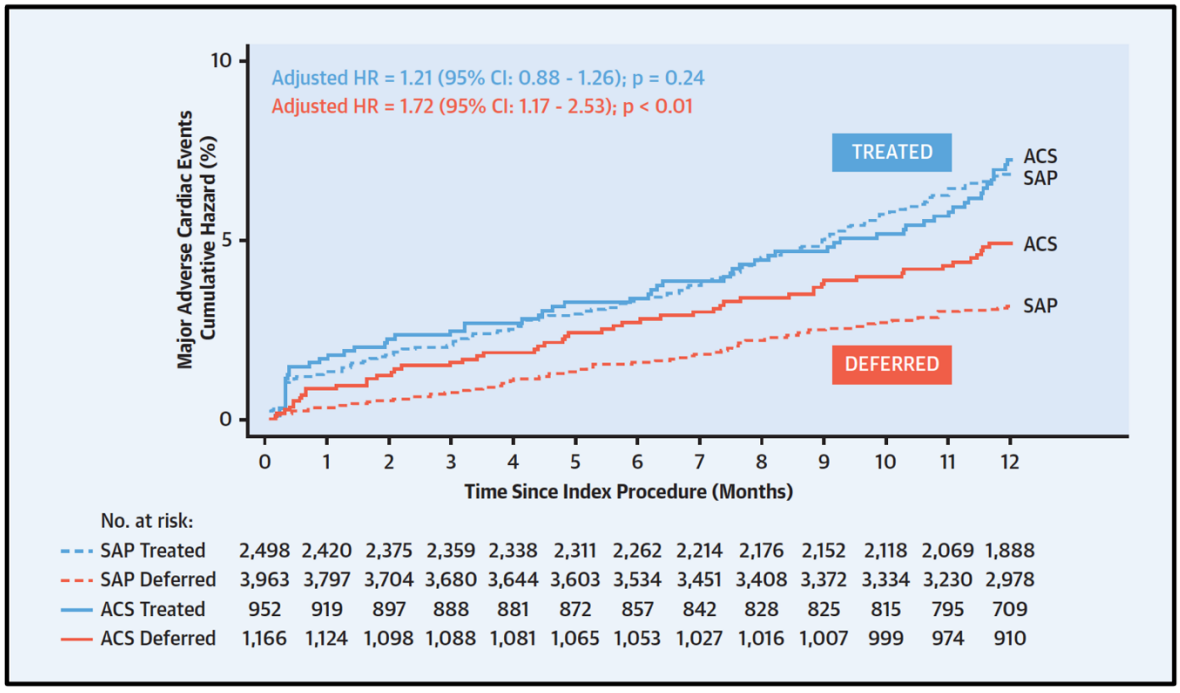
Considering this background, a pooled analysis was performed to investigate the safety of revascularization deferral of non-culprit lesions in patients with ACS in a large study population, obtained from 3 large observational studies and 2 RCTs.

The primary endpoint was MACE at 1-year follow-up. Clinical outcomes of patients with ACS and Stable Angina pectoris (SAP) were compared in both the deferred and the revascularized groups. A total of 8.579 patients were included in the analysis, 6.461 with SAP and 2.118 with ACS and no culprit stenoses. Using FFR, revascularization was deferred in 5.129 patients (59.8%) and performed in 3.450 patients (40.2%).

In the deferred ACS group, a higher MACE rate was observed compared with the deferred SAP group (4.46% vs. 2.83%; adjusted HR: 1.72; 95% CI: 1.17 to 2.53; $p<0.01$). In particular, early

unplanned revascularization (3.34% and 2.04% in ACS and SAP; adjusted HR: 1.81; 95% CI: 1.09 to 3.00; p ¼ 0.02) contributed to this excess in MACE but the difference between the ACS and SAP groups did not reach statistical significance. On the contrary, no differences in outcomes linked to clinical presentation were found in treated patients (MACE rate 6.51% vs. 6.20%; adjusted HR: 1.21; 95% CI: 0.88 to 1.26; p ¼ 0.24) (205).

Kaplan–Meier curves of the pooled analysis.
Clinical outcomes of patients with ACS and SAP, compared between deferred and revascularized groups



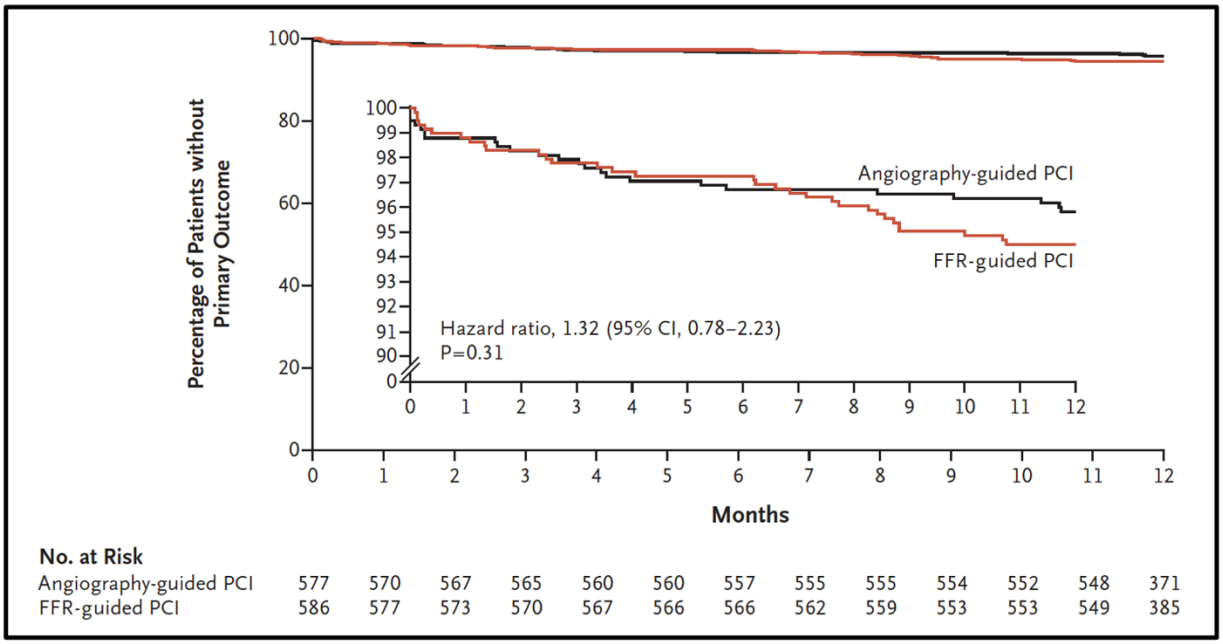
Cerrato, E et al. JACC Cardiovasc Interv 2020 Vol. 13 Issue 16 Pages 1894-1903

Several hypotheses can be put forward to explain the higher risk for MACE found in patients with deferred revascularization of ACS non-culprit stenoses. Compared with patients with SAP: 1) patients presenting with ACS may have an intrinsically higher risk for events during follow-

up; 2) non-culprit vessels in patients with ACS may have more vulnerable atherosclerotic plaques, increasing the chances of a subsequent ACS; 3) misdiagnosis of the ACS culprit vessel might lead to FFR interrogation of the true culprit lesion, especially in unstable angina and non-ST segment elevation myocardial infarction (NSTEMI) subsets, with negative FFR resulting in deferral treatment of a high-risk stenosis; and 4) FFR may have a lower diagnostic yield in patients with ACS because of transient modification of hemodynamic and microcirculatory status, which may underscore the true functional impact of non-culprit stenoses in ACS.

Recently, the FLOWER-MI trial compared a physiology-guided FFR non-culprit lesion PCI strategy to an angiography-guided strategy in STEMI patients with multivessel disease. It did not find superiority of a physiology-based strategy. At 1 year, a primary outcome event occurred in 32 of 586 patients (5.5%) in the FFR-guided group and in 24 of 577 patients (4.2%) in the angiography-guided group (HR: 1.32; 95% CI, 0.78 to 2.23; $p = 0.31$). Death occurred in 9 patients (1.5%) in the FFR-guided group and in 10 (1.7%) in the angiography-guided group; nonfatal MI in 18 (3.1%) and 10 (1.7%), respectively; and unplanned hospitalization leading to urgent revascularization in 15 (2.6%) and 11 (1.9%), respectively (238).

FLOWER-MI. Kaplan–Meier curves for the Primary Endpoint.



Puymirat, E et al. N Engl J Med 2021 Vol. 385 Issue 4 Pages 297-308

This trial has several limitations. First, the trial was underpowered with only 56 primary outcome events, which is too small to result in a major shift in clinical practice. Second, the trial follow-up is only 1 year. As demonstrated in the COMPLETE trial, the benefit of complete revascularization is not apparent until several years after STEMI. Third, the trial had no real hypothesis for superior efficacy of a physiology guided strategy. The benefit of a physiology guided strategy is in avoiding unnecessary PCI procedures, thereby improving safety. It therefore was not able to evaluate the key benefits of a physiology guided strategy.

These analyses have brought to light that it is likely that the coronary tree of patients with ACS has more vulnerable atheroma prone to trigger cardiac events. The prognostic information provided by FFR in a vessel with vulnerable plaques refers strictly to ischemia caused by fixed

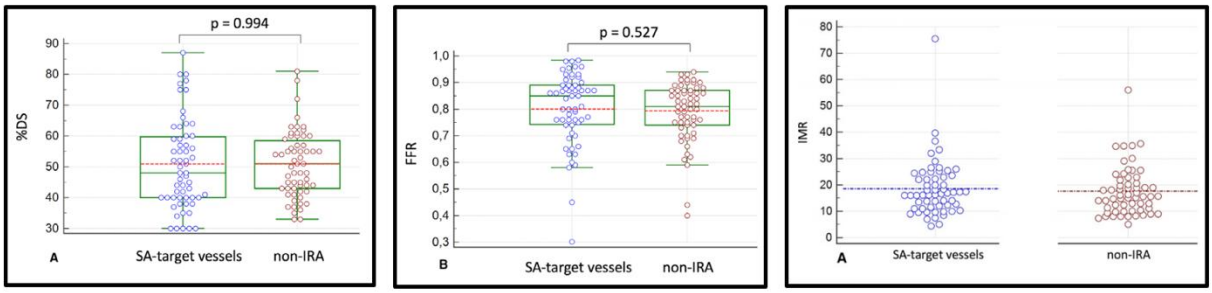
stenoses and not the potential consequence of ulceration and thrombosis of vulnerable lesions present in the interrogated vessel.

It is also important that the accuracy of FFR in predicting outcomes among patients with ACS may not be equivalent to FFR when applied in the stable setting. Mechanistically, this can be explained by a failure to achieve maximal hyperemia during ACS (which is associated with a rise in zero flow pressure and left ventricular filling pressures, enhanced sympathetic drive, and blunted coronary vasodilation) because of transient impairment of the microcirculation (239-241). Notably, decreased coronary flow reserve after an acute MI involves both culprit and non-culprit vessels, owing to the combination of post-occlusive hyperemia, myocardial necrosis, hemorrhagic microvascular injury, compensatory hyperkinesis, and neurohumoral mechanisms.

Interestingly, one small study showed similar microvascular resistance, hyperemic flow, and resistive reserve ratio (a measure of myocardial hyperemia) between patients with SAP and non-culprit stenoses in patients with ACS during the subacute phase of a MI (242). In this observational study, non-infarct related arteries (IRA) underwent FFR, coronary flow reserve, and the index of microcirculatory resistance assessment in 49 acute MI patients (59 non-IRA) and compared with a matched control group of 46 SAP patients (59 vessels). Time between acute MI to physiological interrogation was 5.9$\pm$2.4 days. FFR was similar in both groups (0.79$\pm$0.11 in non-IRA vs 0.80$\pm$0.13 in SAP vessels, p=0.527). No differences were found regarding index of microcirculatory resistance (15.6 [10.4–21.8] in non-IRA vs 16.7 [11.6–23.6]

in SAP vessels, *p*=0.559). This observational study suggested that in the subacute phase of MI, non-IRA microcirculatory resistance and adenosine-induced hyperemic response are similar to those found in SAP patients. From a physiological perspective, these findings support the use of fractional flow reserve to interrogate non-IRA during the subacute phase of myocardial infarction.

Observational analysis. FFR and IMR in SAP compared to non-IRA from ACS in the sub-acute phase.

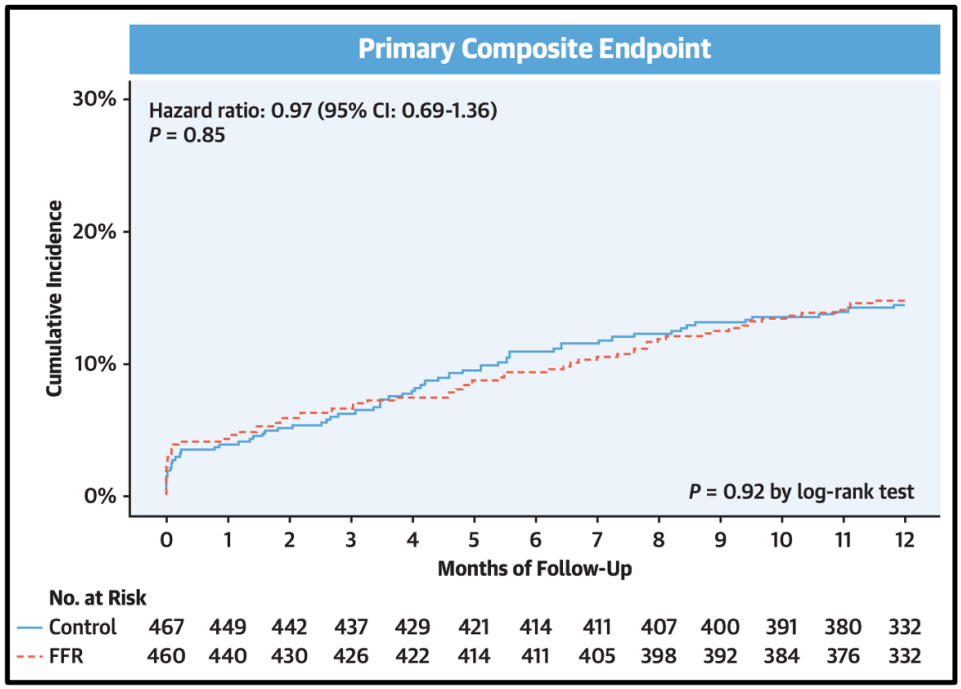


In contrast with these results, there is new evidence supporting the hypothesis that FFR measurements in the acute setting of ACS may lead to misclassification of the severity of non-culprit stenoses in up to 15% of cases, compared with subacute FFR measurements (243). Also, iFR might overestimate the functional impact in the sub-acute phase because of the increased baseline flow. Consequently, there are concerns regarding the use of FFR and resting indices in ACS and the potential inappropriate deferral of ischemia-causing lesions. The accuracy of invasive physiology during ACS and timing of performance deserves further investigation.

The most recent trial regarding ischemia-driven revascularization in ACS patients is the FUTURE (FUnctional Testing Underlying coronary REvascularization) trial, which is a prospective, randomized, open-label, superiority trial involving patients with ACS presentation (stabilized STEMI, NSTEMI and UA) with multivessel CAD (244). At 1-year follow-up, by intention to treat, there were no significant differences in MACE rates between groups (14.6% in the FFR group vs 14.4% in the control group; HR: 0.97; 95% CI: 0.69-1.36; P ¼ 0.85). The difference in all-cause mortality was nonsignificant, 3.7% in the FFR group versus 1.5% in the control group (HR: 2.34; 95% CI: 0.97-5.18; P ¼ 0.06), and this was confirmed with a 24 months' extended follow-up.

FFR significantly reduced the proportion of revascularized patients, with more patients referred to exclusively medical treatment (P ¼ 0.02); but did not reduce the risk of ischemic cardiovascular events or death at 1-year follow-up. The trial was stopped prematurely by the data safety and monitoring board after a safety analysis and 927 patients were enrolled.

FUTURE Trial. Primary Endpoint at 1 Year in Intention-to-Treat Population



Rioufol, G et al. J Am Coll Cardiol 2021 Vol. 78 Issue 19 Pages 1875-1885

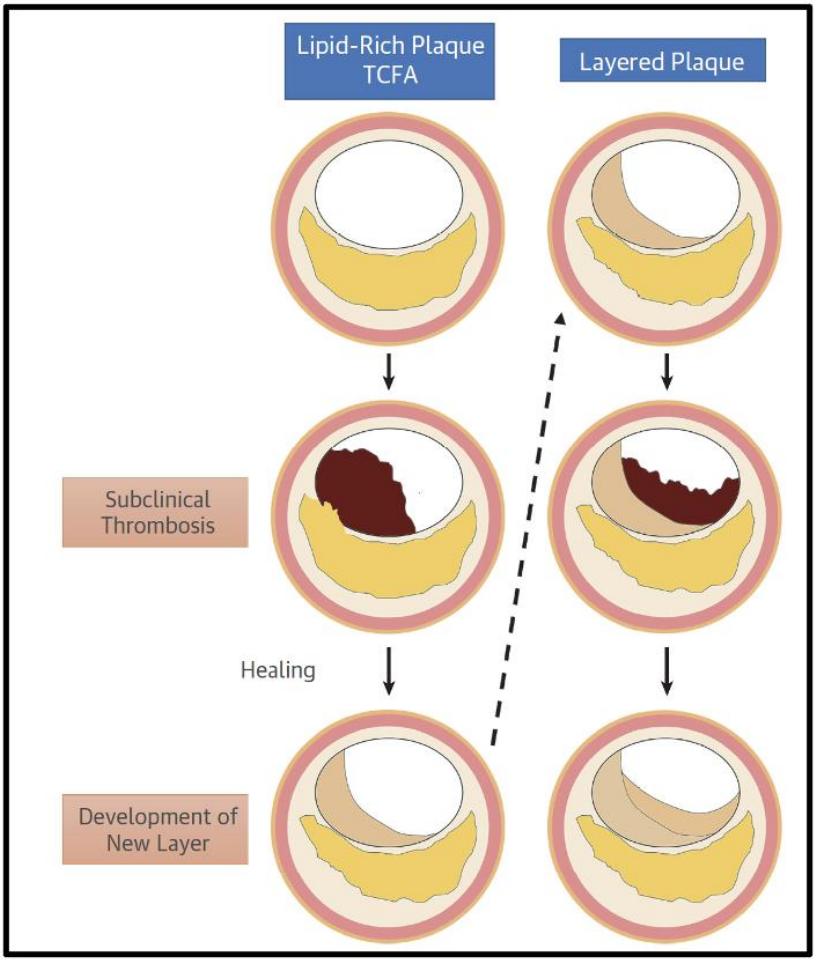
4.7.3 Imaging-Guided Lesion Revascularization

The decision to perform PCI in patients with angiographically intermediate coronary lesions in ACS is challenging. Atherosclerosis had been thought to be a disease of insidious onset and slow process, secondary to smooth muscle cell proliferation (44). However, that concept has been challenged during the past 3 decades by the theory that an alternative mode of rapid stepwise plaque progression may be important (245, 246).

Previous angiographic studies that investigated serial angiograms at intervals, showed that one-third of plaques with progression showed abrupt progression, and two-thirds showed gradual progression (213). A previous study assessed plaque volume at serial angiograms by using intracoronary imaging (IVUS and OCT) and reported that 8.1% of plaques showed gradual linear progression, whereas 9.7% of plaques showed early abrupt progression, and 5.6% showed late, abrupt progressions (247).

Rapid progression of atherosclerotic plaques is the result of plaque disruption and subsequent organization of the thrombus. The organized thrombus with collagen deposition can be detected by OCT as a new layer with a different optical density. A previous study reported that TCFA and intraplaque microchannels predicted plaque progression in the future (182).

Mechanism of Rapid Plaque Progression.

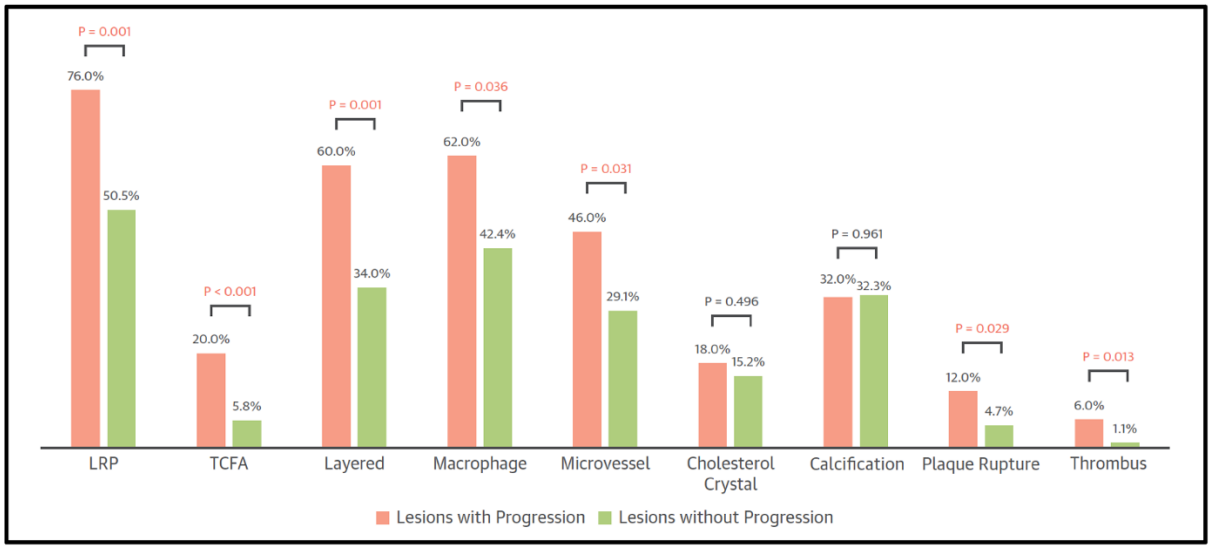


JACC Cardiovasc Imaging. 2021 Aug;14(8):1628-1638.

A recent observational analysis worked on identifying morphological predictors of subsequent rapid plaque progression using OCT. Patients with baseline OCT imaging of major epicardial coronary arteries and repeated coronary angiography at 6 to 9 months were included. Non-culprit lesions with a diameter stenosis ≥30% on index angiography were investigated. Lesions with subsequent rapid progression showed a significantly higher prevalence of lipid-rich plaque (76.0% vs. 50.5%, respectively; $p = 0.001$), TCFA (20.0% vs. 5.8%, respectively; $p < 0.001$),

layered plaque (60.0% vs. 34.0%, respectively; *p* = 0.001), macrophage accumulation (62.0% vs. 42.4%, respectively; *p* = 0.036), micro-vessels (46.0% vs. 29.1%, respectively; *p* = 0.031), plaque rupture (12.0% vs. 4.7%, respectively; *p* = 0.029), and thrombus (6.0% vs. 1.1%, respectively; *p* = 0.013), compared with lesions without rapid progression. Quantitative OCT analysis showed that lesions with subsequent progression had a thinner fibrous cap (116.9 ± 62.3 mm vs. 146.0 ± 73.3 mm, respectively; *p* = 0.016) and greater lipid length (6.0 ± 3.6 mm vs. 4.8 ± 2.8 mm, respectively; *p* = 0.023) and lipid index (1,027.3 ± 829.6° vs. 716.5 ± 625.6°, respectively; *p* = 0.017) than lesions without progression (248).

Prevalence of OCT-Defined Plaque Characteristics in Lesions With or Without Subsequent Rapid Progression.



JACC Cardiovasc Imaging. 2021 Aug;14(8):1628-1638.

Multivariate analysis identified LRP (OR: 2.17; 95% CI: 1.02 to 4.62), TCFA (OR: 5.85; 95% CI: 2.01 to 17.03), and layered plaque (OR: 2.19; 95% CI: 1.03 to 4.17) as predictors of subsequent rapid lesion progression.

Predictor of lesion progression.

TABLE 3 Predictors of Lesion Progression

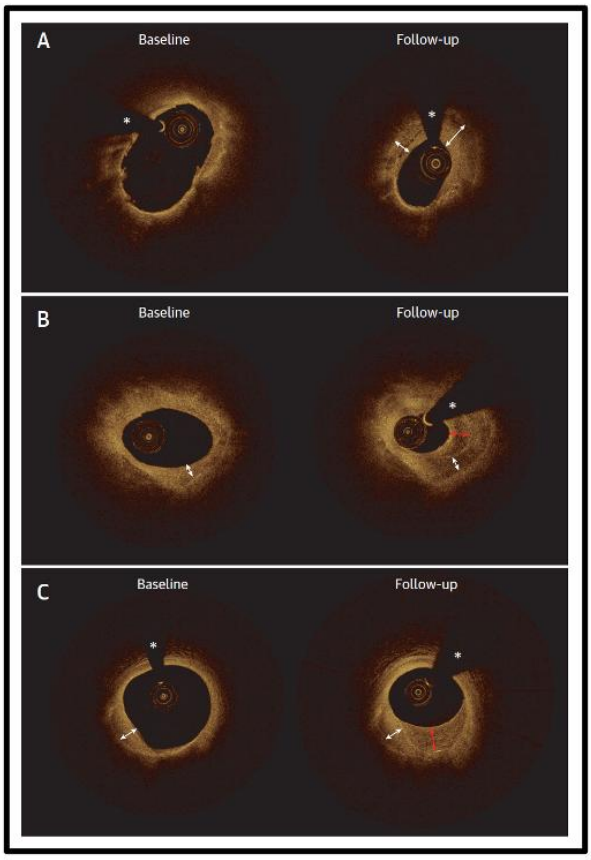
	Univariate			Multivariate		
	Odds Ratio	**95% CI**	**p Value**	**Odds Ratio**	**95% CI**	**p Value**
LRP (non-LRP as reference)						
LRP without thin cap	3.10	1.58-6.06	0.001	2.17	1.02-4.62	0.045
TCFA	4.08	1.85-8.97	<0.001	5.85	2.01-17.03	0.001
Layered plaque	2.91	1.51-5.59	0.001	2.19	1.03-4.17	0.040
Macrophage	2.22	1.05-4.66	0.036	1.23	0.52-2.89	0.643
Microvessels	2.07	1.07-4.02	0.031	1.34	0.67-2.69	0.403
Cholesterol crystal	1.29	0.62-2.67	0.496			
Calcification	0.99	0.53-1.81	0.961			
Rupture	2.76	1.11-6.86	0.029	0.80	0.24-2.68	0.720
Thrombus	5.90	1.45-23.97	0.013	2.52	0.45-14.03	0.290

Variance inflation factor (VIF) analysis showed no indication of multicollinearity.

CI = confidence interval; LRP = lipid-rich plaque; TCFA = thin-cap fibroatheroma.

JACC Cardiovasc Imaging. 2021 Aug;14(8):1628-1638.

Representative Cases of Rapid Plaque Progression.



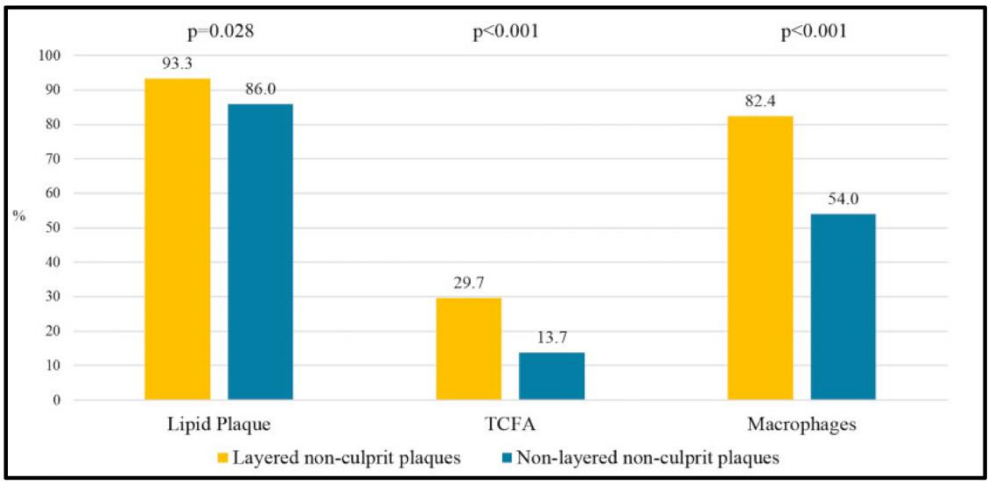
JACC Cardiovasc Imaging. 2021 Aug;14(8):1628-1638.

The main mechanism of rapid stepwise progression is plaque rupture or erosion with subsequent organization of residual thrombus. Plaque disruptions in the coronary arteries without signs of myocardial necrosis are not uncommon (93, 94). Despite of knowing for long time that layered plaque was prevalent in non-culprit segments, this concept has recovered interest lately when this pattern has been associated to rapid plaque progression. There is need to understand better the plaque characteristics associated to this plaque phenotype, as this might play an important role in future cardiovascular events if layered plaque is present in

segments without significant luminal stenosis or no-flow limiting disease by physiology. Layered plaque is a signature of 'biologically active plaque' which is undergoing repetitive episodes of disruption and healing.

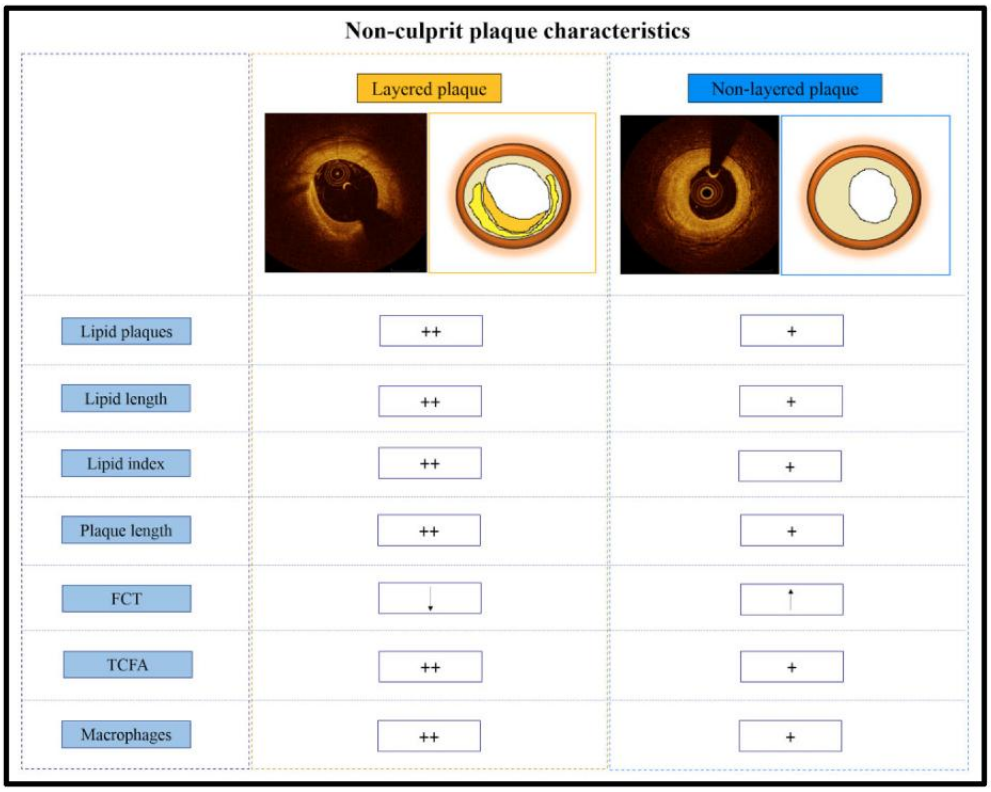
A recent observational analysis described the characteristics of non-culprit plaques in ACS patients with or without a layered plaque at the culprit lesion. Layered plaques showed higher prevalence of lipid plaque (93.3% vs. 86.0%, $p = 0.028$), TCFA (29.7% vs. 13.7%, $p < 0.001$), and macrophage infiltration (82.4% vs. 54.0%, $p < 0.001$), compared to non-layered plaques. They also had thinner fibrous cap, longer plaque length, longer lipid length and greater lipid index than non-culprit plaques with a non-layered phenotype (249).

OCT characteristics of non-culprit plaques with or without a layered phenotype at the non-culprit site.



Eur Heart J Cardiovasc Imaging. 2020 Dec 1;21(12):1421-1430.

Layered vs. non-layered phenotype in non-culprit plaques.



Eur Heart J Cardiovasc Imaging. 2020 Dec 1;21(12):1421-1430.

4.7.4 Ischemia-Driven vs. Imaging-Guided Lesion Revascularization in SAP and ACS

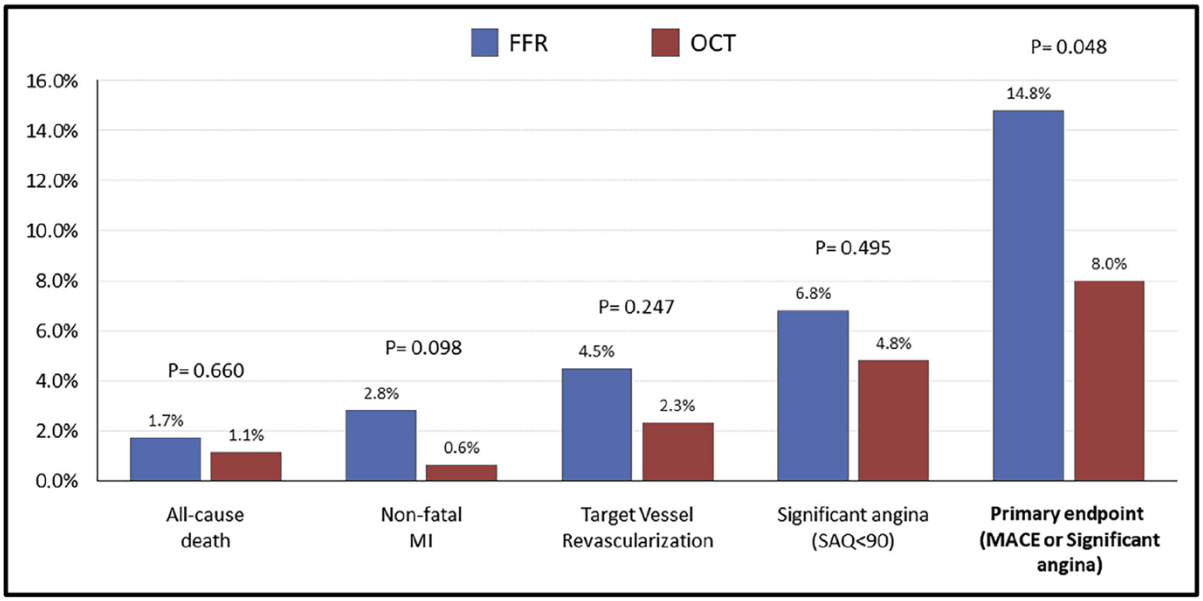
Functional assessment using FFR and vulnerability assessment using intracoronary imaging techniques such IVUS or OCT may be considered for lesion severity evaluation and PCI optimization. Clinical guidelines on myocardial revascularization support the use of physiological assessment to guide revascularization in patients with angiographically intermediate coronary lesions. Intracoronary imaging interest is growing in this setting.

The FORZA (Fractional Flow Reserve vs. Optical Coherence Tomography to Guide Revascularization of Intermediate Coronary Stenoses) study is an open-label, single-center prospective randomized trial comparing clinical outcomes and costs in patients with at least 1 angiographically intermediate coronary lesion randomized to FFR or OCT guidance (250). Patients with SIHD or stabilized ACS (culprit lesion treated previously) were randomized 1:1 to FFR or OCT guided PCI.

PCI was performed when FFR was $\leq$ 0.80, aiming to achieve a post-stenting FFR $\geq$ 0.90 which was defined as optimal result. In the group randomized to imaging, PCI was performed when at least 1 of the following criteria was present in OCT: 1) Area Stenosis > 75%; 2) Area Stenosis between 50% and 75% and MLA < 2.5 mm^2; and 3) Area Stenosis between 50% and 75% and plaque rupture.

From the lesions in the FFR arm, 29.3%; and from the lesions i the OCT imaging arm, 50.7%, were managed with PCI, which translated into a statistically significant higher rate of patients referred for initial medical management with FFR (67.7% vs. 41.1% with OCT imaging; p<0.001). All patients completed 13-month follow-up. The primary endpoint of MACE or significant angina at 13 months occurred in 14.8% of patients in the FFR arm and in 8.0% in the OCT imaging arm (p=0.048). This result was driven by a statistically non-significant lower occurrence of all components of the primary endpoint.

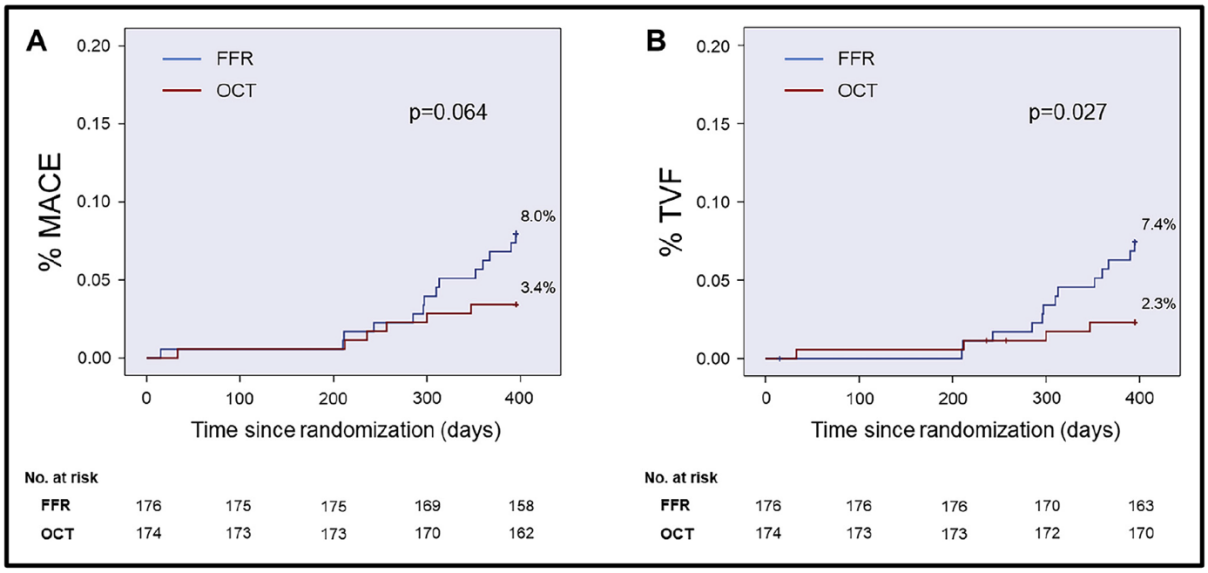
FORZA. Primary Study Endpoint and Its Individual Components at 13-Month Follow-Up.



Burzotta, F et al. JACC Cardiovasc Interv 2020 Vol. 13 Issue 1 Pages 49-58

The MACE rate observed at 13 months was 5.7%, with a non-significant lower incidence in the OCT imaging arm compared with FFR (3.4% vs. 8.0%; *p* = 0.064). Of note, target vessel failure (TVF) occurred significantly less commonly in patients randomized to OCT imaging (2.3% vs. 7.4% with FFR; *p* = 0.027).

FORZA. MACE and TVF Occurring in the FFR and OCT Groups.



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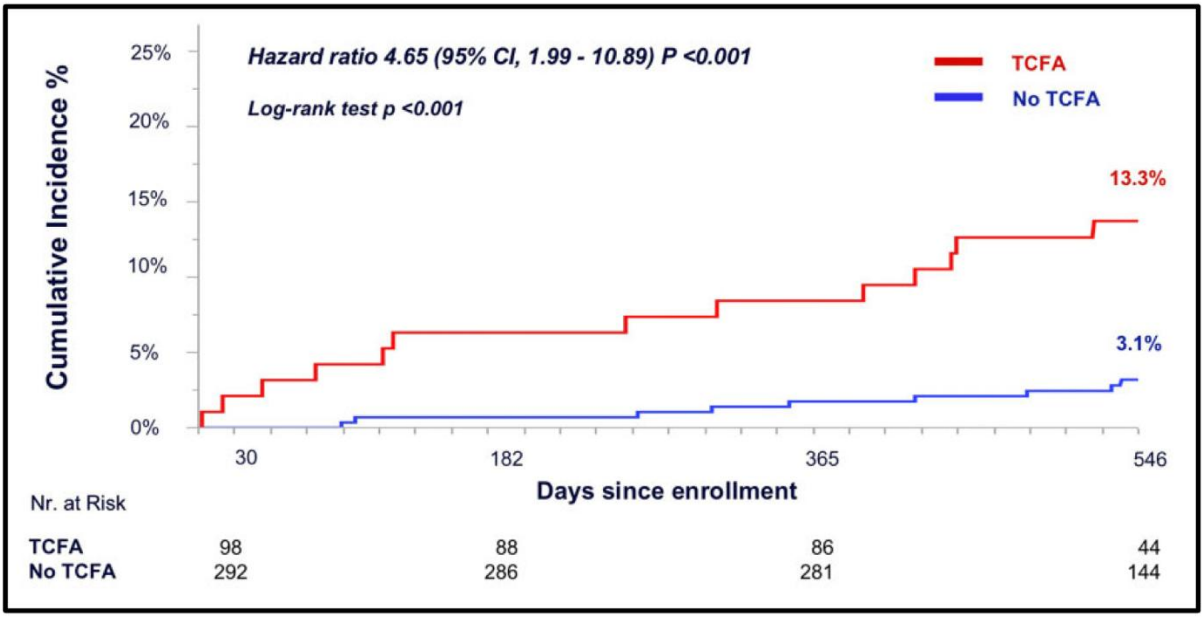
This randomized study showed that the use of OCT is safe, causes a larger number of PCIs, but is associated with a lower occurrence of the combined endpoint of MACE or significant angina and the use of FFR is associated with higher rate of medically managed patients and higher MACE.

The COMBINE FFR-OCT is a prospective, double-blind, international, natural history, investigator-initiated study that recruited diabetic mellitus patients undergoing coronary angiography for either SAP or ACS with at least one de novo native coronary lesion with a diameter of stenosis between 40% and 80% by visual assessment (251).

Revascularization of the target lesions was guided by the FFR findings. Patients with exclusively FFR-positive lesions ≤ 0.80 underwent revascularization. Patients with at least one FFR-negative target lesion > 0.80 underwent OCT assessment and were further treated by guideline recommended optimal medical therapy. Following core lab analysis of the OCT findings, patients with FFR-negative lesions were further classified as 'TCFA-positive' or 'TCFA-negative' depending on presence or absence of at least one TCFA lesion. The final trial population was composed of three groups: group A, patients with at least one FFR-negative/TCFA-negative lesion; group B, patients with at least one FFR-negative/TCFA-positive lesion; and group C, patients with exclusively FFR-positive lesions, who underwent revascularization.

The primary endpoint, a composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization or hospitalization due to unstable or progressive angina at 18 months. The primary endpoint occurred in 13.3% of the patients with FFR-negative/TCFA-positive (group B) as compared to 3.1% of the patients with FFR-negative/TCFA-negative (group A) (HR: 4.65; 95% CI, 1.99–10.89, $p < 0.001$). Interestingly, all target vessel MI at follow-up occurred in the TCFA-positive patients (group B) whereas no target vessel MI was observed in the TCFA-negative patients (group A). Similarly, clinically driven target lesion revascularization and unstable angina pectoris incidence was significantly higher in the FFR-negative/TCFA-positive patients. A significantly higher incidence of clinically driven target lesion revascularization was observed in the FFR-negative/TCFA positive group.

COMBINE. Incidence of the primary endpoint at 18 months.



Kedhi, E et al. Eur Heart J 2021

COMBINE. Patients' clinical outcomes at 18-month follow-up.

Variable	FFR(−)/TCFA(+) (*n* = 98)	FFR(−)/TCFA(−) (*n* = 292)	Hazard ratio (95% confidence interval)	*P*-value
Primary endpoint,[a] *n* (%)	13 (13.3)	9 (3.1)	4.65 (1.99–10.89)	<0.001
Cardiac death, *n* (%)	0 (0)	1 (0.34)	–	–
Death (any), *n* (%)	0 (0)	3 (1.03)	–	–
TV MI, *n* (%)	4 (4.1)	0 (0)	–	–
Spontaneous MI (any), *n* (%)	8 (8.2)	3 (1.0)	8.26 (2.19–31.14)	0.002
CD-TLR, *n* (%)	11 (11.2)	4 (1.4)	8.72 (2.78–27.39)	<0.001
Revascularization (any), *n* (%)	17 (17.3)	17 (5.8)	3.26 (1.66–6.38)	<0.001
Unstable angina requiring hospitalization, *n* (%)	6 (6.1)	5 (1.7)	3.76 (1.15–12.32)	0.03
Cardiac death and TV MI, *n* (%)	4 (4.1)	1 (0.3)	12.84 (1.44–114.92)	0.02
Death and any MI, *n* (%)	9 (9.2)	6 (2.0)	4.70 (1.68–13.22)	0.003
Cardiac Death, TV MI and CD-TLR, *n* (%)	11 (11.2)	5 (1.7)	7.0 (2.43–20.14)	<0.001
Death, MI and revascularization, *n* (%)	17 (17.3)	20 (6.8)	2.77 (1.45–5.28)	0.002

Kedhi, E et al. Eur Heart J 2021

COMBINE findings raised concerns regarding the safety of revascularization deferral based solely on FFR interrogation and support the use of image-based methods for more accurate risk profiling in high-risk populations.

TCFA lesions are frequently associated with compensatory vessel remodeling, 90% of TCFAs are located in large plaques with intermediate or severe cross-sectional stenosis area of > 50% (87). Therefore, future adverse events are likely to originate from TCFA lesions with at least intermediate degree of stenosis. Interestingly in COMBINE, while a LRP was also the predominant plaque phenotype (about 60%) in the TCFA-negative group, the primary endpoint event rate in that group was very low, suggesting that presence of LRP alone, in the absence of TCFA features like thin fibrous cap, macrophage infiltration, and neovascularization, is associated with a low rate of future adverse events and as such a safer substrate (251). These findings may explain why an ischemia-guided revascularization approach can significantly reduce angina but fails to reduce future adverse events, as was recently shown by the ISCHEMIA trial (252).

5 PART II. STATE OF KNOWLEDGE REGARDING TREATMENT OF NON-CULPRIT LESIONS IN PATIENTS PRESENTING WITH STEMI

Cardiovascular diseases are the leading cause of death globally, taking an estimated 17.9 million lives each year. More than four out of five cardiovascular deaths are due to MI, and one third of these deaths occur prematurely in people under 70 years of age. Cardiovascular medicine has changed the prognosis of MI by developing pPCI which is the preferred and fastest method of reperfusion in patients with STEMI, where the "culprit" coronary artery occlusion is opened, restoring blood flow to the myocardium supplied by the IRA.

These patients often have multivessel CAD, with residual stenoses in locations separate from the culprit lesion that caused the acute event. In STEMI, multivessel CAD carries a much worse prognosis, with a 2-fold increase in long-term mortality (2). The management of non-culprit lesions has been intensely debated and has been evaluated in clinical trials (14-17).

The COMPLETE trial is the largest randomized trial in this clinical setting with the longest follow-up and has established the benefit of a complete revascularization strategy in patients with STEMI and multivessel CAD (22). Non-culprit lesions were deemed angiographically significant if they were associated with at least 70% stenosis of the vessel diameter on visual estimation or with 50 to 69% stenosis accompanied by a FFR measurement of 0.80 or less; but the ischemia-

driven strategy was used in a very small number of patients. COMPLETE was not powered to assess the benefit of using physiological assessment in the non-culprit lesions.

COMPLETE showed that complete revascularization reduced the first co-primary outcome of CV death or new MI by 26% compared with the culprit-lesion only strategy (HR 0.74; 95% CI 0.60-0.91; P=0.004). The second co-primary outcome of CV death, new MI or ischemia-driven revascularization was reduced by 49% with complete revascularization (HR 0.51; 95% CI 0.43-0.61; P<0.001).

The results of COMPLETE have had a far-reaching impact on global practice and is being incorporated into guideline recommendations. The recently published 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization, recommends staged PCI of the significant non-IRA stenosis in selected hemodynamically stable patients with STEMI and multivessel disease after successful primary PCI, to reduce the risk of death or MI; with a class of recommendation 1 and a level of evidence A (253). This recommendation is supported by the COMPLETE trial.

Despite the success of angiography in guiding non-culprit PCI, there are potential limitations of an angiography-guided strategy as this approach could select some patients who do not require PCI, resulting in some unnecessary procedures, costs, and PCI-related complications. Besides, visual stenosis severity judged by operators correlates poorly with QCA values measured in an

angiographic core lab. Given these limitations, novel strategies to identify non-culprit lesions likely to benefit from PCI in patients with STEMI are urgently needed.

An ischemia-driven approach addresses many of the limitations of an angiography-guided approach in identifying which non-culprit lesions might benefit from revascularization. In this way, only those lesions that are deemed to be functionally significant by physiology are treated with PCI; lesions that are not functionally significant do not receive PCI and are treated with medical therapy alone.

An ischemia-driven strategy for PCI is well established in patients with stable CAD and has been shown to be superior to an angiography-guided strategy (224, 227, 228, 230). However, there is uncertainty regarding the use of an ischemia-driven strategy in the setting of ACS.

The benefit of a physiology-guided strategy to guide PCI for non-culprit lesions in STEMI is less clear than in stable CAD. A possible concern with a physiology-guided strategy is its inability to account for the impact of plaque morphology on future events. It is possible that a physiology-guided PCI strategy would lead to deferral of lesions that, despite not being physiologically significant, still harbor high-risk morphologic features at high risk for plaque rupture or erosion leading to future cardiovascular events. The potential benefit of an FFR-guided strategy may be attenuated by deferring intervention on such lesions.

Recently, the FLOWER-MI compared a physiology-guided FFR non-culprit lesion PCI strategy to an angiography-guided strategy in STEMI patients, and the FUTURE trial did the same comparison in ACS patients including STEMI, NSTEMI and UA, with multivessel disease. They failed to show superiority of a physiology-based strategy. These trials have several limitations: first, they were underpowered; second, short 1-year follow-up, as demonstrated in the COMPLETE trial, the benefit of complete revascularization is not apparent until several years after STEMI; third, no real hypothesis for superior efficacy of a physiology-guided strategy. The benefit of a physiology guided strategy is in avoiding unnecessary PCI procedures, thereby improving safety, and these trials were not able to evaluate the key benefits of a physiology guided strategy.

Based on this rationale, there is an urgent need for an adequately powered randomized trial comparing a physiology-guided revascularization strategy to an angiography-guided strategy for non-culprit lesion PCI in patients with STEMI and multivessel CAD. A non-inferiority trial would be appropriate for this comparison as a physiology-guided approach may preserve the benefit of an angiography-guided approach on future cardiovascular death, MI, and ischemia-driven revascularization, while reducing important additional outcomes of safety and cost. If a physiology-guided strategy was found to be non-inferior but safer with fewer PCI procedures and lower rates of bleeding, stroke, stent thrombosis and lower costs, it would represent a major advance in the treatment of this life-threatening disorder.

On the other hand, an imaging-guided revascularization strategy would target lesions given their plaque morphology and vulnerability, which is an opposite strategy compared to ischemia-driven, with the risk to over target lesions for revascularization. There are different intracoronary imaging modalities, but the most powerful for vulnerability detection is OCT, as TCFA definition is based on measurements calculated with OCT. We have learned over decades than the concept of atherosclerosis is a diffuse phenomenon, the higher risk patient profile, the more extensive; and these vulnerable plaques could be found in lesions with luminal stenosis and also in coronary segments without stenosis.

Pathology studies have shown that the presence of TCFA in a coronary artery lesion has the highest likelihood of triggering an acute coronary syndrome as they are prone to rupture. Reviews of atherosclerosis have uniformly accepted plaque rupture as the most common critical event leading to coronary artery related death.

However, the translation of the imaging concept into clinical practice is unclear and could transform the therapeutic intervention into preventive intervention. This strategy might also represent a higher cost and increase the risk of PCI complications and stent failure over the long term.

Imaging-guided revascularization strategy has several limitations. First, despite that some observational studies have shown that a MLA of >2 mm^2 often represents FFR negative lesions

(254, 255), there are no clear revascularization indications based on just MLA; then imaging-guided strategy might also addressed non-flow limiting lesions that are unlikely to represent a symptomatic benefit or ischemia myocardium relief. Second, vulnerability criteria are still in evolution, some observational and prospective studies have proposed pre-specified combinations of plaque features including MLA or Area Stenosis, FCT, lipid arc circumferential extension, and presence of macrophages (simultaneous presence in the same plaque) that have been observed to be an independent predictor of future events (203, 250); however, different criteria have been used in these combinations MLA < 2.5 vs. < 3.5 mm^2, Area Stenosis $\geq$ 75% which is a criteria that is used rarely in clinical practice, FCT < 65 vs. 75 vs. 85 µm which is an operator dependant measurement and it is challenging as there is a diffuse transition between fibrous cap and lipidic plaque; and there is not academic or clinical agreement regarding the most powerful predictor pre-specified criteria combination. Third, other plaque characteristics can be misleading as lipid, including macrophages infiltration and superficial thick calcification where the outer border is not captured by the cross-sectional image. Fourth, OCT interpretation requires training as the vulnerability criteria are not automatized by the available software. Then, performing imaging-guided revascularization is not a simple and reassuring task.

OCT as imaging technique has also its own limitations. First, OCT requires contrast for acquisition and the ACS setting is usually associated to a low cardiac output stage that is frequently associated with renal dysfunction and increasing contrast volume during PCI might

increase the risk of contrast induced nephropathy; second, the instrumentation of the coronary vasculature with an additional catheter is not attractive, however, OCT catheter related complications have reported not to be superior to the PCI related risk. Given these technique limitations, OCT has not been used widely in clinical or research practice in ACS and most of the current evidence for imaging-guided revascularization comes from studies stable clinical presentations and complex interventions.

Moreover, OCT has a value not only in plaque morphology and vulnerability characterization, but to optimize PCI. Previous studies have shown that imaging-guided revascularization result in larger final minimum stent area and reduced future risk of target lesion revascularization compared to angiographically guided PCI (256). PCIs guided by imaging use bigger stents, larger post dilation balloons and higher-pressure inflations. Use of OCT image guidance with an external elastic lamina-based sizing was shown to be non-inferior to IVUS on the outcome of minimum stent area (176). This sizing strategy is being compared to angiography guided PCI for complex lesions and high-risk patients in the ongoing ILUMIEN 4 trial (257).

Natural history studies that have explored the TCFA prevalence in ACS populations, have been mostly performed in patients presenting with NSTEMI and UA, and the presence of such vulnerables plaques in patients with STEMI in culprit and non-culprit vessels is unknown; more when the pancoronaritis concept suggests that this high-risk STEMI population has diffuse

atherosclerosis, and these lesions might be present in luminal stenotic and non-stenotic lesions as well.

There are then several reason why this research question of exploring non-culprit lesions in STEMI patients with OCT is attractive and valid; and outcomes from this observation will be important to understand why these patients benefit from complete revascularization and what intravascular imaging has to offer in the plaque characterization and PCI optimization.

6 PART III: THESIS: COMPLETE-OCT Evaluation of non-culprit lesions in patients with STEMI with OCT

6.1 BACKGROUND

PCI has become the preferred method of reperfusion for patients with STEMI who have timely access to catheterization facilities (258). However, successful primary PCI has brought with it new challenges. The optimal management of patients with multi-vessel CAD who have undergone primary PCI to the culprit lesion is one such challenge (2). Whether to routinely revascularize or medically treat the residual non-culprit stenosis found in non-infarct related arteries discovered incidentally during the index coronary angiogram is unknown (259).

The COMPLETE trial is a multinational, randomized trial evaluating a strategy of complete revascularization, consisting of angiography-guided PCI of all suitable non-culprit-lesions versus a strategy of culprit-lesion-only PCI (optimal medical therapy alone), in 4,041 patients from 140 centres in 31 countries undergoing pPCI for acute STEMI (22). Complete revascularization, defined by the angiographic core laboratory as successful treatment of all target lesions, was achieved in 99.1% of patients randomized to this arm of the trial. At a median follow-up of 3 years, complete revascularization reduced the first co-primary outcome of CV death or new MI by 26% compared with the culprit-lesion only strategy (HR 0.74; 95% CI 0.60-0.91; P=0.004). The second co-primary outcome of CV death, new MI or ischemia-driven revascularization was reduced by 49% with complete revascularization (HR 0.51; 95% CI 0.43-0.61; P<0.001). The

results of COMPLETE have had a far-reaching impact on global practice and is being incorporated into guideline recommendations.

6.1.1 Rationale for Optical Coherence Tomography Sub-study in the COMPLETE Trial

In patients with STEMI, angiographic studies have demonstrated the presence of multiple unstable coronary plaques remote from the culprit lesion (10, 11, 260-264). This concept of multiple unstable plaques suggests that ACS implies a diffuse pathophysiology affecting not only the culprit lesion, but the coronary vasculature as a whole. If this concept is correct, non-culprit lesions found at the time of a STEMI may not represent benign, stable plaques, but rather vulnerable plaques that are more susceptible to plaque rupture (264). These vulnerable plaques are more likely to progress and cause myocardial infarction or death (97).

Although the COMPLETE trial utilized visual angiographic assessment of non-culprit lesions to identify targets for revascularization, angiography provides only limited information about coronary stenosis. Intravascular imaging techniques are required to identify vulnerable plaques.

The major characteristics of plaques that are vulnerable to rupture are a thin fibrous cap (<65 µm), lipid rich plaque content, and thrombus near the fibrous cap (39). OCT is an intracoronary imaging modality that uses a single-mode optical fibre to produce two-dimensional tomographic images of coronary plaques at near histologic resolution (10-20 µm). OCT can

identify all of the principal features of vulnerable plaques including characterization of the three primary plaque morphologies (fibrous, calcific and lipid-rich), measurement of fibrous cap thickness, and detection of thrombus (265-267).

OCT studies of patients with NSTEMI have shown that a significantly higher proportion of non-culprit lesions have features of plaque vulnerability compared to stable patients (23). Treatment of such lesions with PCI may be the primary mechanism by which non-culprit PCI may reduce MI and death in patients with STEMI. Conversely, vulnerable plaques may be present at sites in the coronary arteries other than those identified for non-culprit PCI.

While these lesions may not be > 70% stenosed and therefore do not meet the angiographic criteria for PCI, they may still be associated with rapid progression to clinical events. An observational study using Coronary Computed Tomography Angiography in over 3000 stable coronary disease patients showed that patients with vulnerable lesions on Coronary Computed Tomography Angiography imaging had a 16.3% rate of ACS compared to 1.4% for those without vulnerable lesions and experienced a shorter time to event (1.7 years vs. 3.4 years) (128). However, approximately 50% of the vulnerable plaques in this study were found in lesions that were not severely stenotic at baseline. With this background, the COMPLETE OCT substudy sought to evaluate the prevalence of plaques with high-risk features (TCFA) in non-culprit vessels in patients with STEMI.

In the COMPLETE OCT sub-study, evaluation of at least 2 major epicardial coronary arteries not involved in the index STEMI using OCT characterized the prevalence of vulnerable plaques both at lesions sites that have been identified for non-culprit PCI as well as the rest of the coronary vasculature. OCT provides cross-sectional, high-resolution imaging of the coronary arteries.

6.1.2 Study Hypothesis

6.1.2.1. Primary Hypothesis

Patients with STEMI and Multivessel Disease (MVD) present a high (>70%) prevalence of vulnerable plaque in non-culprit lesions.

6.1.2.2. Secondary hypothesis

Patients with STEMI and MVD have vulnerable plaques located in non-culprit segments free of significant angiographic stenosis (<50%).

6.2 STUDY OBJECTIVES

6.2.1 Primary Objective

To determine the prevalence of vulnerable plaque features by OCT in non-culprit lesions undergoing PCI in the COMPLETE Trial.

6.2.2 Secondary Objective

To determine distribution of vulnerable plaques through multi-vessel imaging between lesions undergoing PCI versus lesions not undergoing PCI.

6.3 STUDY DESIGN

Observational, multicenter imaging study in patients randomized to non-culprit PCI in the COMPLETE Trial.

6.3.1 Inclusion Criteria

a. A coronary artery with at least 1 non-culprit lesion with ≥ 70% diameter stenosis (by angiography) (the target lesion for PCI)

   AND

b. A second coronary artery with a 30-69% diameter stenosis that will not be treated with PCI.

6.3.2 Exclusion Criteria

a. Angiographic evidence of severe calcification of the target vessels that would not permit safe imaging.
b. Marked tortuosity of the target vessels that would not permit safe imaging.
c. Chronic total occlusion.
d. GFR<35 mL/min.

6.4 STUDY PROCEDURES AND SAFETY

Patients randomized to non-culprit PCI who were eligible for participation in the sub-study were approached to participate prior to their non-culprit intervention. Upon consent, patients underwent central randomization to blinded pre-stent OCT imaging or unblinded pre-stent OCT imaging. During the PCI procedure, a coronary guide wire was advanced through the target coronary artery and placed distal to the non-culprit lesion site. The OCT catheter was advanced to a point distal to the non-culprit lesion that provided interrogation of the maximum length of coronary artery. A 54 mm or 75 mm pullback; in most of the cases, was recorded after flushing with intracoronary contrast at a rate of 4 cc/sec for a maximum dose of 14 cc in the left coronary system and 3 cc /sec for a maximum dose of 12 cc in the right coronary system. If required to pass the OCT catheter, inflation with a 2 mm balloon at < 10 atmospheres was permitted prior to imaging. Following OCT, the PCI procedure was carried out as per operator preference.

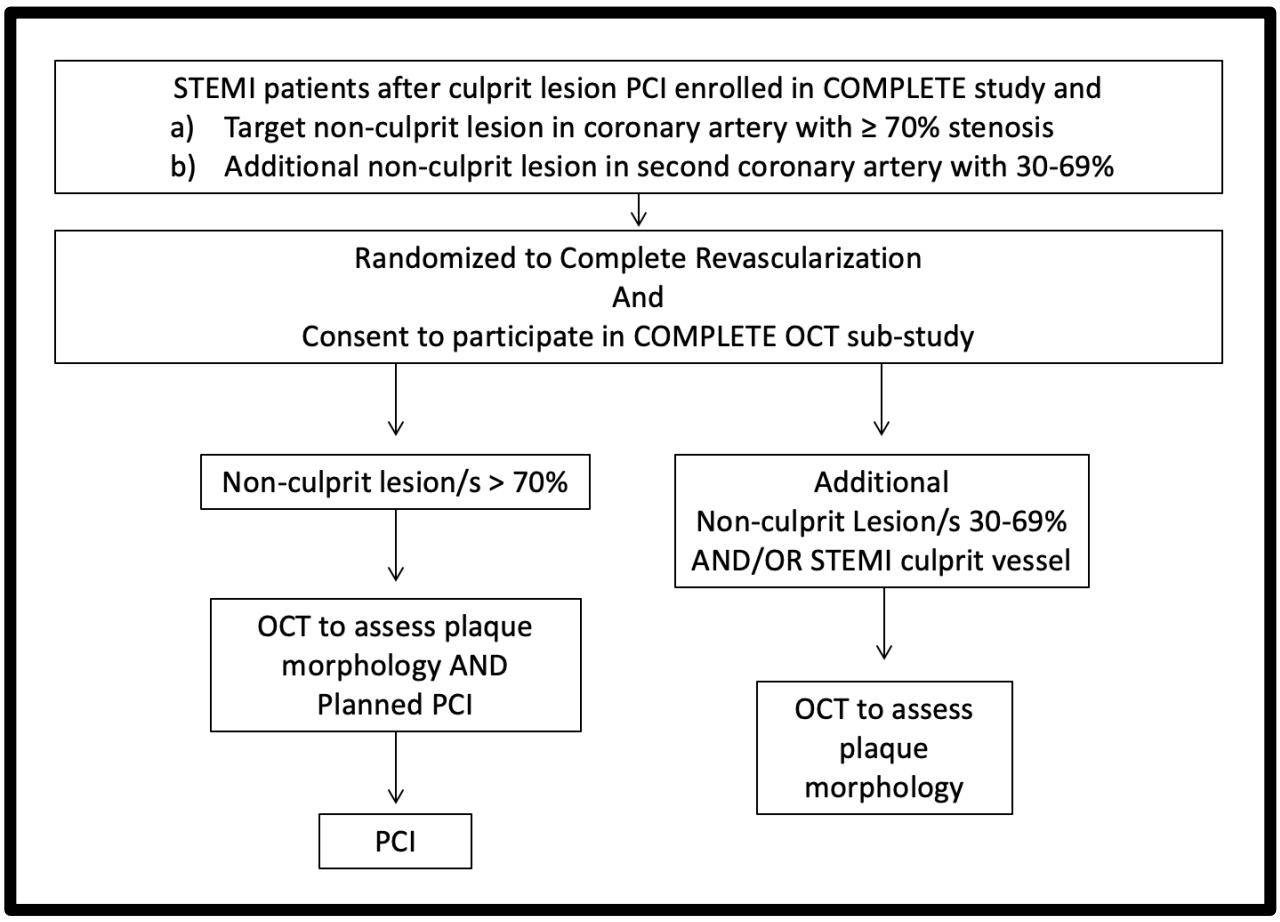
For the second coronary artery with 30-69% stenosis, a coronary guide wire was advanced down the coronary artery and placed distal to the non-obstructive non-culprit lesion site. The OCT catheter was advanced to a point distal to the non-obstructive lesion that provided for interrogation of the maximum length of coronary artery. A 54 mm or 75 mm pullback; in most of the cases, was recorded after flushing with intracoronary contrast at a rate of 4 cc/sec for a maximum dose of 14 cc in the left coronary system and 3 cc /sec for a maximum dose of 12 cc

in the right coronary system. Since these lesions were <70% in severity, pre-dilation was not necessary for imaging.

Imaging of a major side branch of one of these principal vessels or a third vessel; the culprit vessel for most of the cases, was performed at the discretion of operator.

Performance of OCT requires the same equipment as a PCI and does not result in additional procedural risk to the patient beyond what is required for the PCI itself.

6.5 STUDY FLOW CHART



6.6 STUDY OUTCOMES

6.6.1 Primary Outcome

The frequency of lesions defined by OCT with vulnerable plaque (lipid rich plaque and thin cap fibroatheroma or thrombus).

6.6.2 Secondary Outcome

The prevalence of vulnerable plaques at lesions undergoing non-culprit PCI versus lesions not undergoing PCI.

6.7 IMAGING DEFINITIONS AND ANALYSIS

6.7.1 Imaging Endpoints and Definitions

6.7.1.1 Lesion Definition

- A lesion was defined by the number of consecutive frames containing > 1 diseased quadrant.
- Plaque composition was analyzed at 1 mm intervals over the length of the lesion using standard definitions.
- To be considered as 2 separate lesions in the same vessel, the segment between them had to have at least a single frame with > 3 quadrants of at least 3-layer normal artery, the 4th quadrant should not be lipid. If not, they were considered 1 long lesion.

6.7.1.2 Quantitative

- Lesion length was defined as number of mm with more than 1 diseased quadrant.
- Fibrous cap thickness was measured at its thinnest part 3 times, the average value was calculated.
- The minimum value of fibrous cap thickness in each lesion was selected.

- Lipid arc was measured at every 1 mm interval throughout the entire lesion, the average value was calculated.
- Lipid length was defined as number of mm with contiguous lipid arc > 90^{o}.
- Lipid volume index was defined as the averaged lipid arc multiplied by lipid length.

6.7.1.3 Qualitative

- A TCFA was defined as a lesion with a mean fibrous cap thickness < 65 µm overlying a lipid-rich plaque (lipid arc > 90^{o}).
- Complex TCFA: TCFA with at least one of the following:
  - Microvessel was characterized by a black hole or tubular structure within a lesion with a diameter of 50 to 300 µm that was seen on at least 3 consecutive frames.
  - Macrophage accumulation on the lesion was characterized by increased signal intensity within the lesion, accompanied by heterogeneous backward shadows.
  - Cholesterol crystals was characterized by the presence of linear and highly reflecting structures within the lesion.
- Plaque rupture was identified by fibrous cap discontinuity usually associated with cavity formation.
- Intracoronary thrombus was defined as an irregular mass protruding into the lumen or a luminal mass that is not connected to the vessel wall, including red thrombus (red blood cell-rich) which was highly backscattering with high attenuation, and

white thrombus (platelet-rich) which was less backscattering and homogeneous with low attenuation.

- TCFA, microvessel, macrophage, cholesterol crystals, plaque rupture, intact fibrous cap and intracoronary thrombus were recorded only for their presence.

A vulnerable plaque was be defined as a lipid rich plaque with a thin fibrous cap or a lesion with thrombus.

6.7.2 Imaging Analysis

Image analysis was performed at the Imaging Core Laboratory of the Interventional Cardiology Research Group at Hamilton Health Sciences by Dr. Natalia Pinilla-Echeverri and Dr. Tej Sheth. Image interpretation was performed independently and blinded to clinical and angiographic information. Any discrepancies were resolved by consensus.

6.8 SAMPLE SIZE

The primary objective of this study as to assess the prevalence of vulnerable plaque in non-culprit lesions undergoing PCI following STEMI. Based on prior studies of non-culprit lesions in NSTEMI, we hypothesized that the lesion-based prevalence of vulnerable plaque was going to be 70%. The prevalence of subcomponents of vulnerable plaque was going to be: TCFA 45%, LRP 70%, and thrombus 20%. We assumed that 90% of imaged lesions were going to be assessable. Intraclass correlation was estimated by analysis of variance method. As a result, sample size was inflated by a design effect of 1.4. With a two-sided confidence level of 0.05 and precision of 5%, a total sample size of 100 was required for this sub-study.

Category	Anticipated Frequency	Number of Patients	Number of Lesions Imaged	Number of Imaged Lesions that can be evaluated	95% confidence Interval (Design effect = 1)	95% confidence Interval (Design effect= 1.4)
TCFA	45%	100	200	180	37.73-52.27	36.40-53.60
		200	400	360	39.86-50.14	38.93-51.07
		250	500	450	40.40-49.60	39.57-50.43
		300	600	540	40.80-49.20	40.04-49.96
LRP	70%	100	200	180	63.31-76.69	62.08-77.92
		200	400	360	65.27-74.73	64.41-75.59
		250	500	450	65.77-74.23	65.00-75.00
		300	600	540	66.13-73.87	65.43-74.57
Thrombus	20%	100	200	180	14.16-25.84	13.09-26.91
		200	400	360	15.87-24.13	15.12-24.88
		250	500	450	16.30-23.70	15.63-24.37
		300	600	540	16.63-23.37	16.01-23.99

6.9 STUDY ORGANIZATION

The study was coordinated by the Population Health Research Institute in Hamilton, Canada. The existing study infrastructure (database and case report forms) for the COMPLETE Trial were utilized for demographic, procedure, and angiographic core lab information. A specific COMPLETE OCT case report form was designed to collect OCT information.

COMPLETE OCT was conducted at 6 centers in Canada between January 18, 2016 to November 20, 2017. The sub-study was funded by Hamilton Health Sciences, Population Health Research Institute and Abbott Vascular. It was approved by the local human research ethics committees of the recruiting hospitals. Informed consent was provided by all patients enrolled. Anonymized OCT images were transferred to PHRI via a secure SFTP site for analysis.

6.10 SIGNIFICANCE OF STUDY

The COMPLETE trial is the largest randomized trial to address the role of non-culprit PCI in patients undergoing primary PCI. Given its large size, this trial had sufficient power to determine if a non-culprit PCI strategy was to reduce MI and death. The biological rationale for this approach is that non-culprit lesions; are vulnerable plaques, that are at risk for rapid progression and without a complete revascularization approach would leave untreated. Therefore, an OCT sub-study was crucial to provide mechanistic insights into the results of this global trial.

6.11 STATISTICAL ANALYSIS

Baseline and procedural characteristics were reported as mean/SD for continuous variables and proportion of prevalence for categorical variables. To account for the potential underlying correlation among multiple lesions in the same patient, the primary outcome was analyzed using a logistic mixed-effects model with patient as a random effect. Imaging findings were analyzed using a linear mixed model for continuous variables, a negative binomial mixed model for count variables and a logistic mixed model for categorical variables. All the reported means with 95% CI for continuous/count variables and prevalence for categorical variables were adjusted for multiple lesions per patient. Continuous variables that violated the normality assumption based on residual analysis were transformed to achieve normality, and the adjusted means were thereafter back-transformed to the original scale. The intraclass (patient) correlation coefficient, which evaluates the correlation among lesions within the same patient, was reported for each imaging parameter except for count variables as there is no generally accepted method for calculating intraclass (patient) correlation coefficient in a negative binomial mixed model. Statistical analyses were conducted with the use of SAS 9.4 software (SAS Institute, Inc, Cary, NC). All P values were 2-sided with significance level at $P<0.05$. Considering the exploratory nature of the study, we did not adjust for multiple comparisons.

6.12 RESULTS

A total of 129 patients were screened for the COMPLETEOCT sub-study during the recruitment period, 25 patients were ineligible, and 5 eligible patients did not have OCT imaging performed. Of the 99 patients that underwent OCT imaging, 6 had nonassessable morphology of the non-culprit lesions randomized to PCI due to either inadequate blood clearance (n=5) or significant disruption of the underlying plaque (n=1). Overall, 93 patients had diagnostic OCT images that were included in the analysis.

Patient baseline characteristics are shown in Table 1, and PCI data are shown in Table 2. Reasons for patient exclusion from recruitment and analysis in Table 3. Baseline (Table 4) and procedure characteristics (Table 5) in patients undergoing OCT compared with those without OCT imaging in the complete revascularization arm in the COMPLETE trial.

Table 1. Patient baseline characteristics

	All (N=93)
Age (year) - mean±SD	61.2±10.0
Gender (male) - no.(%)	77 (82.8)
Diabetes - no.(%)	12 (12.9)
Chronic renal insufficiency - no.(%)	1 (1.1)
Prior myocardial infarction - no.(%)	8 (8.6)
Current smoker - no./total no.(%)	35/91 (38.5)
Hypertension - no. (%)	39 (41.9)
Dyslipidemia - no. (%)	40 (43.0)
Prior stroke - no. (%)	1 (1.1)
Body mass index (BMI) (kg/m^2) - mean±SD	29.8±5.8
Hemoglobin A1C (%) – median (IQR)	5.7 (5.4 – 6.2)
LDL cholesterol (mmol/L) - mean±SD	2.9±1.0
Peak creatinine (μmol/L) - mean±SD	82.0±18.0

Table 2. Procedure Characteristics

	All (N=93)
Radial access - no.(%)	86 (92.5)
Number of residual diseased vessels (core lab) - no./total no.(%)	
1	55/86 (64.0)
≥2	31/86 (36.0)
Non-culprit lesion location (core lab) - no./total lesions (%)	
Left main	0 (0.0)
Left anterior descending (LAD)	55/134 (41.0)
Proximal LAD	14/134 (10.4)
Mid LAD	33/134 (24.6)
Apical LAD	2/134 (1.5)
Diagonals	6/134 (4.5)
Circumflex	43/134 (32.1)
Prox LCx and OM/Ramus	31/134 (23.1)
Distal LCx and PLV	12/134 (9.0)
RCA	36/134 (26.9)
RCA before the Crux	34/134 (25.4)
RCA beyond the Crux	2/134 (1.5)
Non-culprit lesion diameter stenosis (visual) - no./total lesions (%)	
70-79%	50/123 (40.7)
80-89%	39/123 (31.7)
90-99%	33/123 (26.8)
100%	1/123 (0.8)
Non-culprit lesion diameter stenosis (visual) - mean±SD	79.3±8.4
Non-culprit lesion reference diameter (core lab) - mean±SD	2.8±0.4

Table 3. Reasons for patient exclusion from recruitment and analysis

Exclusion from COMPLETE-OCT sub-study	Number of patients
Ineligible	**25**
• Target non-culprit vessel not suitable for OCT imaging	
– Severe calcification	7
– Severe tortuosity	13
• Target non-culprit lesion is a CTO	1
• Target non-culprit lesion had negative FFR	1
• Cross-over to culprit only PCI	3
Eligible but OCT was not performed	**5**
• PCI not performed due to operator decision	2
• Patient deceased before staged PCI	1
• PCI not performed (no significant disease in the staged procedure	1
• Catheter related dissection during staged PCI	1
OCT was not performed, but image was non-assessable	**6**
• Inadequate blood clearance	5
• Disruption of the underlying plaque in the non-culprit lesion	1

Table 4. Baseline characteristics. Comparative table according to OCT imaging

Patients undergoing OCT in the COMPLETE OCT sub-study compared to those without OCT imaging in the complete revascularization arm in the main COMPLETE trial

	OCT patients (N=93)	**Non-OCT patients (N=1960)**	**P Value**
Age (year) - mean±SD	61.2±10.0	61.7±10.7	0.67
Gender (male) - no.(%)	77 (82.8)	1577 (80.5)	0.58
Diabetes - no.(%)	12 (12.9)	377 (19.2)	0.13
Chronic renal insufficiency - no.(%)	1/93 (1.1)	36/1828 (2.0)	>0.99
Prior myocardial infarction - no.(%)	8 (8.6)	143 (7.3)	0.64
Current smoker - no./total no.(%)	35/91 (38.5)	793/1960 (40.5)	0.70
Hypertension - no.(%)	39 (41.9)	957 (48.8)	0.19
Dyslipidemia - no.(%)	40 (43.0)	740 (37.8)	0.31
Prior stroke - no.(%)	1 (1.1)	63 (3.2)	0.36
Body mass index (kg/m^2) - mean±SD	29.8±5.8	28.4±5.9	0.029
Hemoglobin A1C (%) - median(IQR)	5.7 (5.4-6.2)	5.8 (5.5-6.4)	0.46
LDL cholesterol (mmol/L) - mean±SD	2.9±1.0	3.1±1.2	0.09
Peak creatinine (µmol/L) - mean±SD	82.0±18.0	84.8±31.1	0.15

Table 5. Procedure characteristics. Comparative table according to OCT imaging

Patients undergoing OCT in the COMPLETE OCT sub-study compared to those without OCT imaging in the complete revascularization arm in the main COMPLETE trial

	OCT patients (N=93)	**Non-OCT patients (N=1960)**	**P Value**
Radial access - no.(%)	86 (92.5)	1577 (80.5)	0.004
Number of residual diseased vessels (core lab) - no./total no.(%)			
1	55/86 (64.0)	1427/1862 (76.6)	0.007
≥2	31/86 (36.0)	435/1862 (23.4)	0.007
Non-culprit lesion location (core lab) - no./total lesions (%)			
Left main	0/134 (0.0)	10/2644 (0.4)	0.99
Left anterior descending (LAD)	55/134 (41.0)	1002/2644 (37.9)	0.46
Proximal LAD	14/134 (10.4)	257/2644 (9.7)	0.78
Mid LAD	33/134 (24.6)	573/2644 (21.7)	0.42
Apical LAD	2/134 (1.5)	67/2644 (2.5)	0.77
Diagonals	6/134 (4.5)	105/2644 (4.0)	0.99
Circumflex	43/134 (32.1)	965/2644 (36.5)	0.30
Prox LCX and OM/Ramus	31/134 (23.1)	723/2644 (27.3)	0.29
Distal LCX and PLV	12/134 (9.0)	242/2644 (9.2)	0.83
RCA	36/134 (26.9)	667/2644 (25.2)	0.68
RCA before the Crux	34/134 (25.4)	576/2644 (21.8)	0.34
RCA beyond the Crux	2/134 (1.5)	91/2644 (3.4)	0.68
Non-culprit lesion diameter stenosis (visual) - no./total lesions (%)			0.72
50-69%	0/123 (0.0)	21/2537 (0.8)	
70-79%	50/123 (40.7)	1045/2537 (41.2)	
80-89%	39/123 (31.7)	852/2537 (33.6)	
90-99%	33/123 (26.8)	565/2537 (22.3)	
100%	1/123 (0.8)	54/2537 (2.1)	

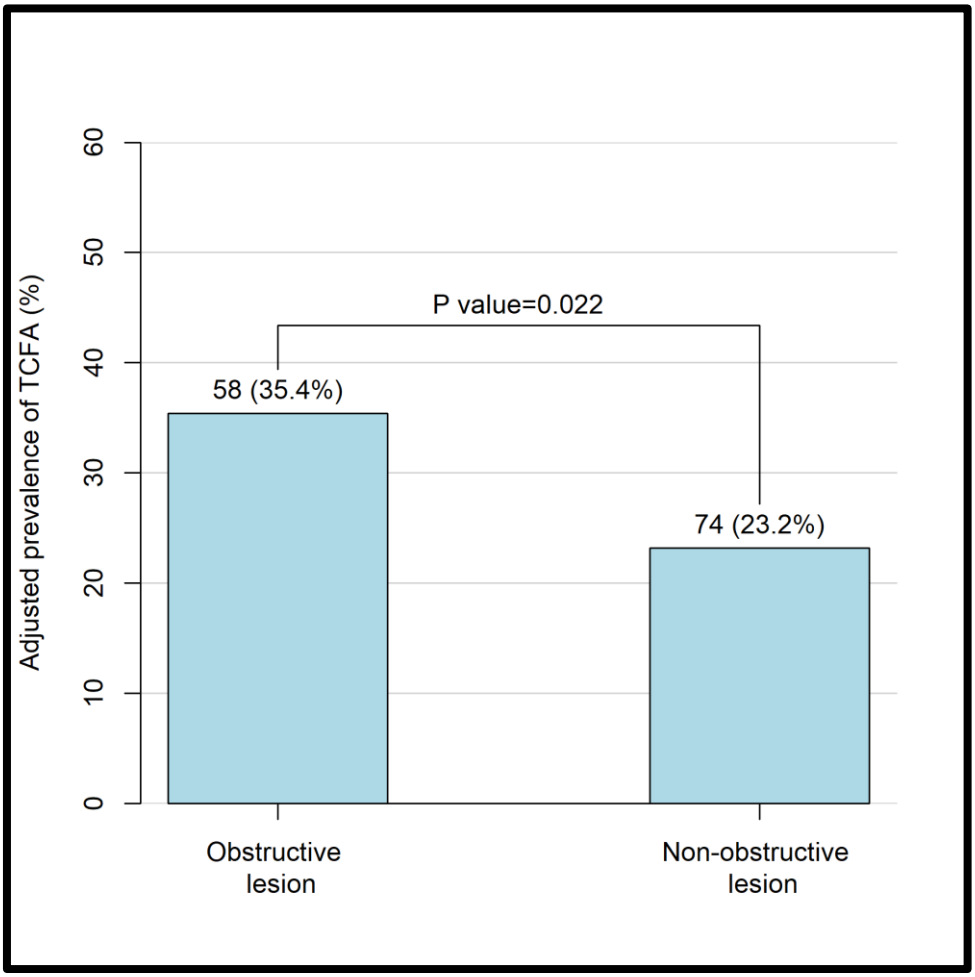
	OCT patients (N=93)	Non-OCT patients (N=1960)	P Value
Non-culprit lesion diameter stenosis (visual) - mean±SD	79.3±8.4	79.3±8.1	0.79
Non-culprit lesion reference diameter (core lab) - mean±SD	2.8±0.4	2.8±0.5	0.81

Staged non-culprit lesion PCI in the COMPLETE OCT sub-study was performed with a mean timing of 2.9 ± 4.8 days from index culprit lesion PCI. OCT imaging was performed in at least 2 vessels in all patients, with mean of 2.82 ± 0.95 OCT pullbacks per patient. Mean unstented coronary length imaged per patient was 152.5 ± 53.9 mm. Balloon dilatation was performed before OCT intracoronary imaging in 7 obstructive TCFA lesions (12.1%) and 21 obstructive non TCFA lesions (22.8%).

Primary Outcome

For the primary outcome of TCFA frequency in obstructive and nonobstructive non-culprit lesions, there were 58 TCFAs among 150 obstructive non-culprit lesions compared with 74 TCFAs among 275 nonobstructive lesions (adjusted TCFA prevalence: 35.4% versus 23.2%, P=0.022) in Figure 1.

Figure 1. Adjusted* prevalence of TCFA in Obstructive and Non-obstructive lesions.



* Prevalence of TCFA was adjusted for multiple lesions per patient using logistic mixed-effects model.

TCFA frequency in obstructive and non-obstructive non-culprit lesions. 58 TCFAs were detected among 150 obstructive non-culprit lesions compared with 74 TCFAs among 275 non-obstructive lesions (adjusted TCFA prevalence: 35.4% vs. 23.2%, p=0.022)

Obstructive Lesions

Obstructive TCFA and obstructive non-TCFA had similar lesion length (23.1 versus 20.8 mm, P=0.16) and MLA (1.9 versus 1.7 mm2, P=0.52); however, obstructive TCFA lesions had a higher number of lipid quadrants (55.2 versus 19.2, P<0.001) and greater mean lipid arc (203.8° versus 84.5°, P<0.001) compared with obstructive non-TCFA lesions which were predominantly fibrotic and calcific in composition (Table 6). Obstructive TCFA lesions also showed lower mean FCT (54.5 versus 152.2 µm, P<0.001) and higher frequencies of macrophages (97.1% versus 54.4%, P<0.001) and cholesterol crystals (85.8% versus 44.3%, P<0.001) compared with the obstructive non-TCFA. A sensitivity analysis that excluded all predilated lesions demonstrated similar results, with no heterogeneity in Table 7. A scatterplot of number of lipid quadrants by MLA for obstructive TCFA and non-TCFA lesions is shown in Figure 2. An MLA>2 mm^2 was observed in 31% of the obstructive TCFA lesions and 25% of obstructive non-TCFA lesions.

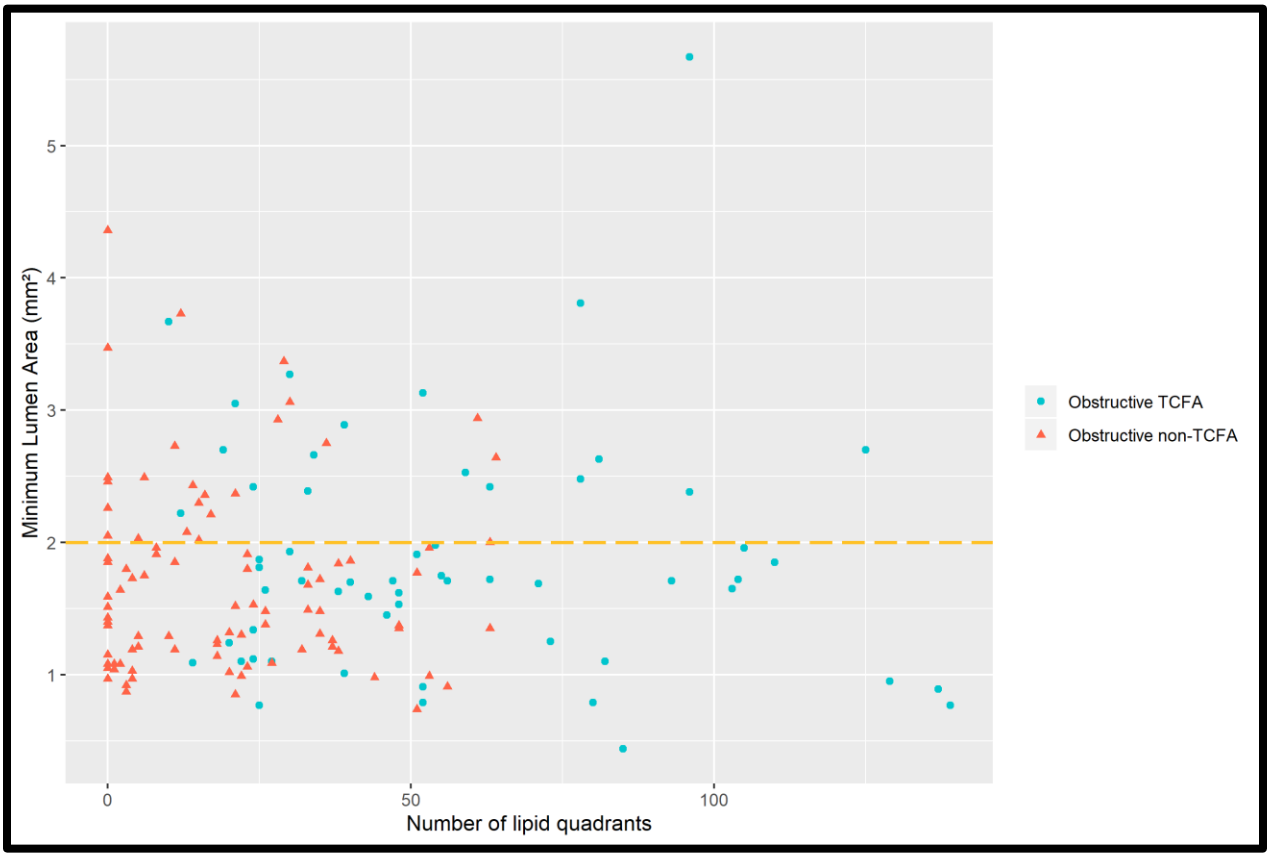
Table 6. OCT imaging findings by lesions

					P value for pairwise comparison			
	Group 1: Obstructive TCFA (N=58)	**Group 2: Non-obstructive TCFA (N=74)**	**Group 3: Obstructive non-TCFA (N=92)**	**Group 4: Non-obstructive non-TCFA (N=201)**	**Group 1 vs. 2**	**Group 1 vs. 3**	**Group 2 vs. 4**	**ICC**
	Adjusted mean (95% CI)	*Adjusted mean (95% CI)*	*Adjusted mean (95% CI)*	*Adjusted mean (95% CI)*				
Lesion Length (mm)	23.1(20.4-25.7)	16.7(14.2-19.1)	20.8(18.7-22.9)	14.6(12.9-16.3)	<0.001	0.16	0.11	0.242
Plaque type by quadrant								
Lipid								
Number of quadrants	55.2(39.9-76.2)	36.4(27.2-48.7)	19.2(14.8-25.0)	13.5(11.1-16.4)	0.05	<0.001	<0.001	-
% of quadrants	78.4(70.6-86.2)	76.8(69.6-83.9)	36.5(30.2-42.9)	35.8(30.8-40.8)	0.73	<0.001	<0.001	0.254
Fibrous								
Number of quadrants	9.4(7.2-12.1)	7.1(5.6-9.0)	21.2(17.3-26.0)	14.2(12.1-16.6)	0.10	<0.001	<0.001	-
% of quadrants	16.9(9.6-24.3)	16.2(9.5-22.9)	43.7(37.8-49.6)	45.5(41.0-50.1)	0.88	<0.001	<0.001	0.180
Calcified								
Number of quadrants	2.5(1.5-4.3)	1.7(1.0-2.8)	9.8(6.4-15.0)	5.4(3.8-7.6)	0.26	<0.001	<0.001	-
% of quadrants	4.1(0.0-9.5)	7.0(2.0-12.0)	20.1(15.7-24.6)	19.0(15.4-22.5)	0.39	<0.001	<0.001	0.257
Maximum Lipid Arc	342.2(312.0-372.3)	304.0(276.6-331.4)	212.5(188.4-236.6)	170.2(152.5-188.0)	0.06	<0.001	<0.001	0.101
Mean Lipid Arc	203.8(183.9-223.7)	191.8(173.5-210.0)	84.5(68.4-100.5)	84.2(71.8-96.6)	0.34	<0.001	<0.001	0.191
Mean FCT (μm)	54.5(51.3-57.9)	54.5(51.6-57.6)	152.2(141.0-164.3)	143.9(136.6-151.6)	0.98	<0.001	<0.001	0.098
Minimum Lumen Area	1.9(1.4-2.4)	4.8(4.4-5.2)	1.7(1.3-2.1)	4.1(3.9-4.4)	<0.001	0.52	0.009	0.017
	Event No. (adjusted prevalence[%])	*Event No. (adjusted prevalence[%])*	*Event No. (adjusted prevalence[%])*	*Event No. (adjusted prevalence[%])*				
Macrophages	55 (97.1)	65 (93.7)	48 (54.4)	93 (47.8)	0.28	<0.001	<0.001	0.325
Microvessels	19 (32.0)	23 (30.6)	28 (29.8)	44 (21.4)	0.86	0.77	0.12	0.032
Cholesterol Crystals	48 (85.8)	29 (37.6)	42 (44.3)	58 (25.8)	<0.001	<0.001	0.09	0.149

Table 7. OCT imaging findings by lesions (pre-dilated lesions excluded)

					P value for pairwise comparison			
	Group 1: Obstructive TCFA (N=51)	**Group 2: Non-obstructive TCFA (N=74)**	**Group 3: Obstructive non-TCFA (N=71)**	**Group 4: Non-obstructive non-TCFA (N=201)**	**Group 1 vs. 2**	**Group 1 vs. 3**	**Group 2 vs. 4**	**ICC**
	Adjusted mean (95% CI)	*Adjusted mean (95% CI)*	*Adjusted mean (95% CI)*	*Adjusted mean (95% CI)*				
Lesion Length (mm)	23.4(20.7-26.2)	16.6(14.2-19.0)	20.0(17.6-22.4)	14.5(12.8-16.1)	<0.001	0.05	0.10	0.231
Plaque type by quadrant								
Lipid								
Number of quadrants	56.3(39.8-79.5)	36.4(27.2-48.8)	18.8(14.0-25.4)	13.6(11.2-16.5)	0.05	<0.001	<0.001	-
% of quadrants	78.1(69.7-86.5)	77.1(69.9-84.4)	38.4(31.2-45.6)	35.9(30.9-41.0)	0.85	<0.001	<0.001	0.234
Fibrous								
Number of quadrants	9.7(7.3-12.9)	7.1(5.5-9.1)	19.8(15.6-25.0)	14.1(12.0-16.6)	0.09	<0.001	<0.001	-
% of quadrants	17.4(9.6-25.2)	16.1(9.3-22.8)	42.8(36.1-49.5)	45.4(40.9-49.9)	0.79	<0.001	<0.001	0.157
Calcified								
Number of quadrants	2.6(1.5-4.7)	1.8(1.1-2.9)	9.8(6.1-15.7)	5.8(4.1-8.2)	0.26	<0.001	<0.001	-
% of quadrants	3.8(0.0-9.5)	6.7(1.7-11.7)	19.2(14.3-24.1)	19.1(15.7-22.5)	0.42	<0.001	<0.001	0.218
Maximum Lipid Arc	344.9(313.0-376.9)	304.4(277.1-331.6)	212.7(185.5-240.0)	170.7(153.1-188.2)	0.05	<0.001	<0.001	0.089
Mean Lipid Arc	203.2(181.8-224.6)	192.4(173.9-210.9)	87.7(69.4-106.0)	84.6(72.2-97.1)	0.42	<0.001	<0.001	0.176
Mean FCT (μm)	54.2(50.9-57.8)	54.5(51.6-57.6)	158.8(146.3-172.4)	144.0(136.7-151.7)	0.90	<0.001	<0.001	0.088
Minimum Lumen Area	1.9(1.4-2.5)	4.8(4.4-5.3)	1.8(1.3-2.2)	4.2(3.9-4.4)	<0.001	0.68	0.012	0.014
	Event No. (adjusted prevalence[%])	*Event No. (adjusted prevalence[%])*	*Event No. (adjusted prevalence[%])*	*Event No. (adjusted prevalence[%])*				
Macrophages	48 (96.9)	65 (93.7)	33 (48.9)	93 (48.2)	0.34	<0.001	<0.001	0.318
Microvessels	19 (36.4)	23 (30.4)	23 (31.5)	44 (21.2)	0.50	0.58	0.13	0.045
Cholesterol Crystals	42 (86.6)	29 (37.5)	31 (41.8)	58 (25.6)	<0.001	<0.001	0.10	0.175

Figure 2. Scatter Plot of Minimum Lumen Area Vs. Number of Lipid Quadrants for Obstructive TCFA (blue) and Obstructive Non-TCFA (orange)



Number of lipid quadrants by MLA for obstructive TCFA and non-TCFA lesions. A MLA > 2mm^2 was seen in 31% of obstructive TCFA and 25% of obstructive non-TCFA lesions

Non-obstructive Lesions

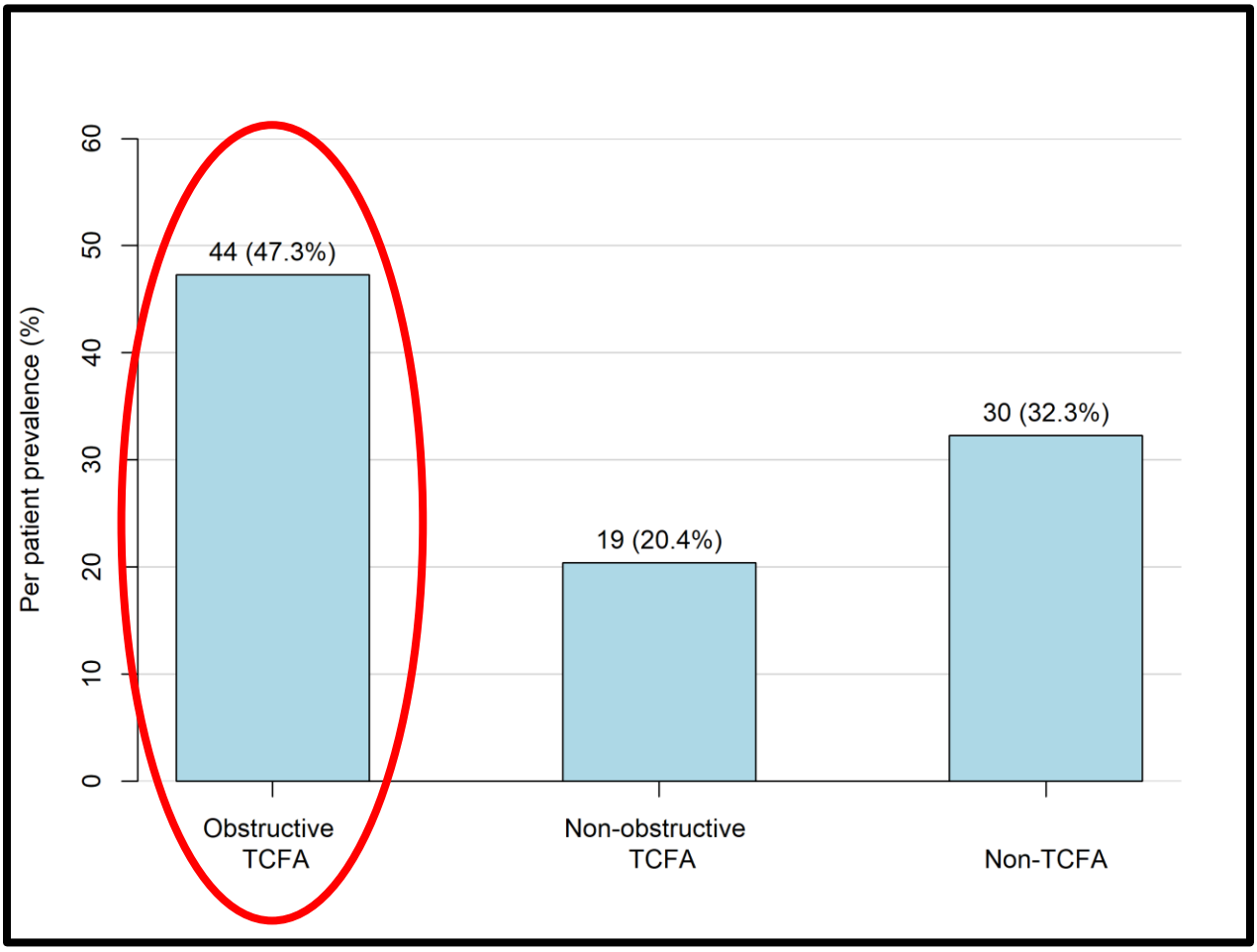
There were 275 non-obstructive lesions of which 74 (27%) were non-obstructive TCFA and 201 (73%) were non-obstructive non-TCFA lesions. These lesions showed similar lesion lengths (16.7 versus 14.6 mm, P=0.11) that were shorter than obstructive lesions. Nonobstructive TCFA had a higher number of lipid quadrants (36.4 versus 13.5, P<0.001) and greater mean lipid arc (191.8° versus 84.2°, P<0.001) compared with nonobstructive non-TCFA lesions.

TCFA Lesions

Obstructive TCFA and nonobstructive TCFA lesions had similar percentage of lipidic (78.4% versus 76.8%, P=0.73), fibrotic (16.9% versus 16.2%, P=0.88) and calcific (4.1% versus 7%, P=0.39) plaque, similar mean FCT (54.5 versus 54.5 µm, P=0.98) and mean lipid arc (203.8° versus 191.8°, P=0.34). However, obstructive TCFA lesions were longer (23.1 versus 16.7 mm, P<0.001) and had a smaller mean MLA (1.9 versus 4.8 mm^2, P<0.001).

On a per-patient basis, obstructive TCFA with or without nonobstructive TCFA was observed in 47.3% of patients, nonobstructive TCFA only in 20.4%, and no TCFA in 32.3% (Figure 3).

Figure 3. Per Patient Prevalence of TCFA



Lesions were ranked from high-risk to low-risk as obstructive TCFA>non-obstructive TCFA>no-TCFA, and each patient was classified into one of these 3 categories based on highest-risk lesion. Obstructive TCFA with or without non-obstructive TCFA was seen in 47.3% of patients, non-obstructive TCFA only in 20.4%, and no-TCFA in 32.3%.

Baseline characteristics between patients who had at least 1 TCFA and patients with no TCFA are shown in Table 8. Levels of LDL cholesterol were significantly higher in patients with at least 1 TCFA versus patients with no TCFA (3.1 versus 2.5 mmol/L, P=0.025).

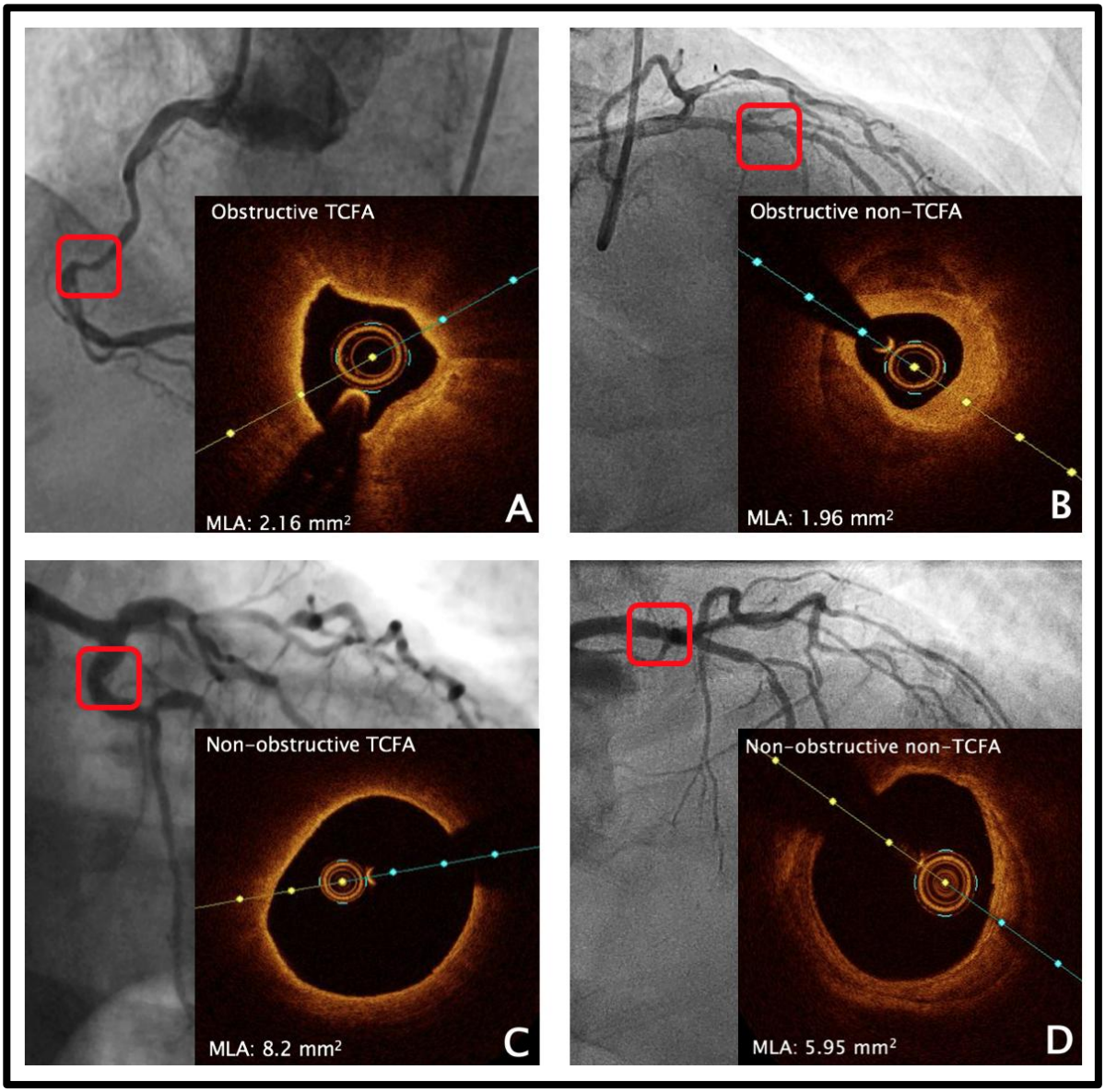
Table 8. Baseline characteristics. Comparative table according to vulnerable plaque.

(Patients with at least 1 TCFA lesion vs. patients with no TCFA lesions)

	Patients with at least 1 TCFA (N=63)	**Patients with no TCFA (N=30)**	**P Value**
Age (year) - mean±SD	60.8±10.0	62.2±10.2	0.51
Gender (male) - no.(%)	52 (82.5)	25 (83.3)	0.92
Diabetes - no.(%)	9 (14.3)	3 (10.0)	0.75
Chronic renal insufficiency - no.(%)	1 (1.6)	0 (0.0)	>0.99
Prior myocardial infarction - no.(%)	6 (9.5)	2 (6.7)	>0.99
Current smoker - no./total no.(%)	24/62 (38.7)	11/29 (37.9)	0.94
Hypertension - no.(%)	29 (46.0)	10 (33.3)	0.25
Dyslipidemia - no.(%)	25 (39.7)	15 (50.0)	0.35
Body mass index (kg/m^2) - mean±SD	30.1±5.9	29.1±5.6	0.45
Hemoglobin A1C (%) - median(IQR)	5.6 (5.4-6.2)	5.7 (5.7-6.0)	0.30
LDL cholesterol (mmol/L) - mean±SD	3.1±0.9	2.5±1.0	0.025
Peak creatinine (µmol/L) - mean±SD	81.5±18.1	82.9±18.0	0.75

Examples illustrating the 4 plaque types are shown in Figure 4.

Figure 4. Representative angiographic and OCT images of (A) obstructive TCFA, (B) obstructive non-TCFA, (C) non-obstructive TCFA and (D) non-obstructive non-TCFA lesions



A. Mid RCA obstructive TCFA, MLA 2.16mm^2; circumferential lipid, macrophages and cholesterol crystals.

B. Mid LAD obstructive non-TCFA, MLA 1.96mm^2; fibrotic and deep calcific plaque.

C. Proximal LCX non-obstructive TCFA, MLA 8.2mm^2; lipidic plaque with superficial calcification.

D. Left main non-obstructive non-TCFA, MLA 5.95mm^2; circumferential calcium.

6.13 DISCUSSION

In this prospective COMPLETE OCT sub-study, we evaluated non-culprit lesions in patients after STEMI who were randomized to non-culprit lesion PCI in the COMPLETE trial and demonstrated that: 1) obstructive lesions more commonly contained vulnerable plaque morphology compared with non-obstructive lesions, 2) obstructive TCFAs had increased lipid content and other plaque features of vulnerability compared with obstructive non-TCFA lesions, 3) obstructive TCFAs in these STEMI patients with multivessel disease were common, with about 47% of patients having at least one obstructive non-culprit lesion TCFA.

Obstructive TCFA lesions demonstrated extensive lipid infiltration, small MLA, and vulnerable plaque features. Such lesions may carry a high risk of subsequent cardiovascular events. In the PROSPECT study, the risk of future cardiac events associated with TCFA was 3.35-fold higher than non-TCFA lesions (97). Similarly, in the ATHEROREMO-IVUS (The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis - Intravascular Ultrasound) study risk of future cardiac events was 2.51-fold higher when virtual histology – IVUS derived TCFA was detected (168).

The lipid-rich plaque study showed the ability to predict future non-culprit segment related major adverse cardiovascular events by detecting vulnerable plaque with near-infrared spectroscopy- IVUS (201). Increased plaque lipid content on OCT is a predictor of non-culprit

lesion progression with a predicted rate of events that is 3 times that of nonlipid rich plaques (200).

Macrophages and cholesterol crystals are OCT detected features of plaque instability (67, 182, 200, 268). Consistent with prior reports (182, 268), we found these lesion characteristics more commonly in obstructive TCFA compared with obstructive non-TCFA lesions.

TCFA is as a precursor lesion for plaque rupture (67). Optimal medical therapy with high intensity statin improves clinical outcomes in patients with coronary atherosclerosis and induces plaque level changes detectable by imaging (269). A meta-analysis by Ozaki et al (270) showed that statin therapy induced a significant increase in FCT as assessed by OCT. A recent multimodality imaging study in non-infarct related arteries in the STEMI population found a significant increase in minimum FCT, reduction in macrophage accumulation, and frequent regression of TCFAs to other plaque phenotypes in non-culprit lesions of patients with STEMI treated with high-intensity statin therapy (271).

We have demonstrated in the COMPLETE trial that angiography-guided PCI of non-culprit lesions was associated with a reduction in subsequent cardiovascular events. Most patients in the COMPLETE trial, including those in this sub-study, did not have FFR evaluation of the non-culprit lesion. We observed an MLA of >2 mm^2 in 31% of obstructive TCFA lesions, a value that

often represents FFR negative lesions (254, 255). In FFR-guided non-culprit lesion PCI, 30% to 45% of lesions identified as obstructive on angiography are deferred after FFR (14, 16). Therefore, it is possible that an FFR-guided non-culprit lesion PCI strategy would lead to deferral of lesions that, despite being FFR negative, still have high-risk morphological features for future cardiovascular events. To the extent that future events are driven by plaque vulnerability, the potential benefit of an FFR-guided strategy may be attenuated by deferring intervention on such lesions.

The FORZA study (Fractional Flow Reserve or Optical Coherence Tomography Guidance to Revascularize Intermediate Coronary Stenosis Using Angioplasty), recruited patients with angiographically intermediate coronary lesions to undergo either FFR or OCT-guided PCI and showed that OCT guidance was associated with lower composite of major adverse cardiac events or significant angina at 13 months follow-up and FFR-guidance was associated with higher rate of deferred PCI and medical management (250).

Non-obstructive TCFAs were more numerous than obstructive TCFAs but had fewer features of lesion complexity. This finding is consistent with prior observations that TCFAs with <70% stenosis are more frequent than TCFAs with >70% stenosis but have lower plaque burden by IVUS and fewer features of plaque vulnerability by OCT (272). The small plaque burden of non-obstructive TCFAs is associated with recurrent cardiac events only over the long-term, whereas short-term events (<6 months) are predicted by the presence of large plaque TCFA burden (168).

There is an ongoing randomized studies of optimal medical therapy alone versus PCI examining if preventive coronary intervention on functionally insignificant vulnerable coronary stenosis can reduce the incidence of the future major adverse cardiovascular events: PREVENT (The Preventive Coronary Intervention on Stenosis With Functionally Insignificant Stenosis With Vulnerable Plaque Characteristics; URL: https://www.clinicaltrials. gov. Unique identifier: NCT02316886) using multimodality imaging (NIRS, OCT, virtual histology-IVUS, and IVUS).

At least one non-culprit obstructive TCFA was found in 47% of patients in the COMPLETE-OCT sub-study. This finding is consistent with other studies, highlighting the increased frequency of additional vulnerable plaques in ACS compared with stable angina patients. The reduction of future events observed with complete revascularization in the COMPLETE trial suggests that non-culprit lesion PCI may effectively pacify these lesions.

6.14 CONCLUSIONS

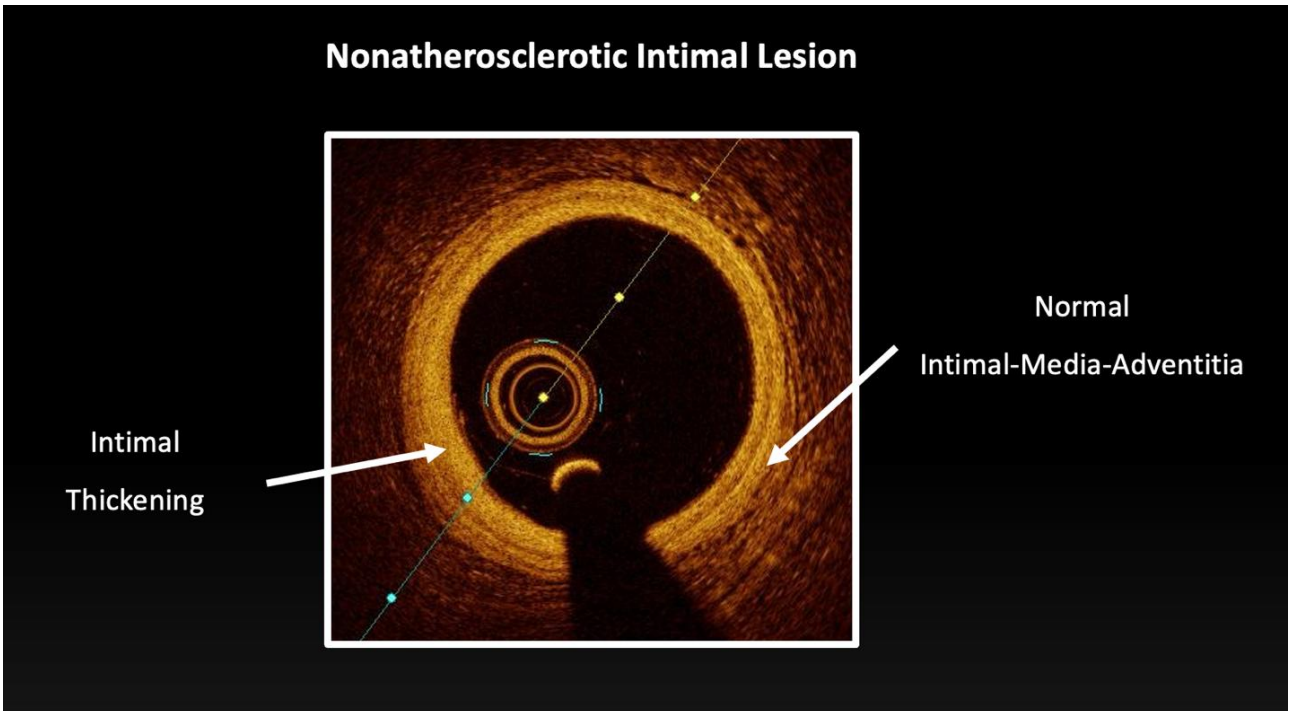
Among patients who underwent OCT imaging in the COMPLETE trial, nearly 50% had at least one obstructive non-culprit lesion containing complex vulnerable plaque morphology. Obstructive lesions more commonly harbored vulnerable plaque morphology than non-obstructive lesions. This may help explain the benefit of routine PCI of obstructive non-culprit lesions in patients with STEMI and multivessel disease.

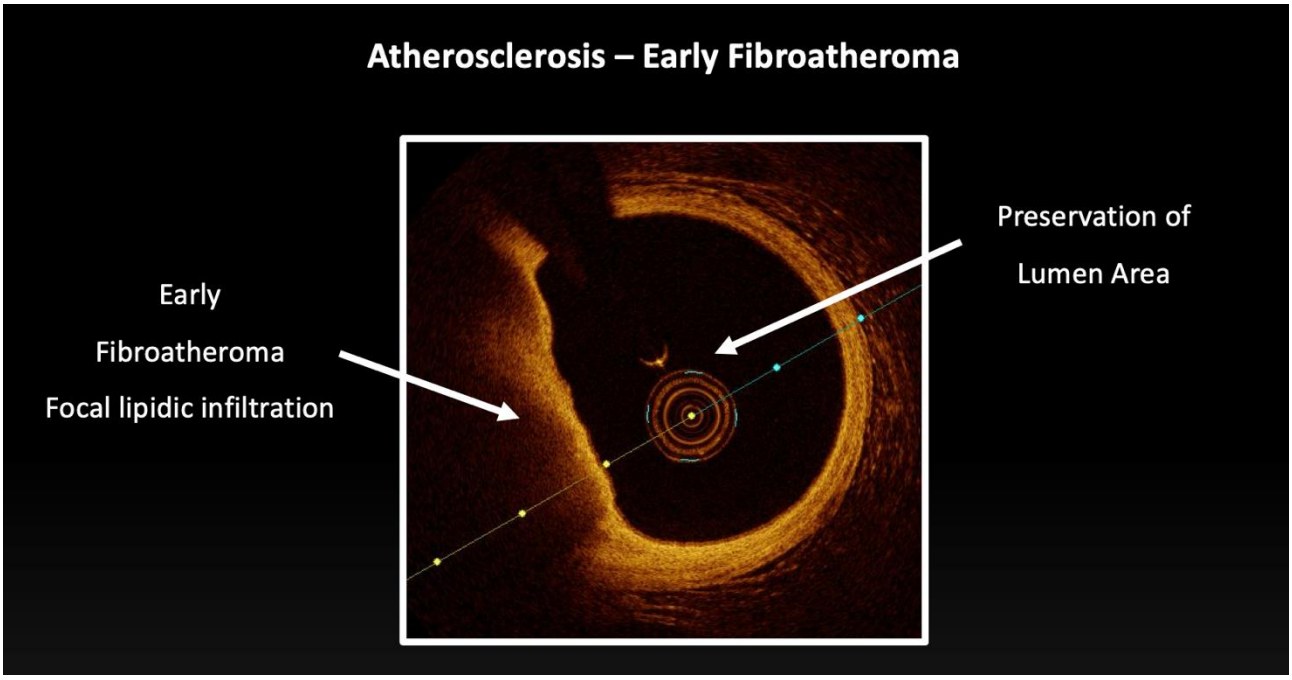
6.15 FINANCIAL SUPPORT

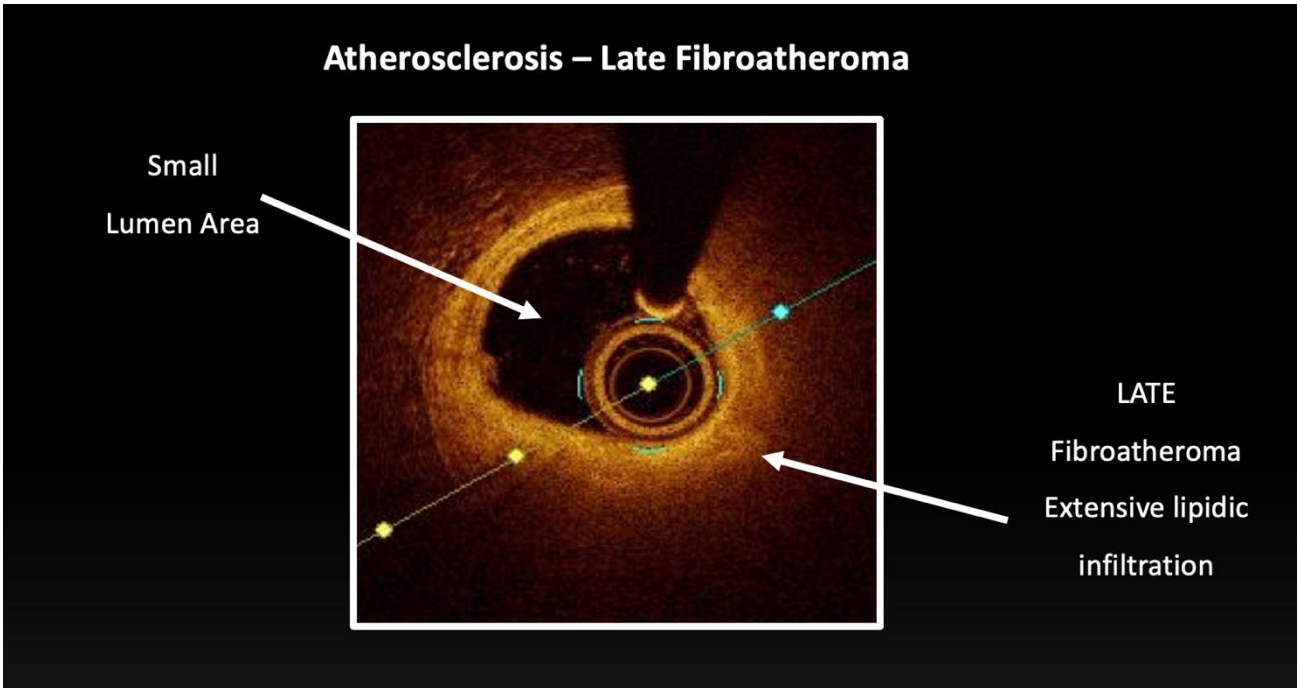
Dr Pinilla-Echeverri had a research grant support from the Fundación Alfonso Martin Escudero (Spain) that supported her international stay in McMaster University and a new investigation fund grant from Hamilton Health Sciences (Canada).

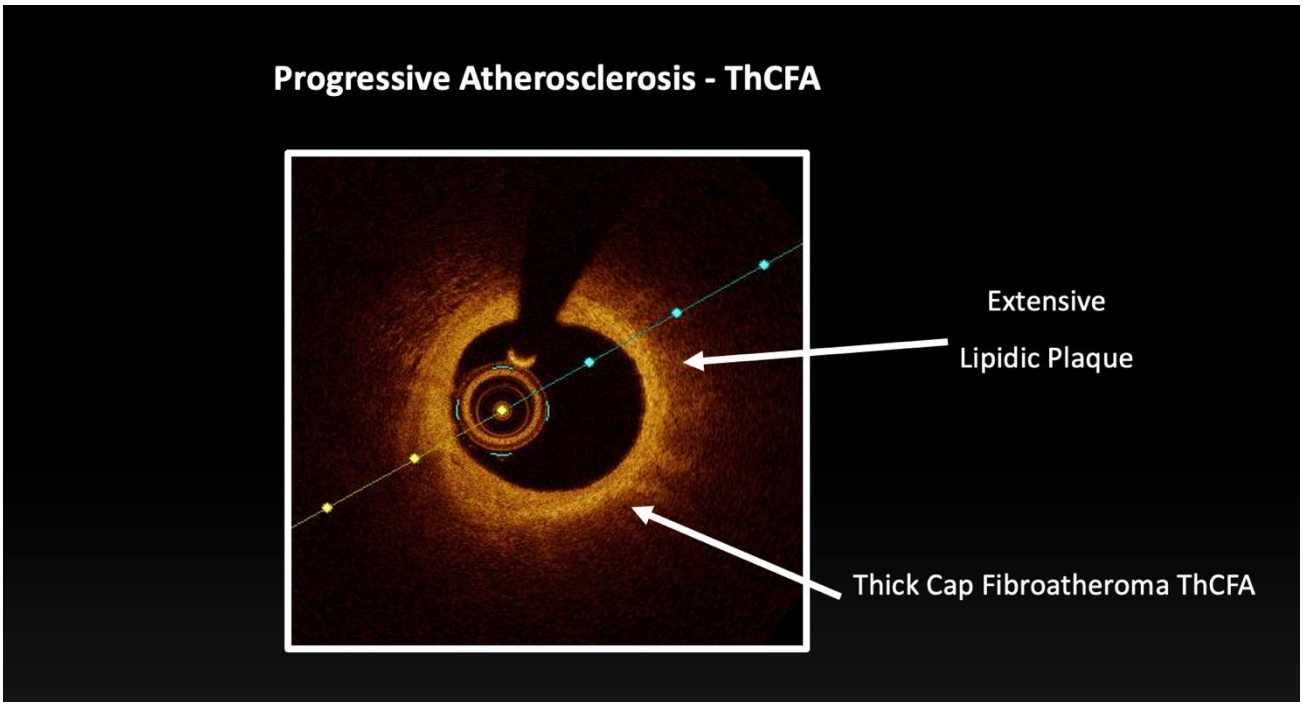
7 PART IV. COMPLETE-OCT ATLAS

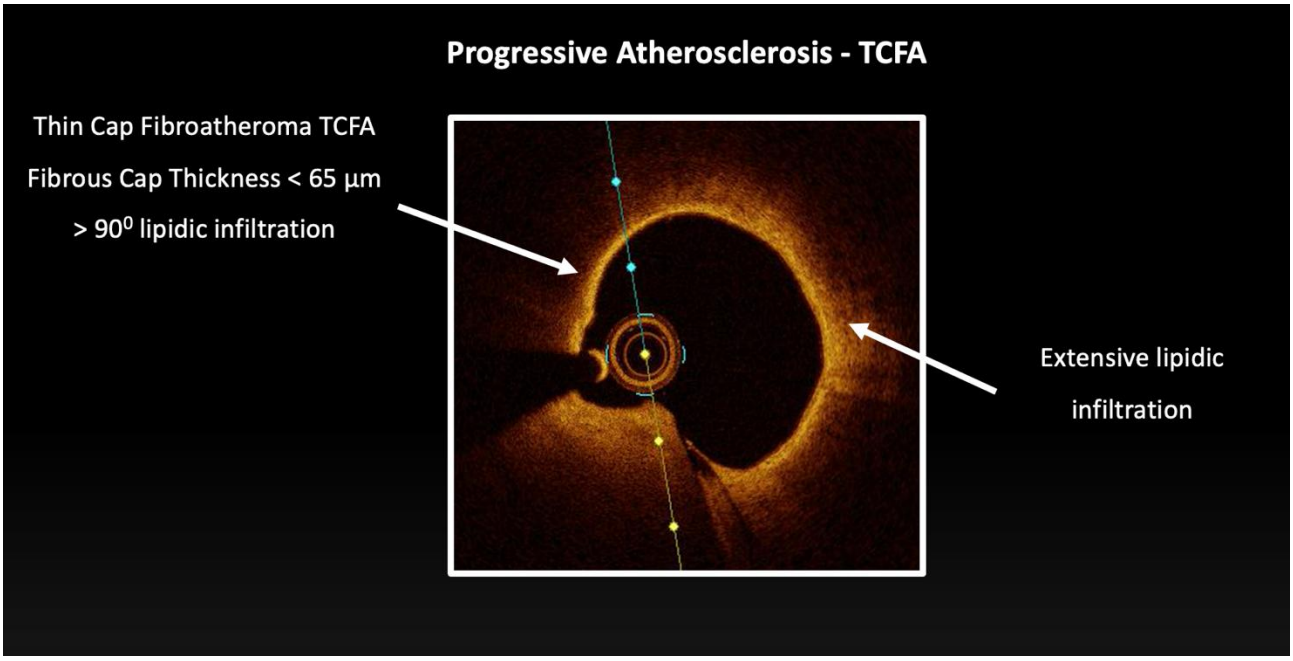
This section presents a compendium of original OCT images from the COMPLETE-OCT substudy (COMPLETE OCT Atlas), showing a variety of early and late stages of atherosclerosis, lesion progression characteristics, vulnerable plaque features and complicated lesions documented in vivo. These OCT images were collected along the culprit and non-culprit vessels in patients presenting with STEMI that were recruited in the COMPLETE trial and were randomized to the complete revascularization arm.

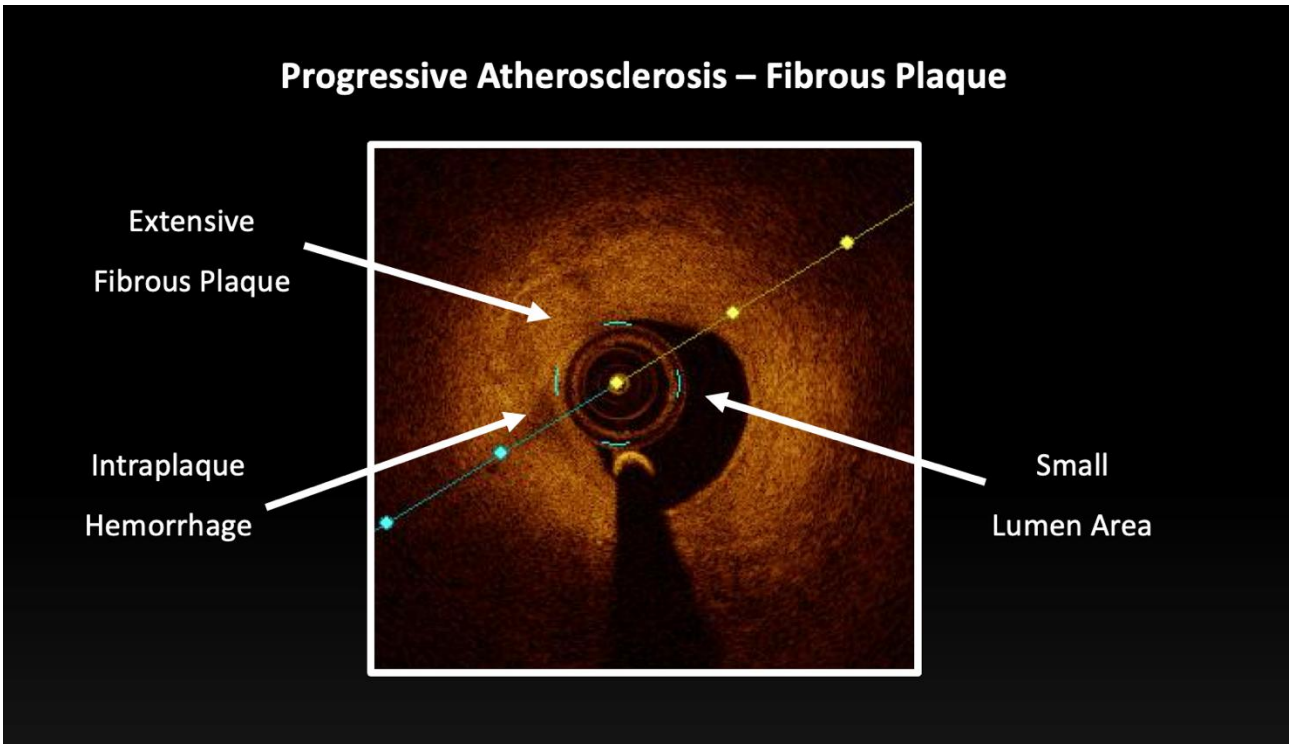


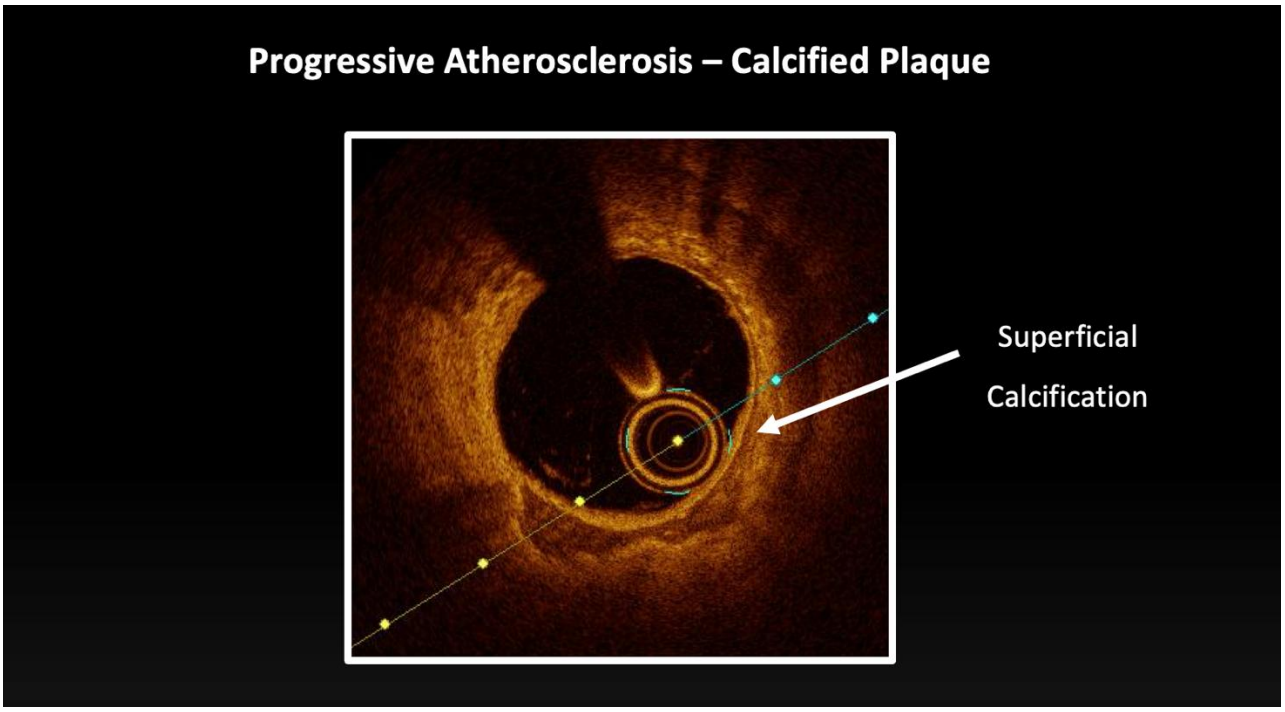

Atherosclerosis – Early Fibroatheroma
Early
Fibroatheroma
Focal lipidic infiltration
Preservation of
Lumen Area

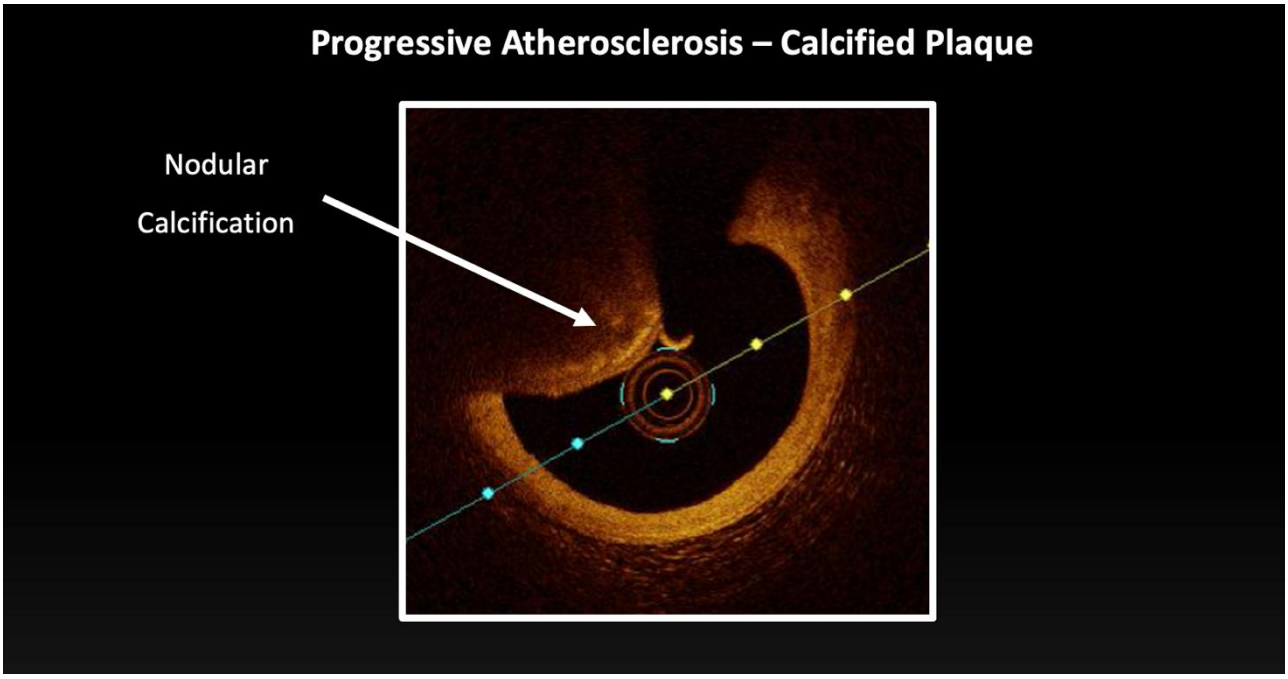

Atherosclerosis – Late Fibroatheroma
Small
Lumen Area
LATE
Fibroatheroma
Extensive lipidic
infiltration

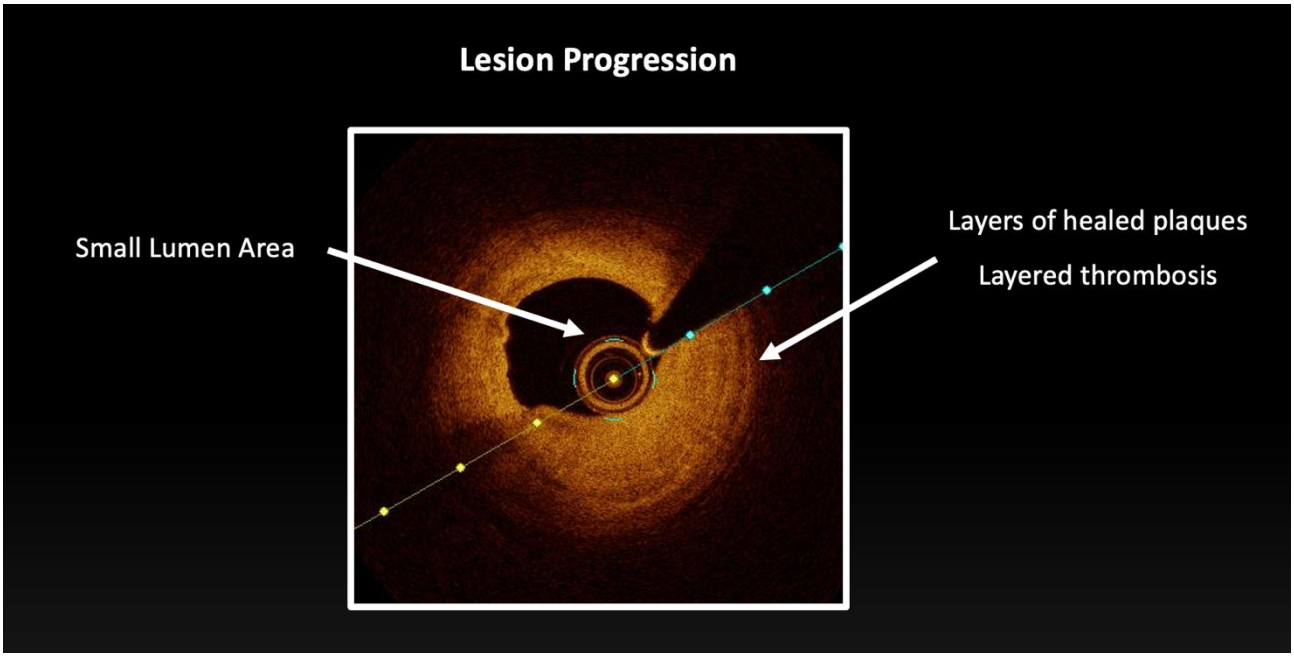

Progressive Atherosclerosis - ThCFA
Extensive
Lipidic Plaque
Thick Cap Fibroatheroma ThCFA

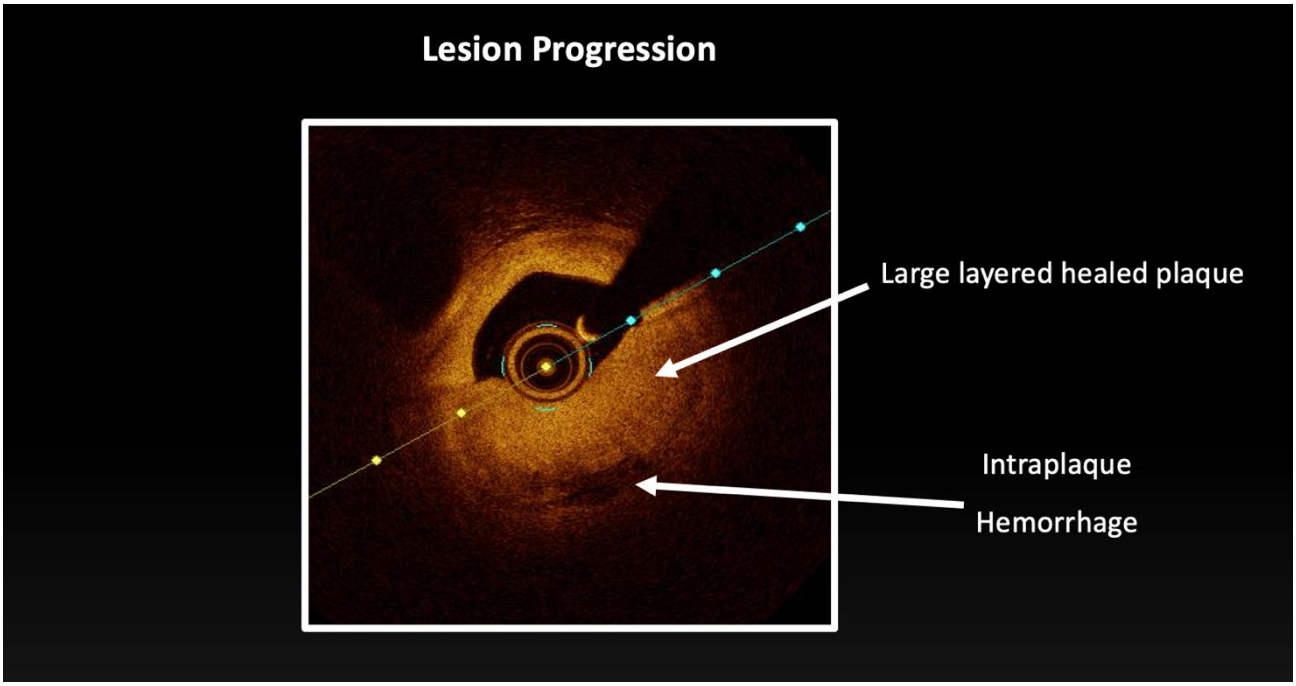

Progressive Atherosclerosis - TCFA
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm
> 90⁰ lipidic infiltration
Extensive lipidic
infiltration

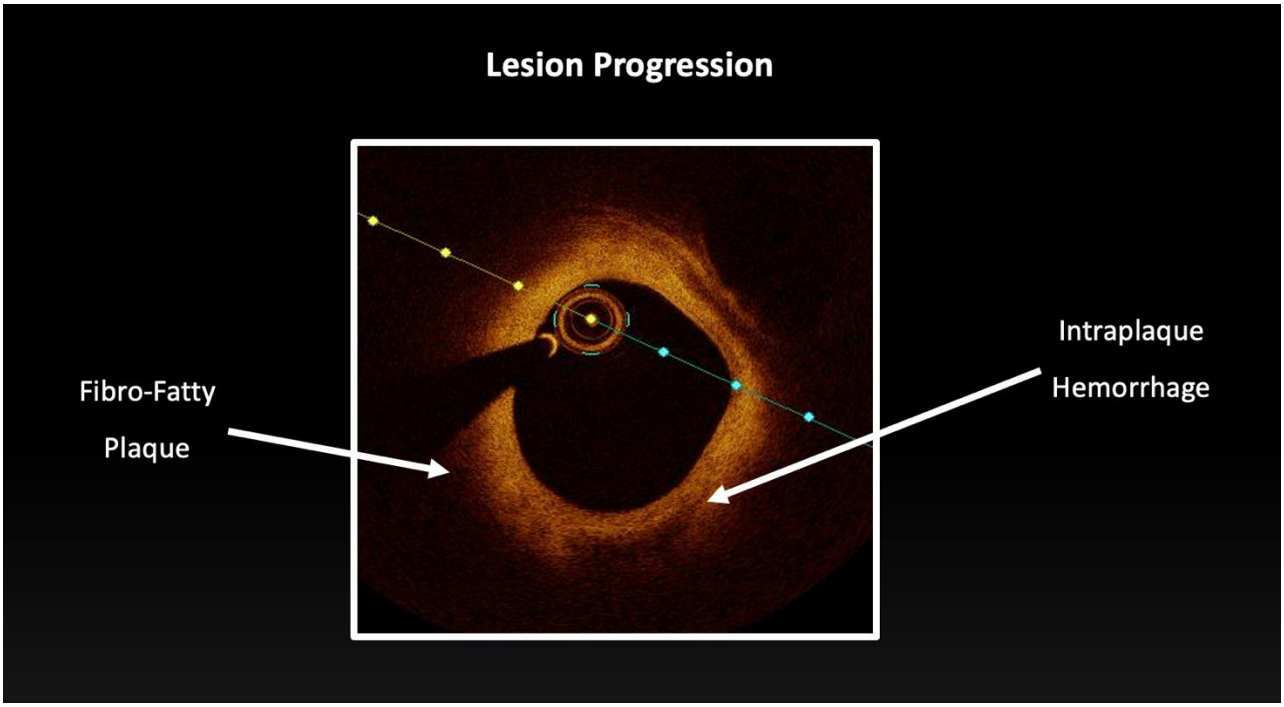

Progressive Atherosclerosis – Fibrous Plaque
Extensive
Fibrous Plaque
Intraplaque
Hemorrhage
Small
Lumen Area

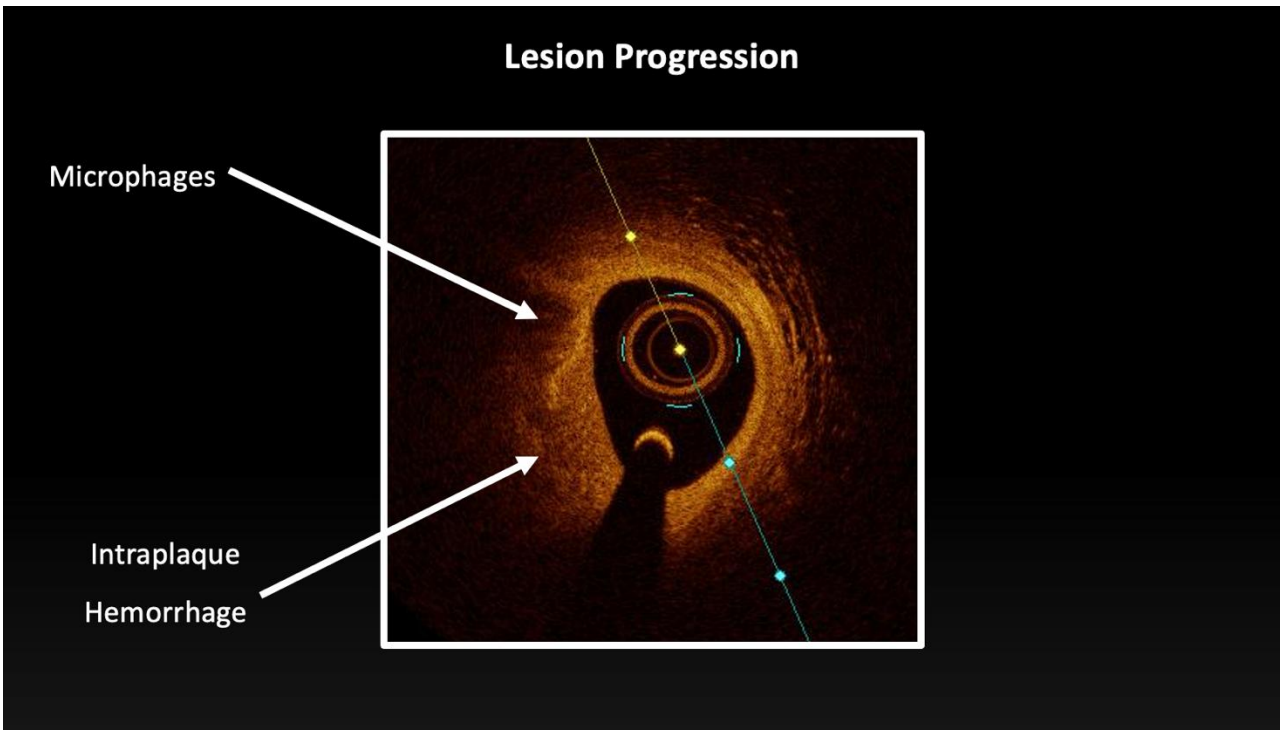

Progressive Atherosclerosis – Calcified Plaque
Superficial
Calcification

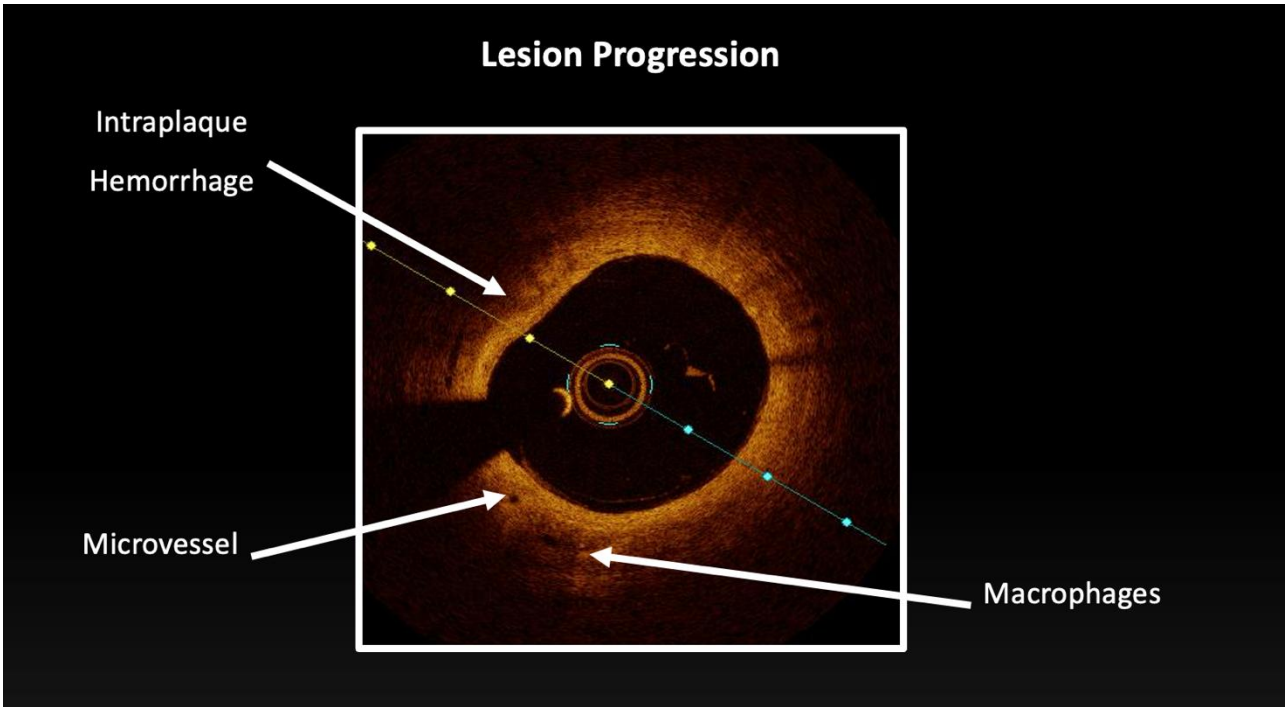

Progressive Atherosclerosis – Calcified Plaque
Nodular
Calcification

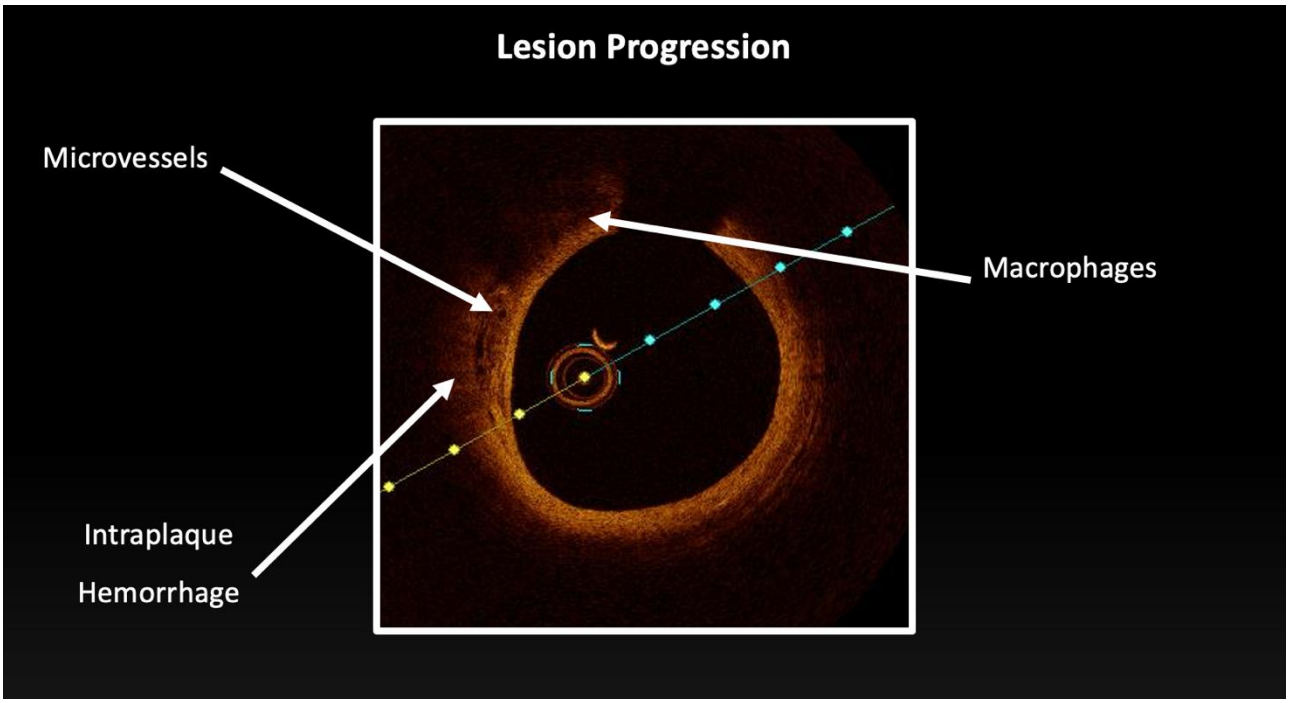

Lesion Progression
Small Lumen Area
Layers of healed plaques
Layered thrombosis

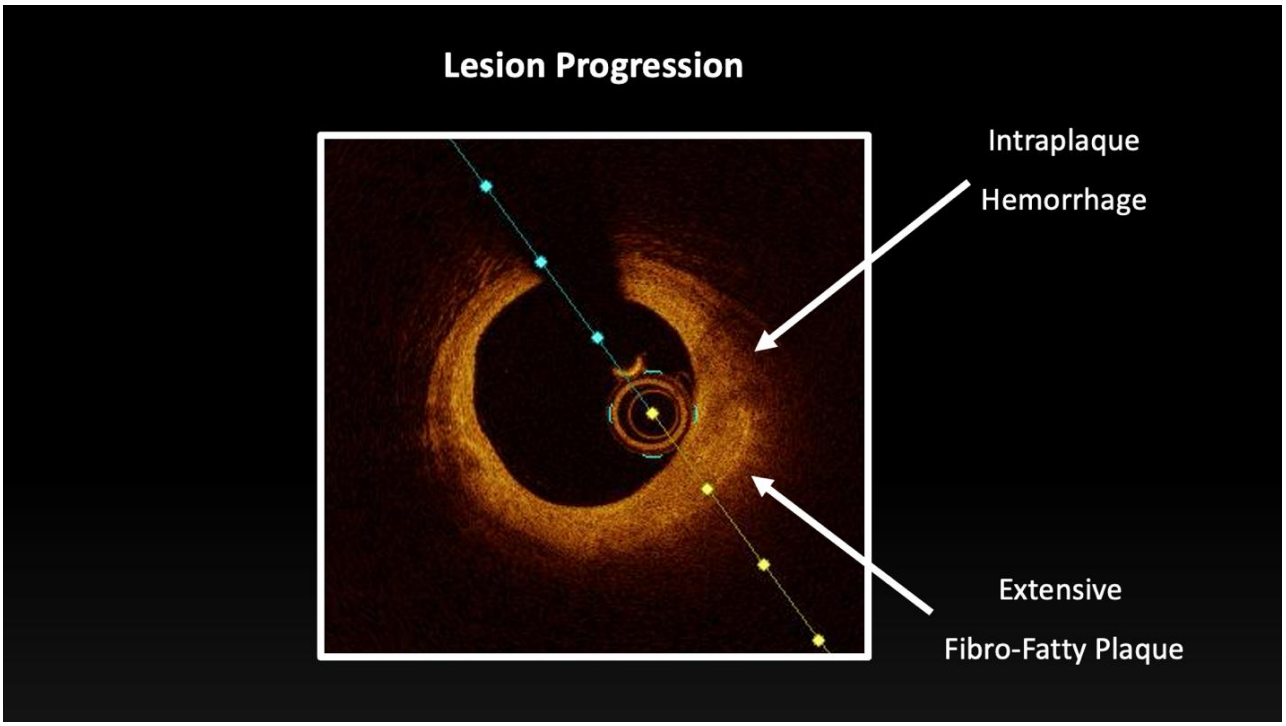

Lesion Progression
Large layered healed plaque
Intraplaque
Hemorrhage

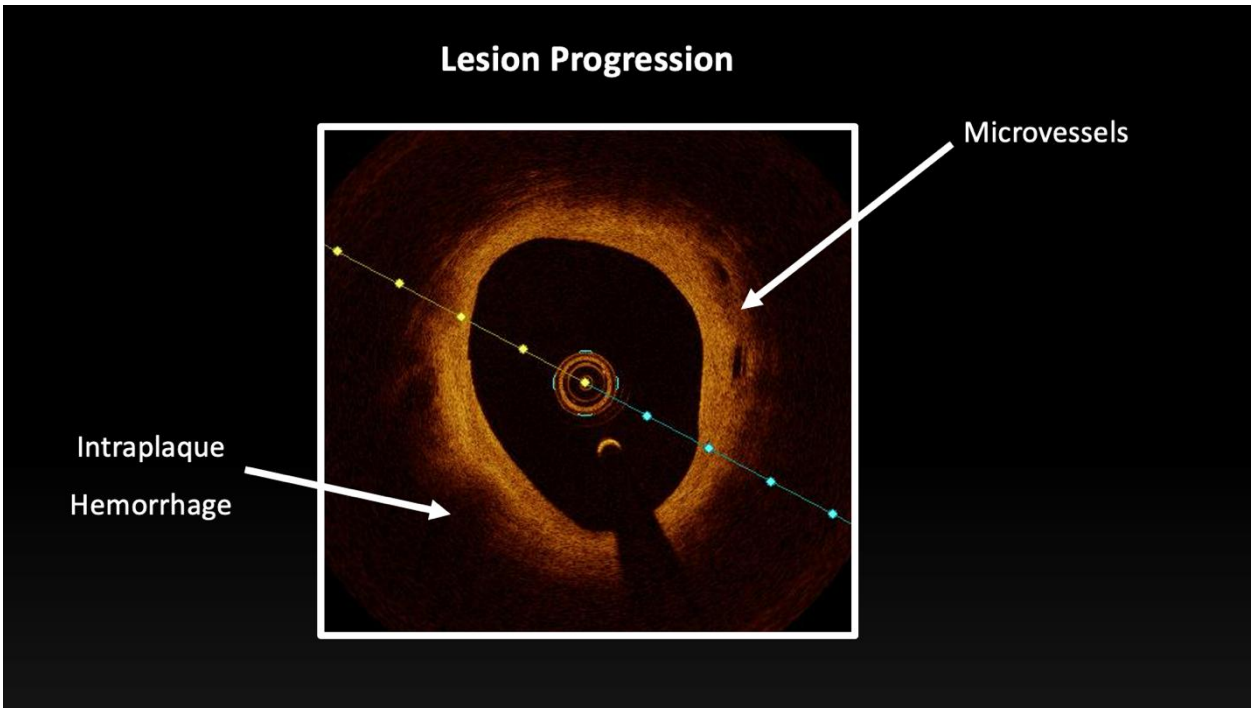

Lesion Progression
Fibro-Fatty
Plaque
Intraplaque
Hemorrhage

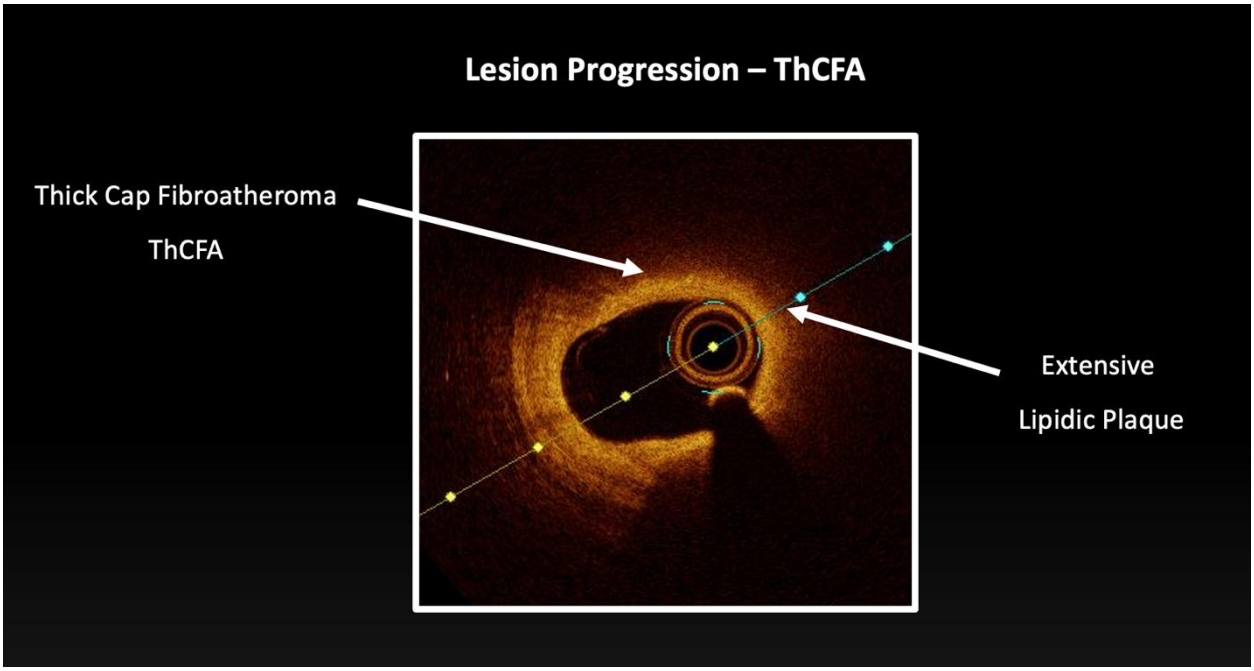

Lesion Progression
Microphages
Intraplaque
Hemorrhage

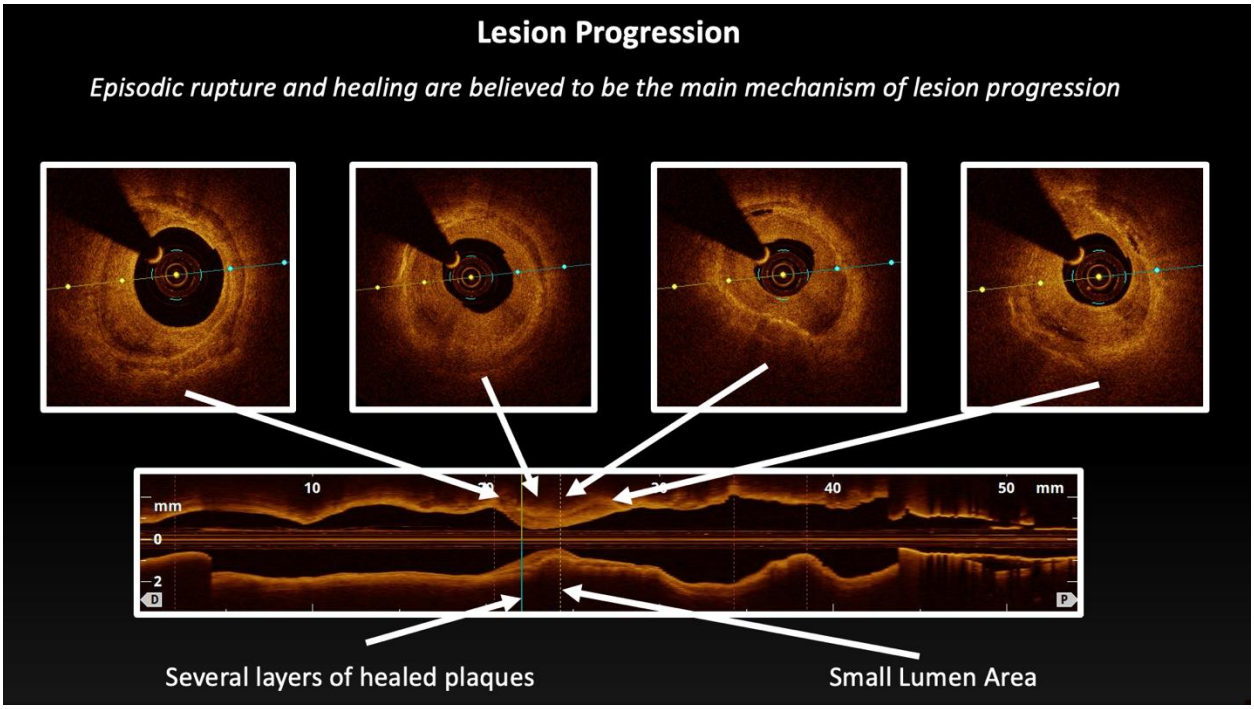

Lesion Progression
Intraplaque
Hemorrhage
Microvessel
Macrophages

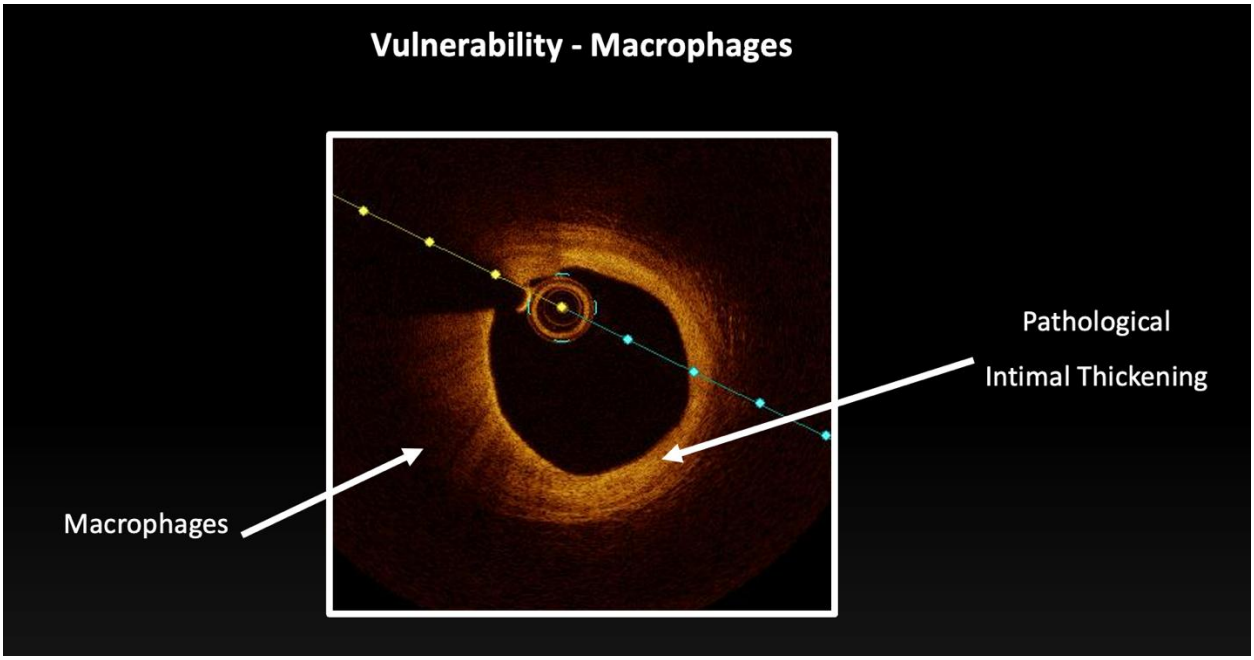

Lesion Progression
Microvessels
Macrophages
Intraplaque
Hemorrhage

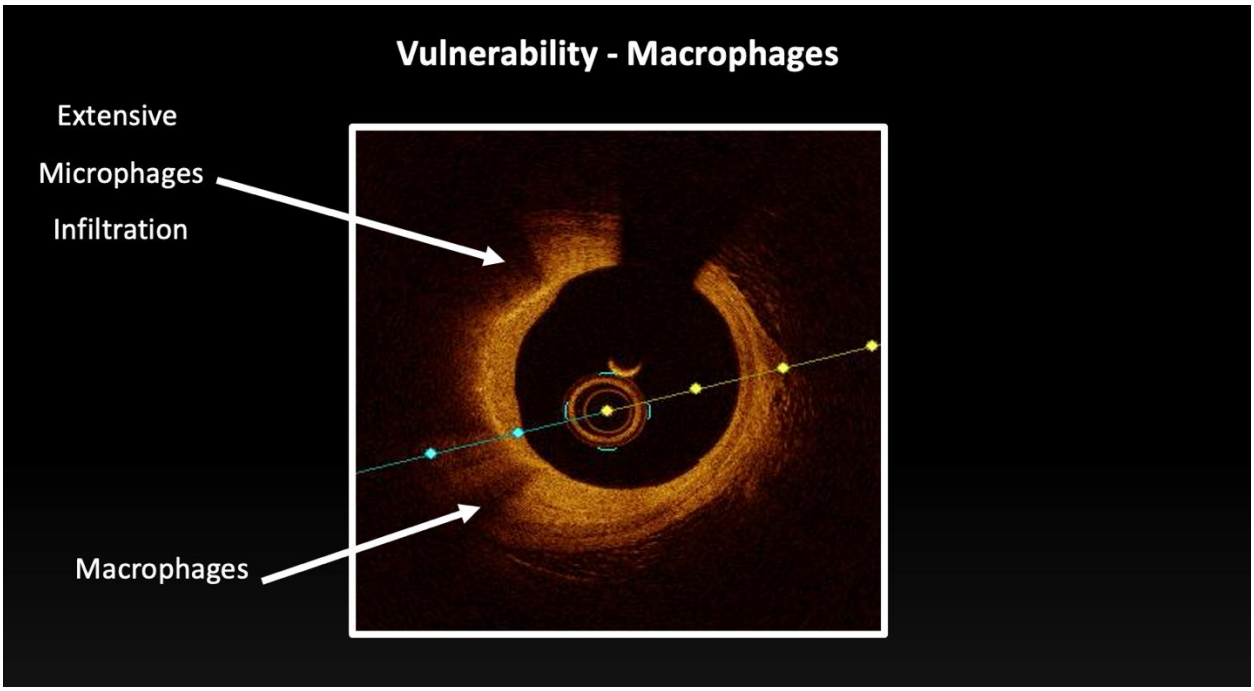

Lesion Progression
Intraplaque
Hemorrhage
Extensive
Fibro-Fatty Plaque

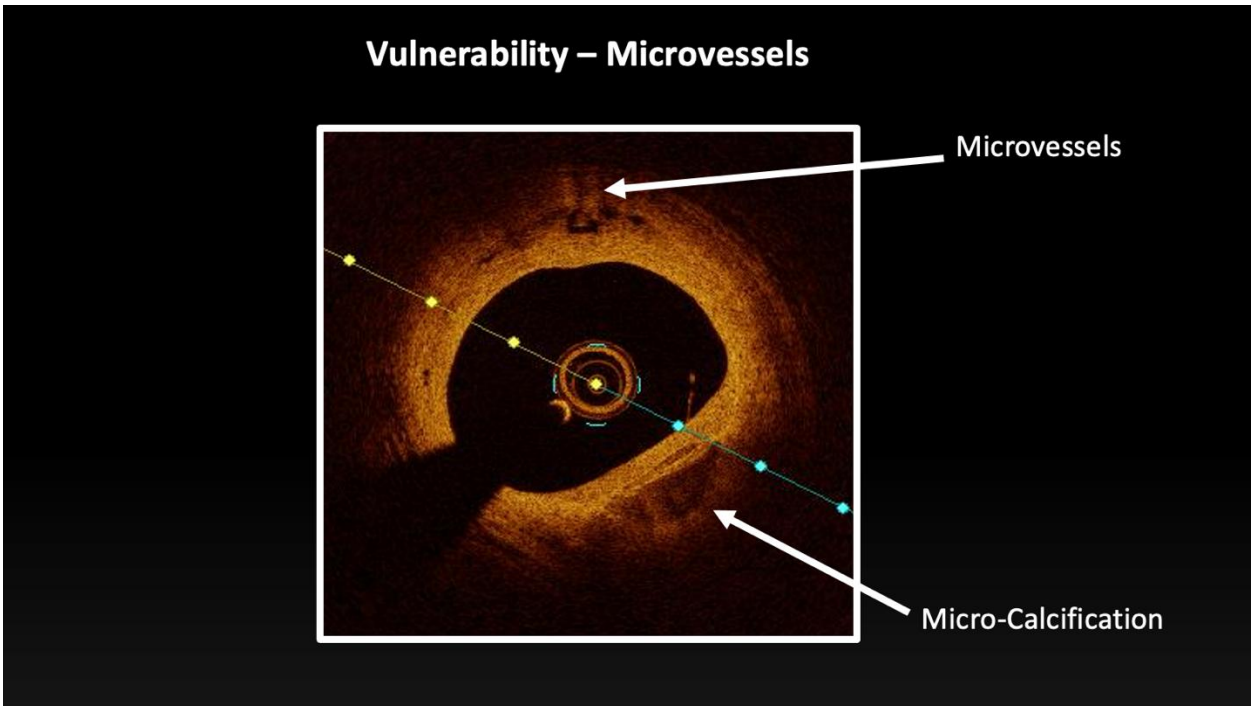

Lesion Progression
Microvessels
Intraplaque
Hemorrhage

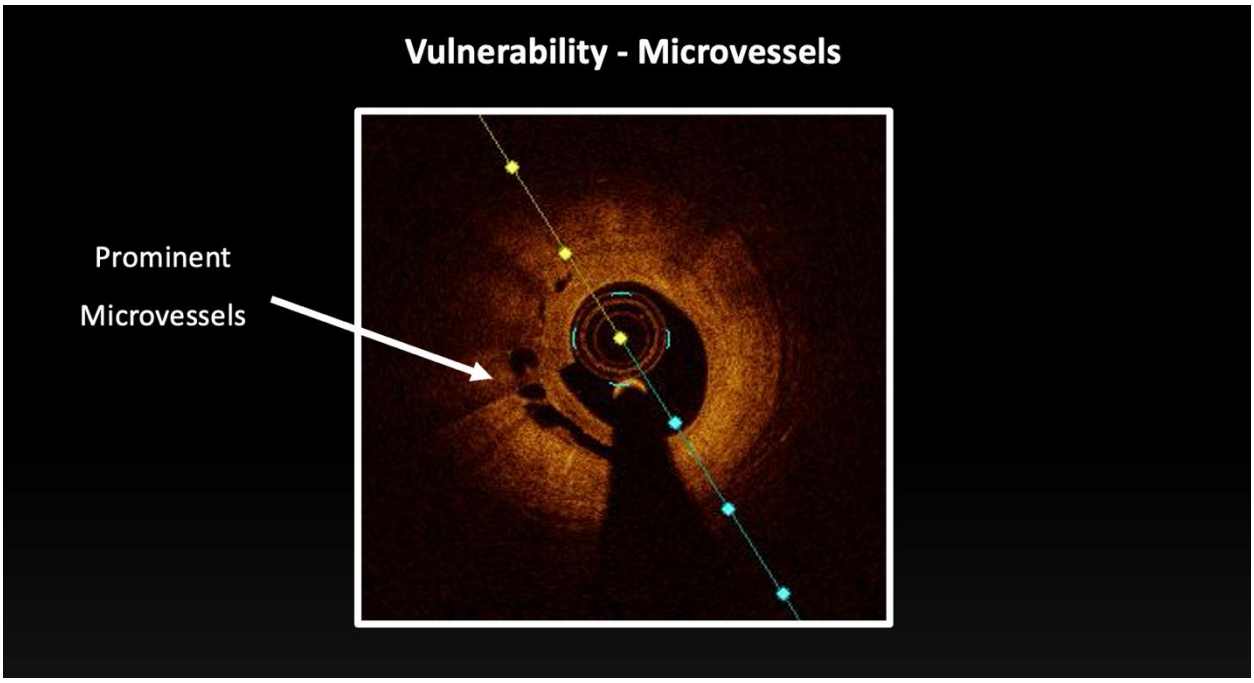

Lesion Progression – ThCFA
Thick Cap Fibroatheroma
ThCFA
Extensive
Lipidic Plaque

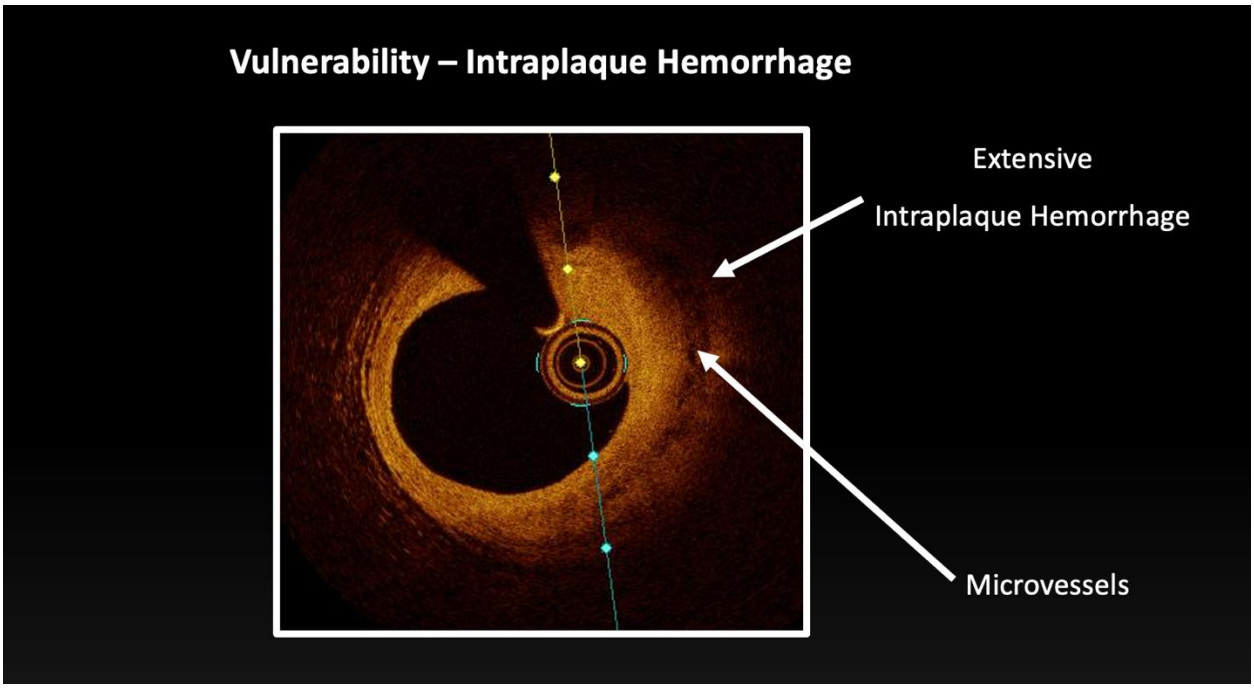

Lesion Progression
Episodic rupture and healing are believed to be the main mechanism of lesion progression
10
40
50
mm
mm
0
2
D
P
Several layers of healed plaques
Small Lumen Area

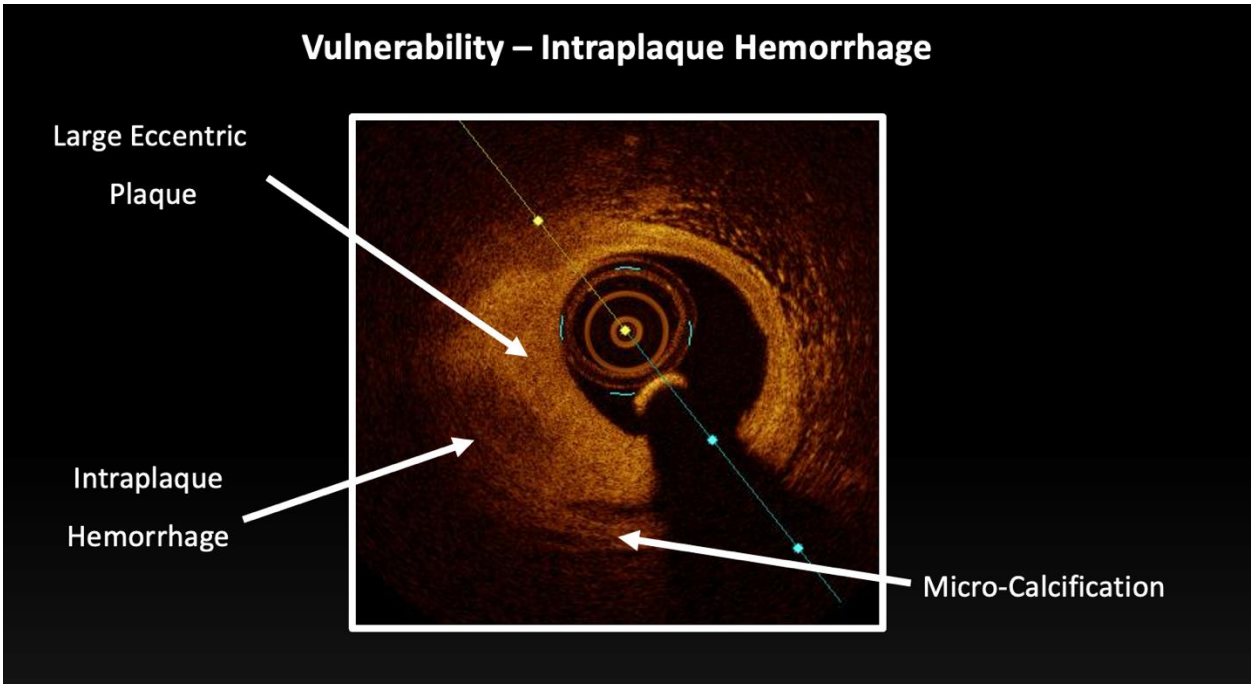

Vulnerability - Macrophages
Pathological
Intimal Thickening
Macrophages

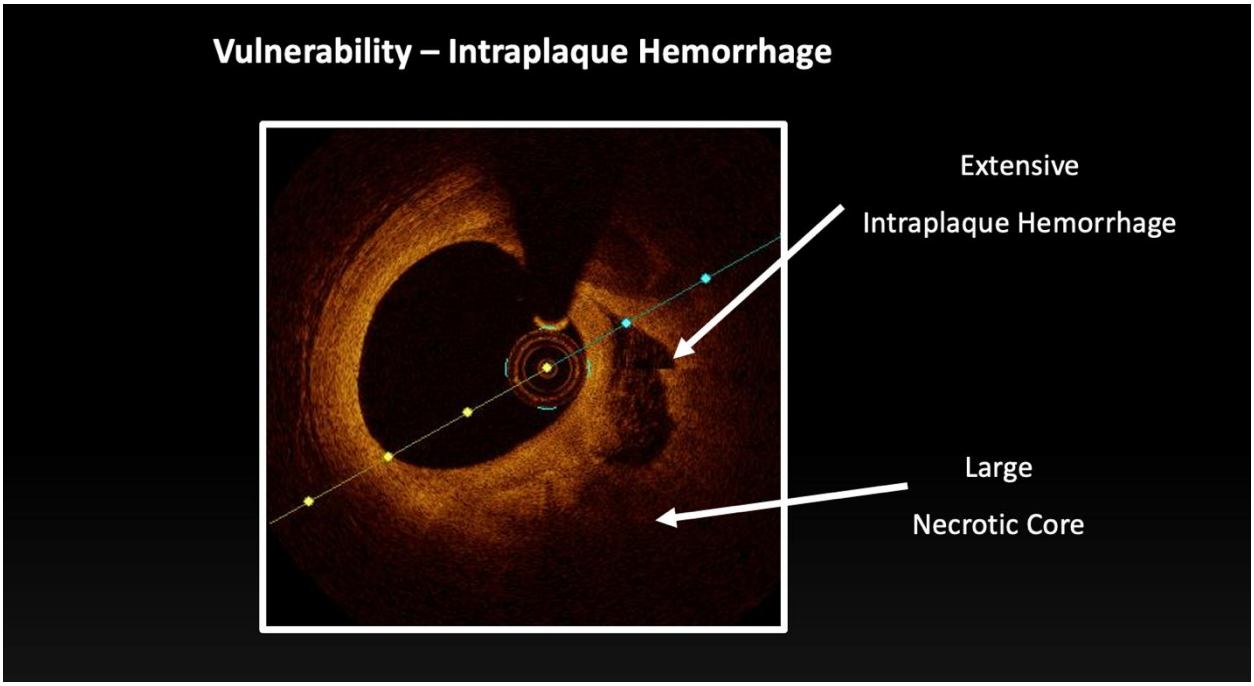

Vulnerability - Macrophages
Extensive
Microphages
Infiltration
Macrophages

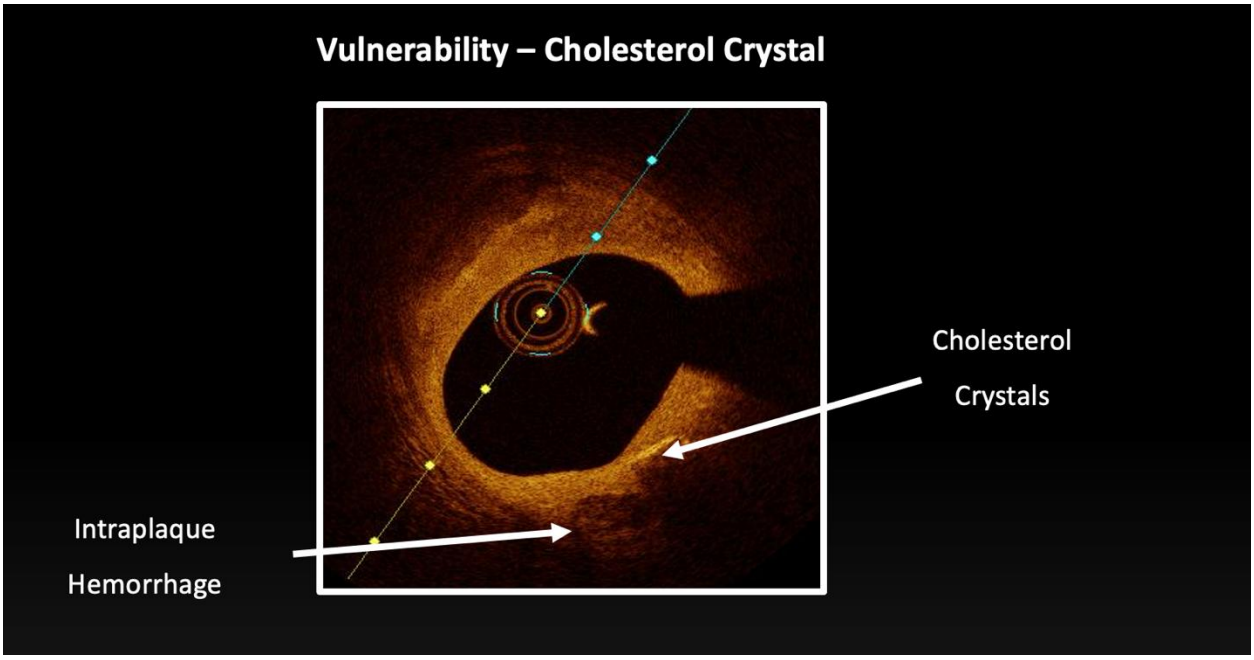

Vulnerability – Microvessels
Microvessels
Micro-Calcification

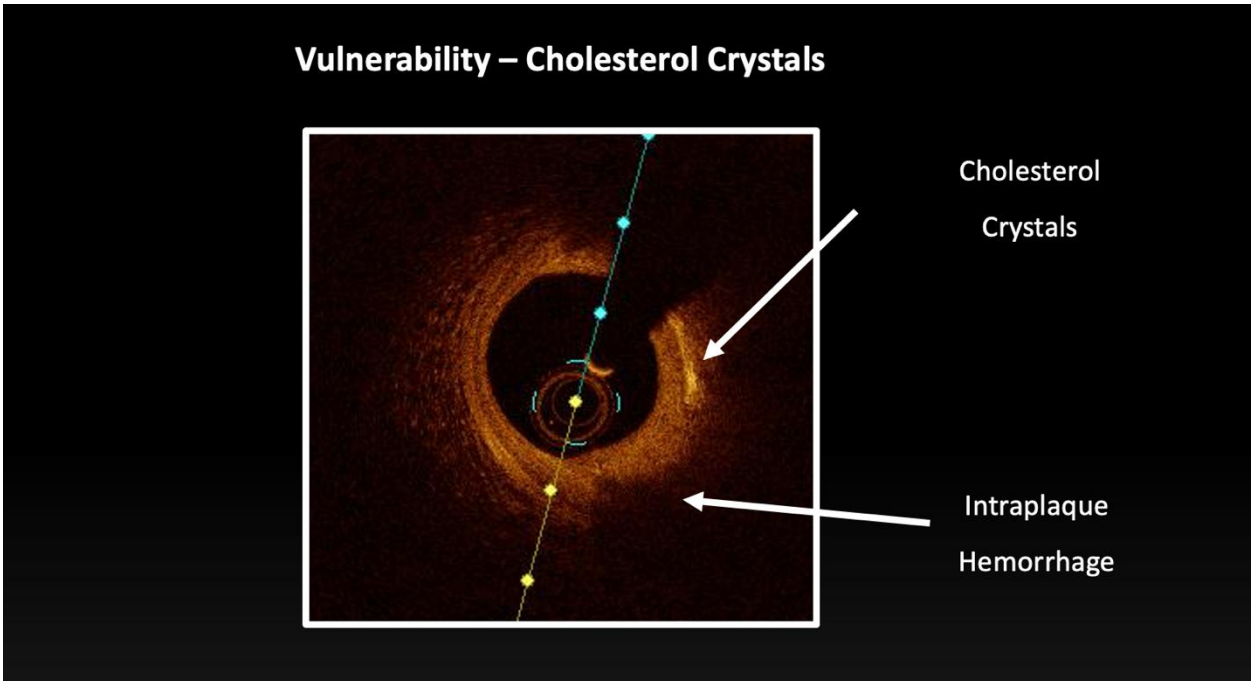

Vulnerability - Microvessels
Prominent
Microvessels

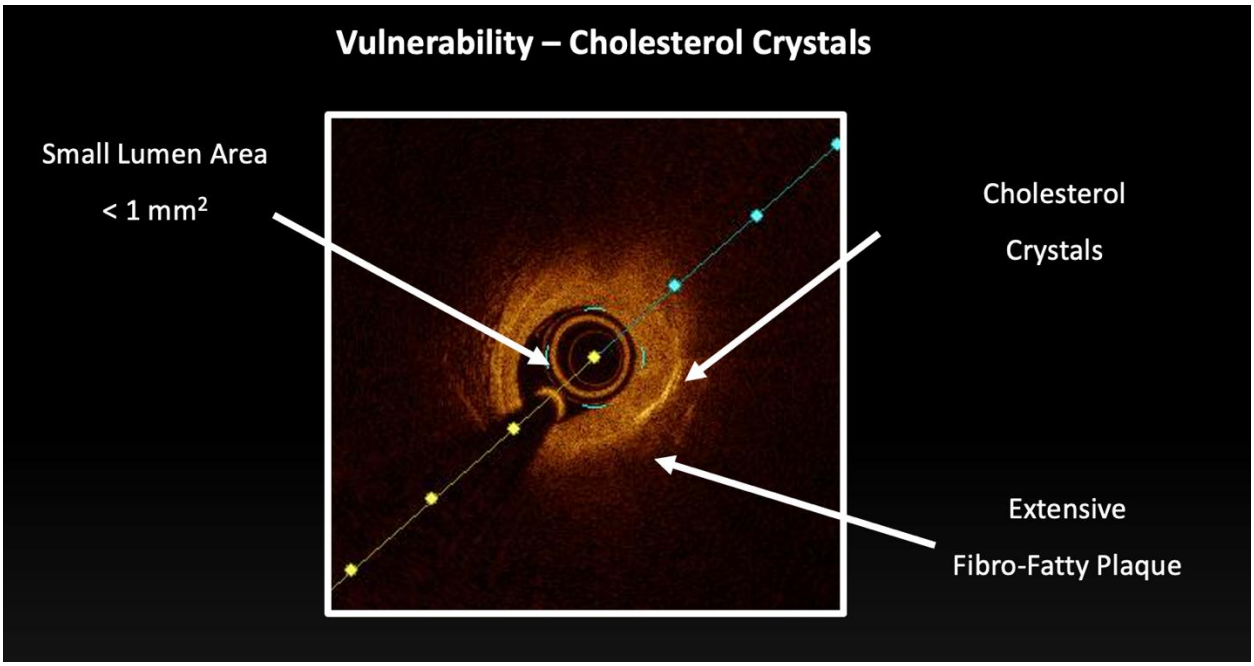

Vulnerability – Intraplaque Hemorrhage
Extensive
Intraplaque Hemorrhage
Microvessels

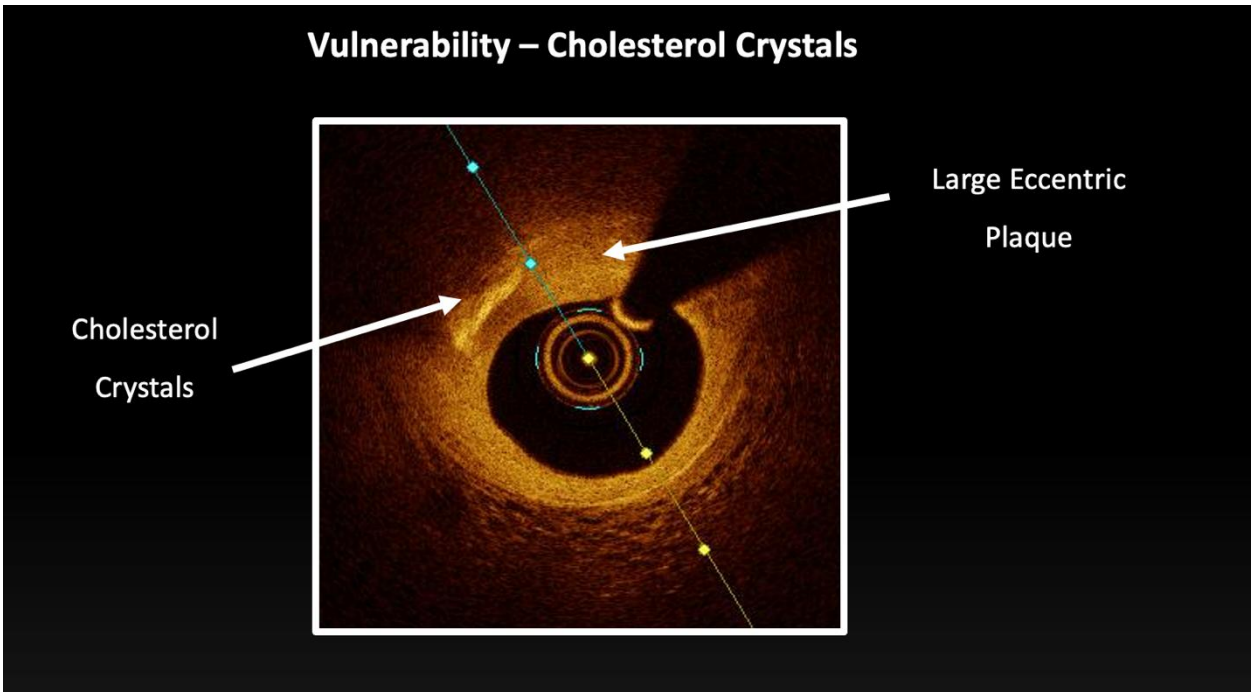

Vulnerability – Intraplaque Hemorrhage
Large Eccentric
Plaque
Intraplaque
Hemorrhage
Micro-Calcification

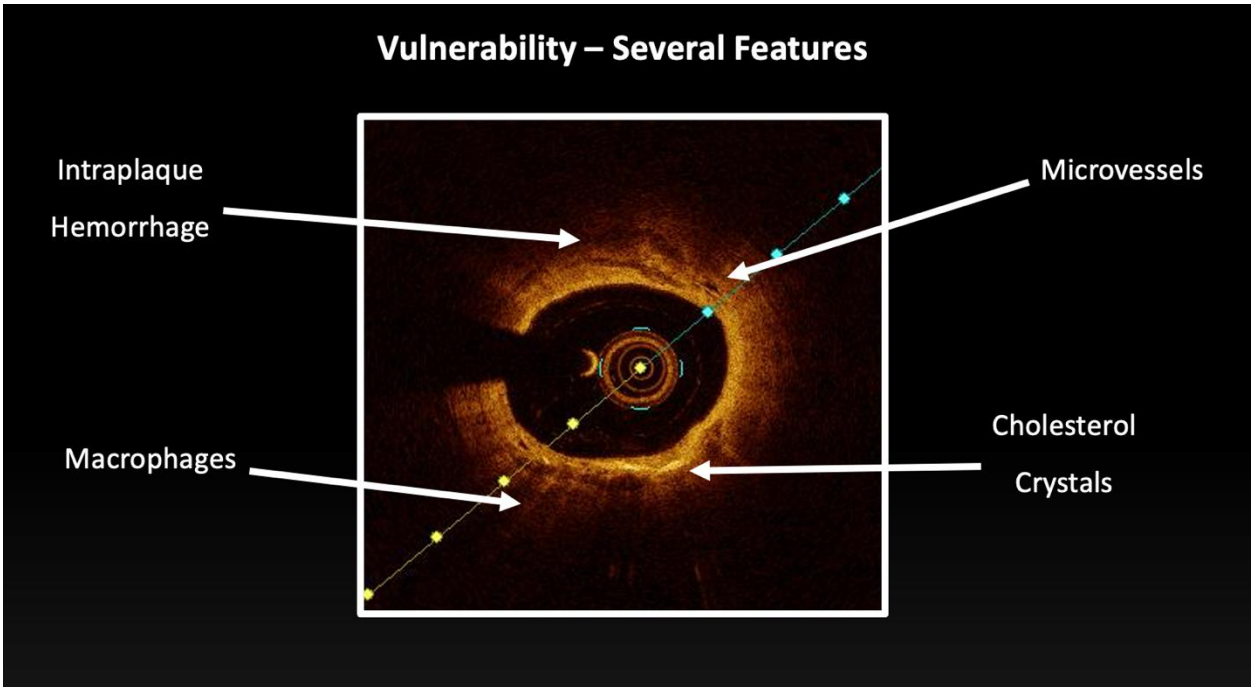

Vulnerability – Intraplaque Hemorrhage
Extensive
Intraplaque Hemorrhage
Large
Necrotic Core

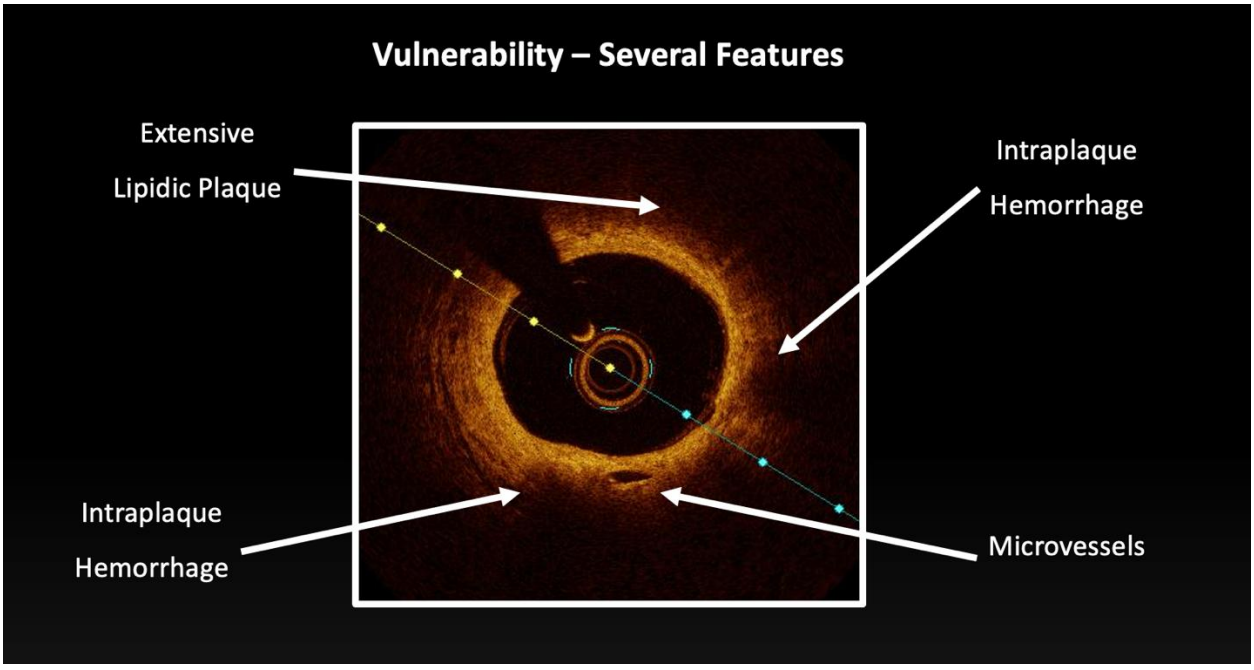

Vulnerability – Cholesterol Crystal
Cholesterol
Crystals
Intraplaque
Hemorrhage

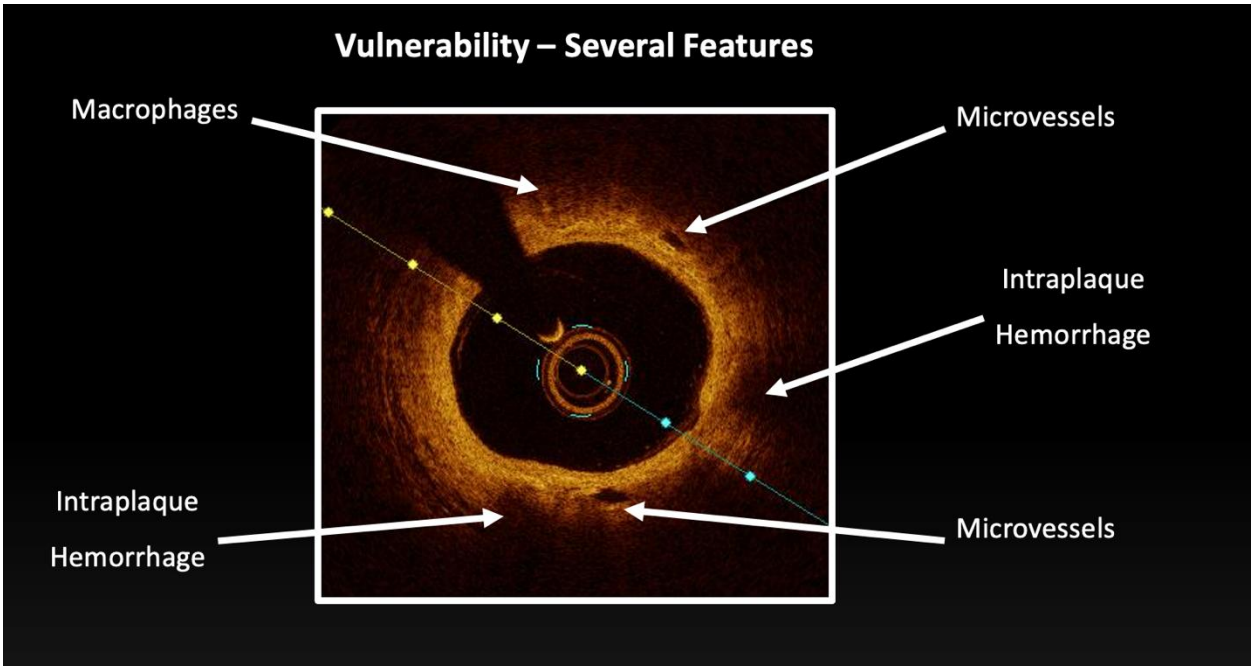

Vulnerability – Cholesterol Crystals
Cholesterol
Crystals
Intraplaque
Hemorrhage

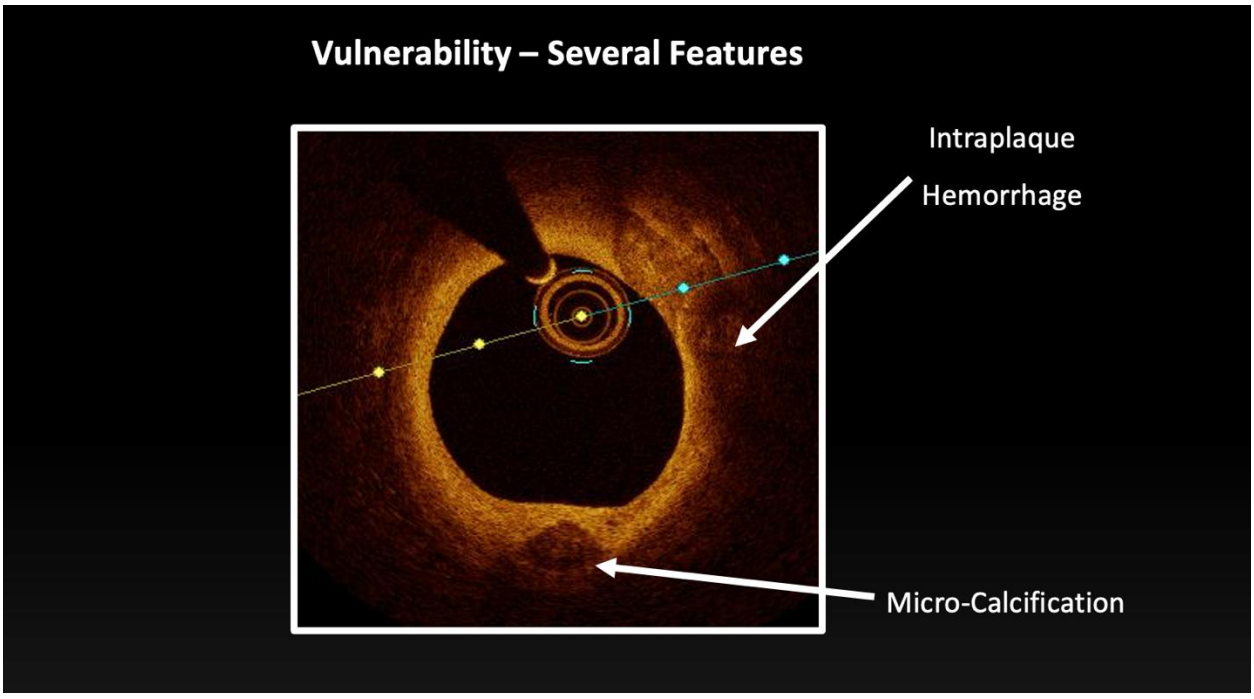

Vulnerability – Cholesterol Crystals
Small Lumen Area
< 1 mm²
Cholesterol
Crystals
Extensive
Fibro-Fatty Plaque

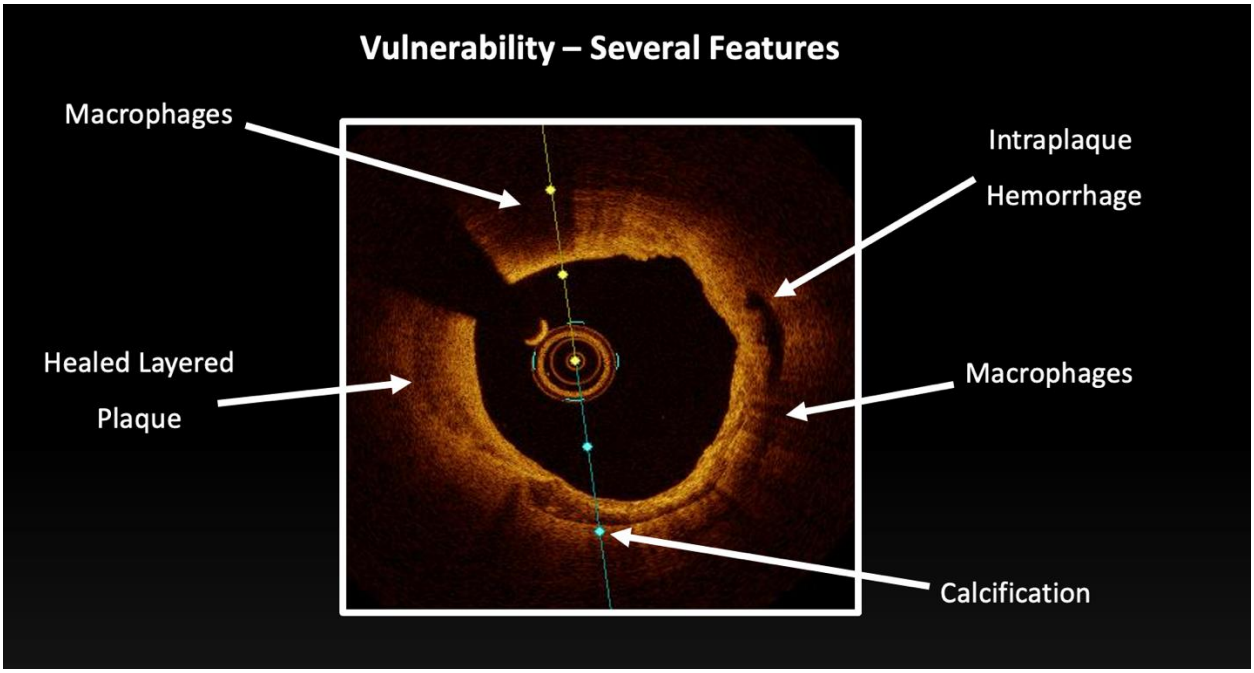

Vulnerability – Cholesterol Crystals
Large Eccentric
Plaque
Cholesterol
Crystals

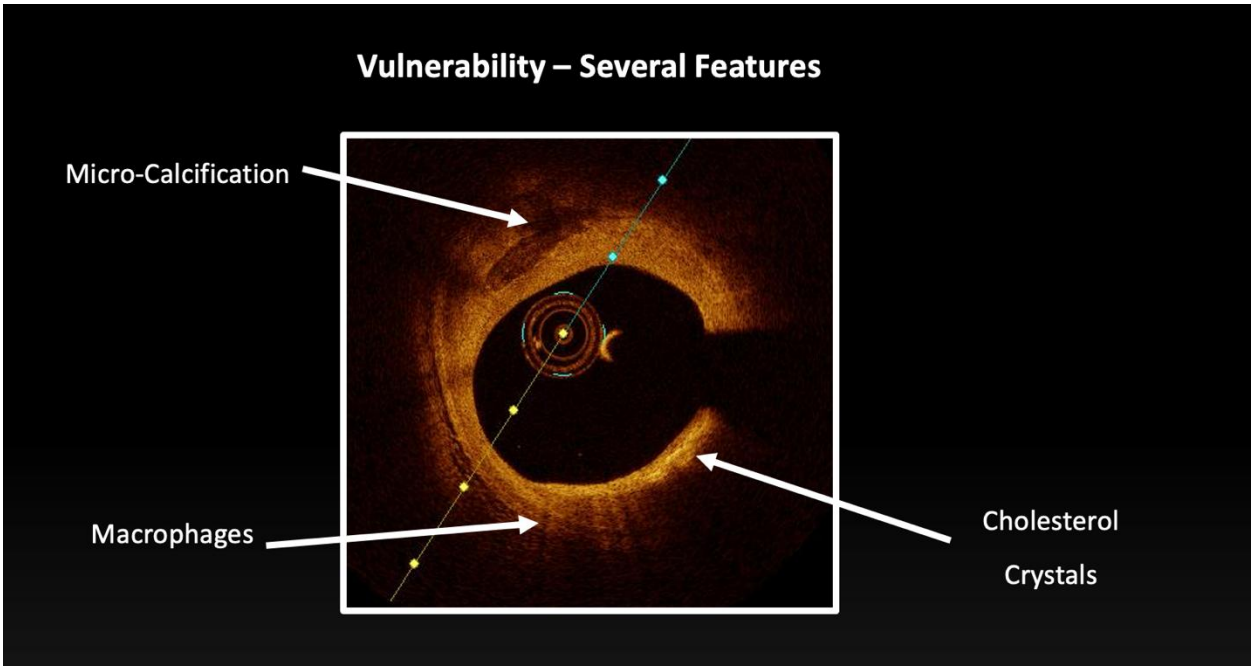

Vulnerability – Several Features
Intraplaque
Hemorrhage
Microvessels
Macrophages
Cholesterol
Crystals

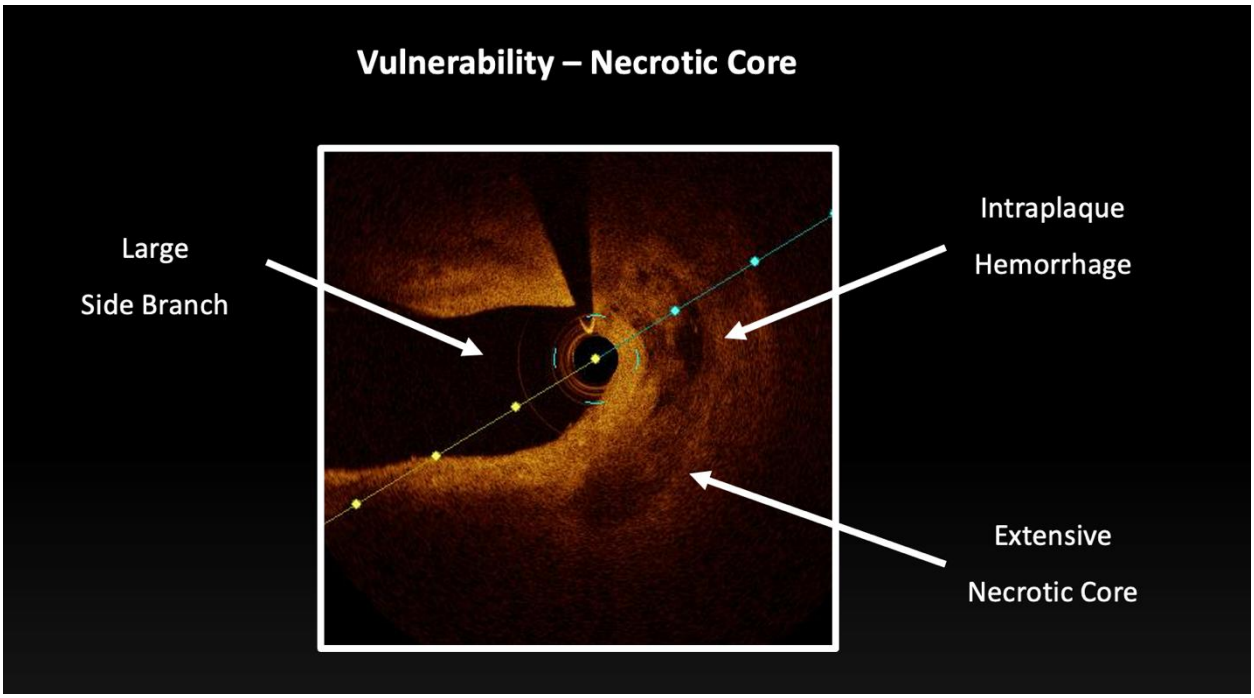

Vulnerability – Several Features
Extensive
Lipidic Plaque
Intraplaque
Hemorrhage
Intraplaque
Hemorrhage
Microvessels

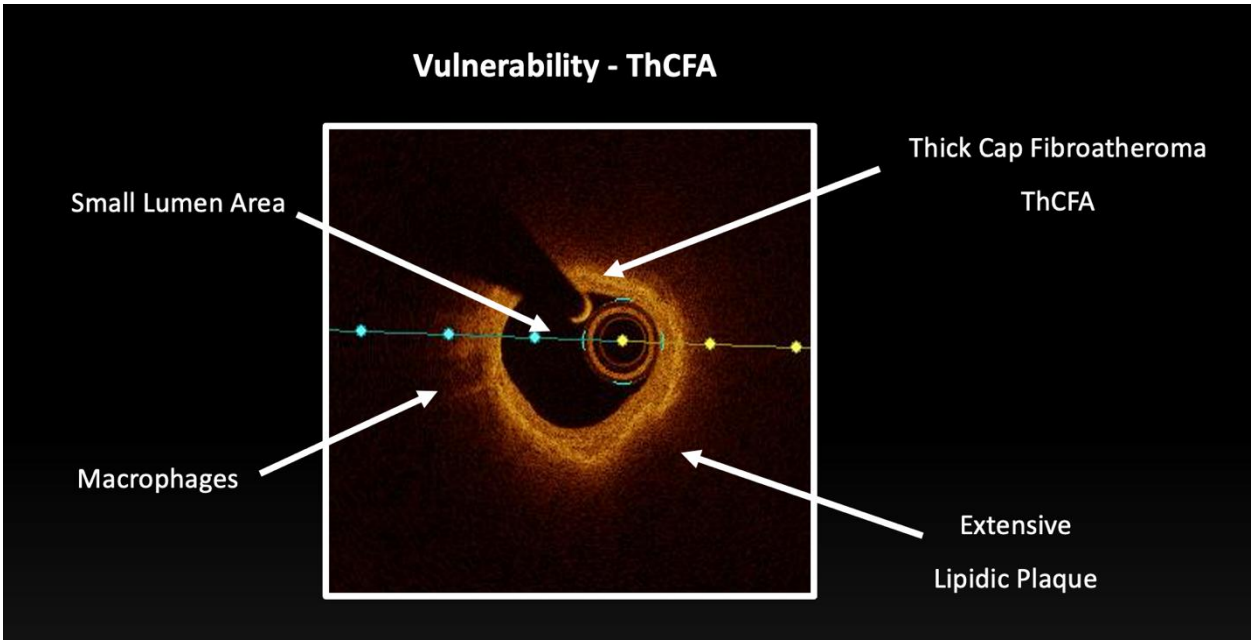

Vulnerability – Several Features
Macrophages
Microvessels
Intraplaque
Hemorrhage
Intraplaque
Hemorrhage
Microvessels

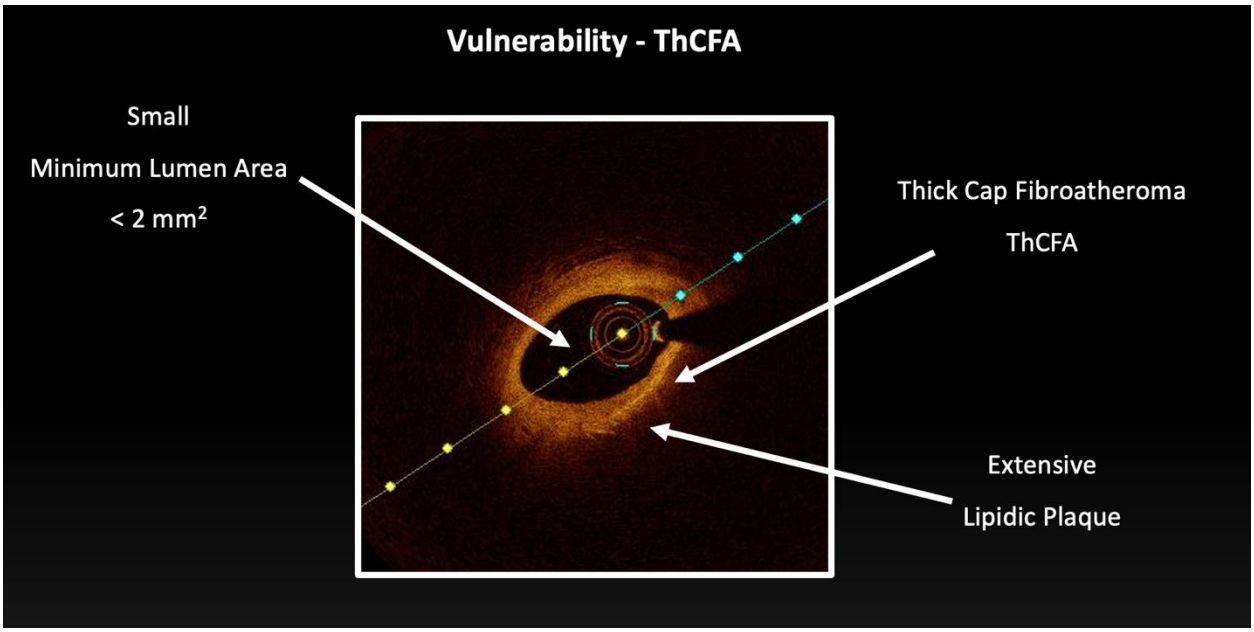

Vulnerability – Several Features
Intraplaque
Hemorrhage
Micro-Calcification

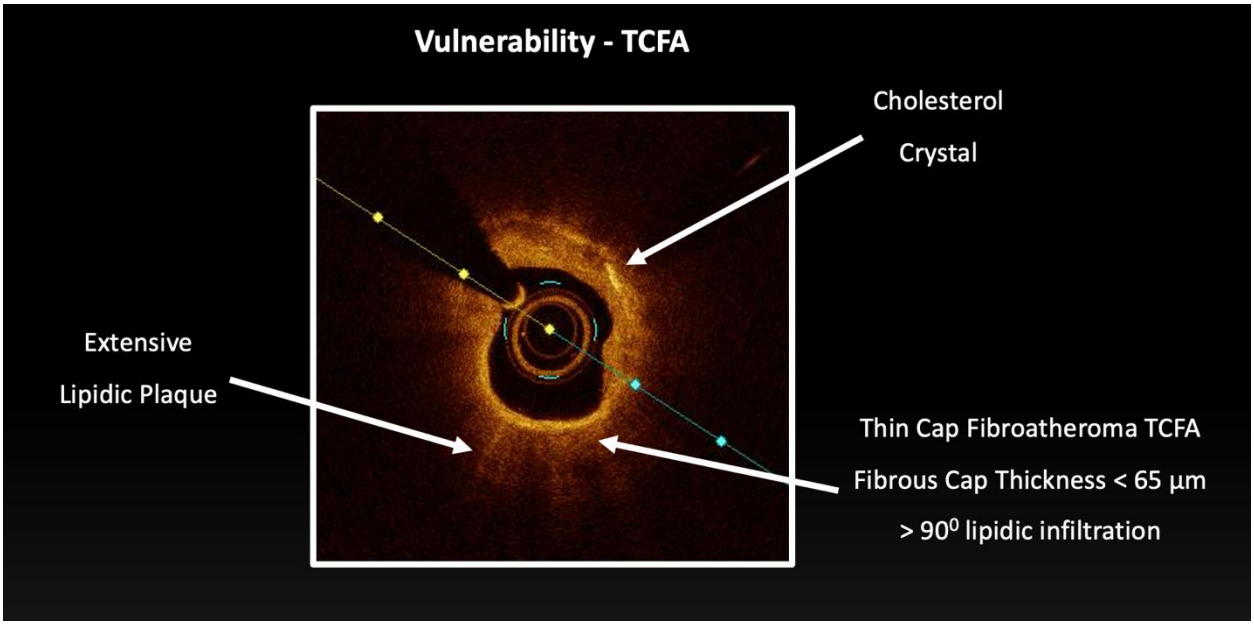

Vulnerability – Several Features
Macrophages
Intraplaque
Hemorrhage
Healed Layered
Plaque
Macrophages
Calcification

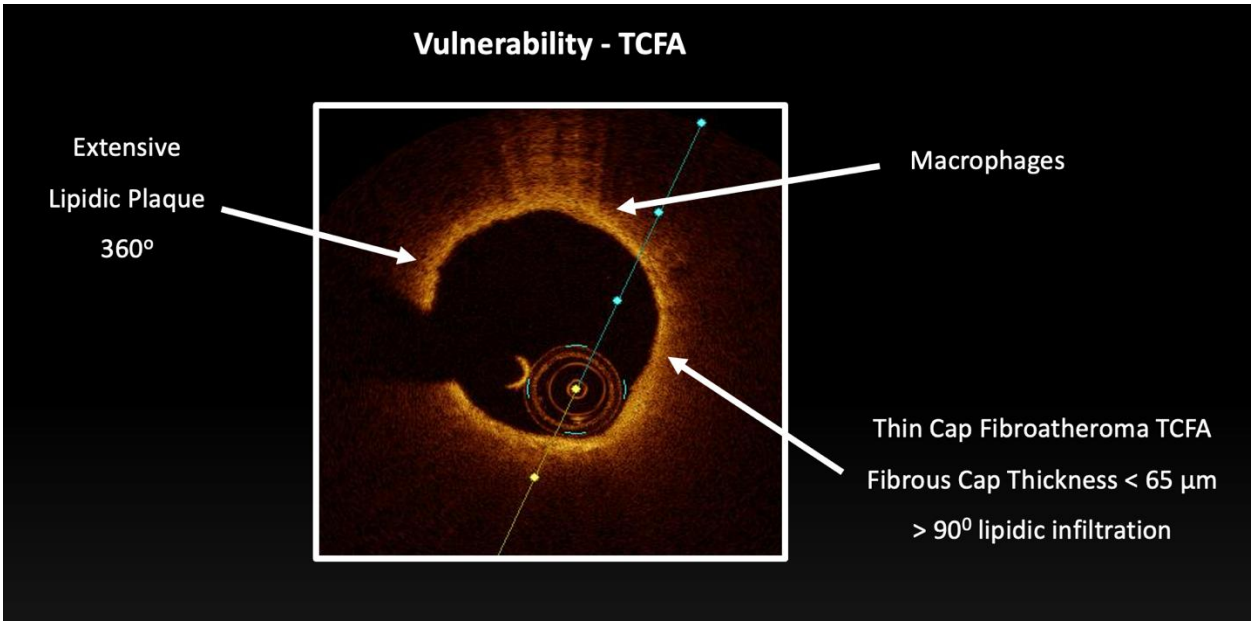

Vulnerability – Several Features
Micro-Calcification
Macrophages
Cholesterol
Crystals

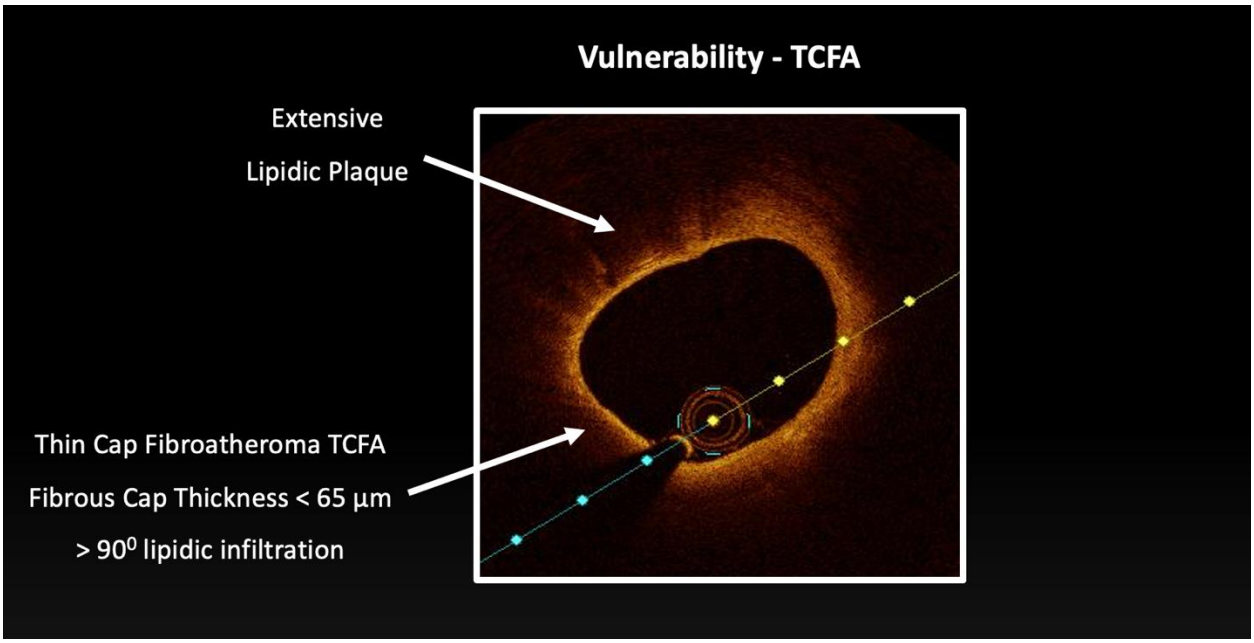

Vulnerability – Necrotic Core
Large
Side Branch
Intraplaque
Hemorrhage
Extensive
Necrotic Core

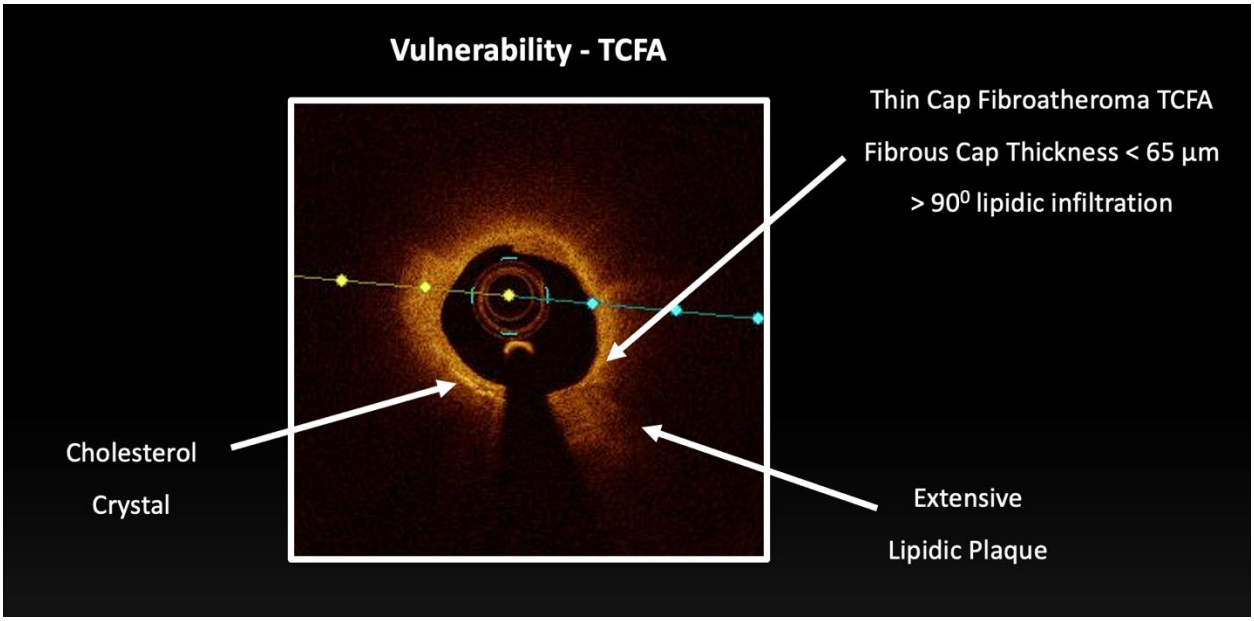

Vulnerability - ThCFA
Small Lumen Area
Thick Cap Fibroatheroma
ThCFA
Macrophages
Extensive
Lipidic Plaque

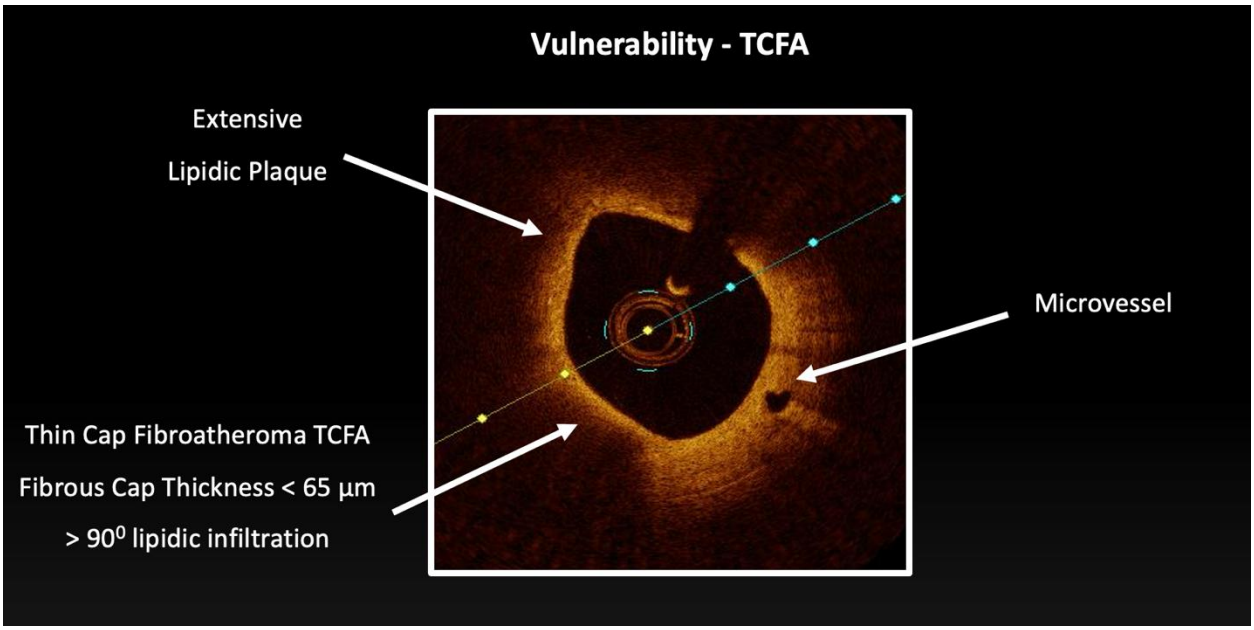

Vulnerability - ThCFA
Small
Minimum Lumen Area
< 2 mm²
Thick Cap Fibroatheroma
ThCFA
Extensive
Lipidic Plaque

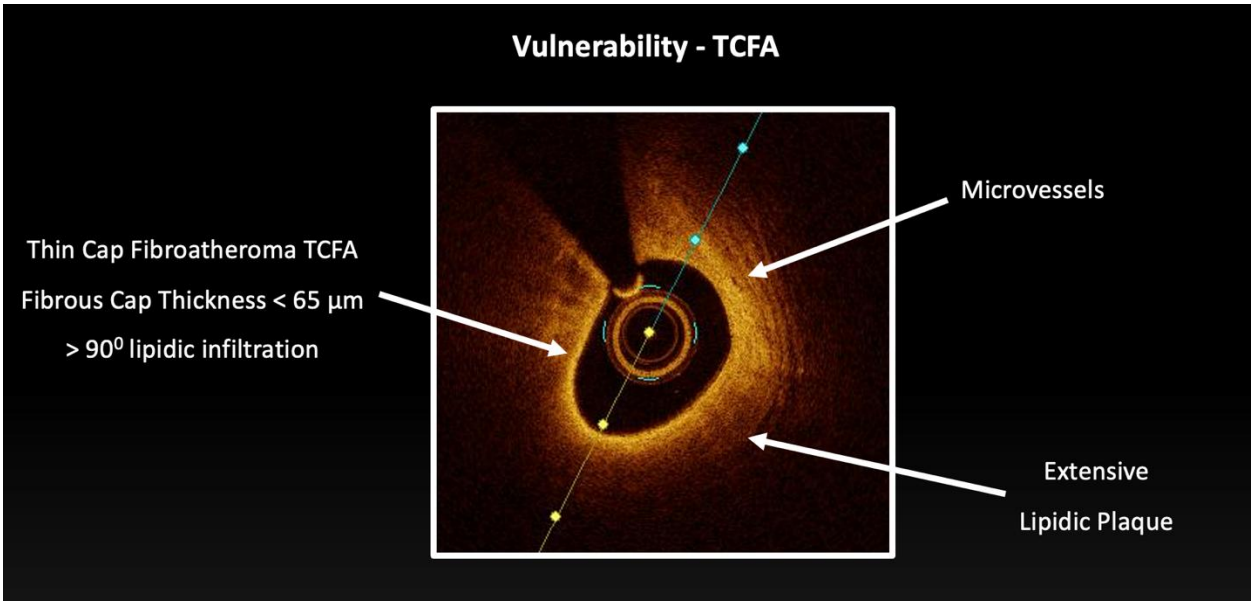

Vulnerability - TCFA
Cholesterol
Crystal
Extensive
Lipidic Plaque
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm
> 90⁰ lipidic infiltration

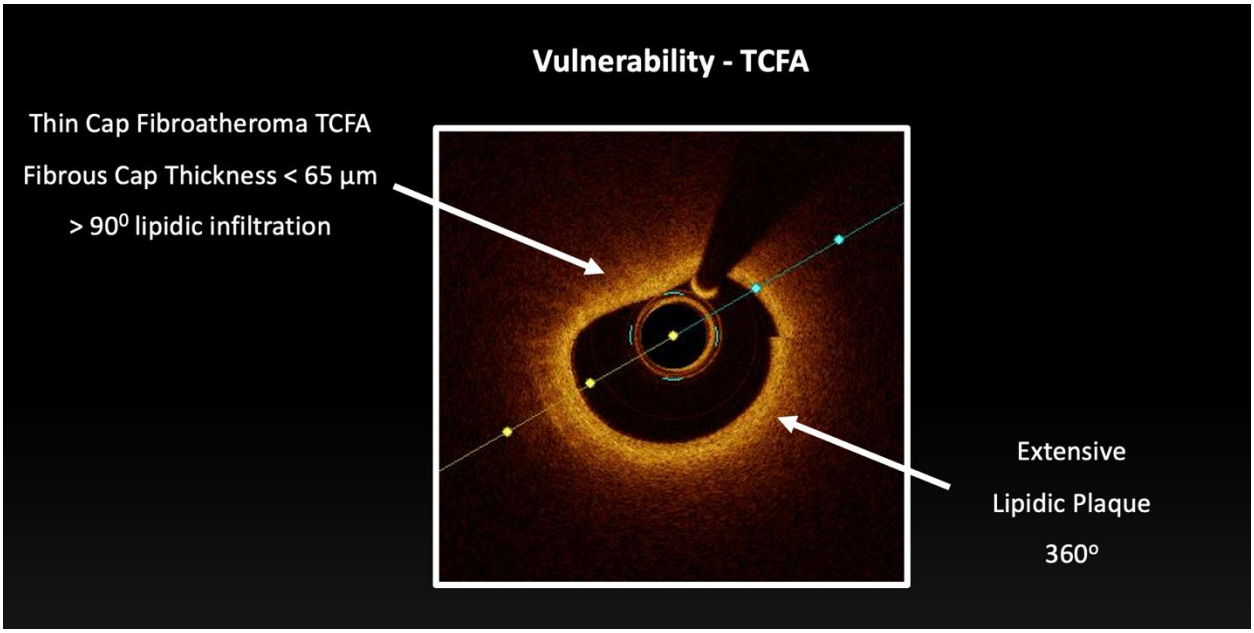

Vulnerability - TCFA
Extensive
Lipidic Plaque
360º
Macrophages
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm
> 90⁰ lipidic infiltration

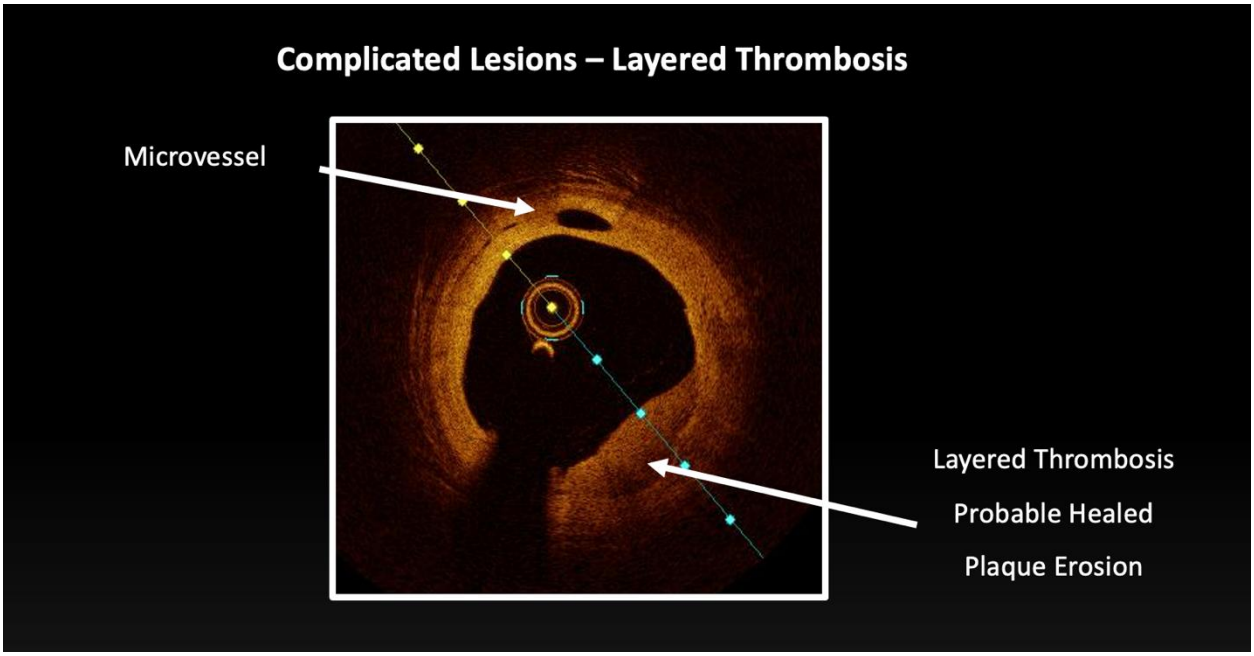

Vulnerability - TCFA
Extensive
Lipidic Plaque
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm
> 90⁰ lipidic infiltration

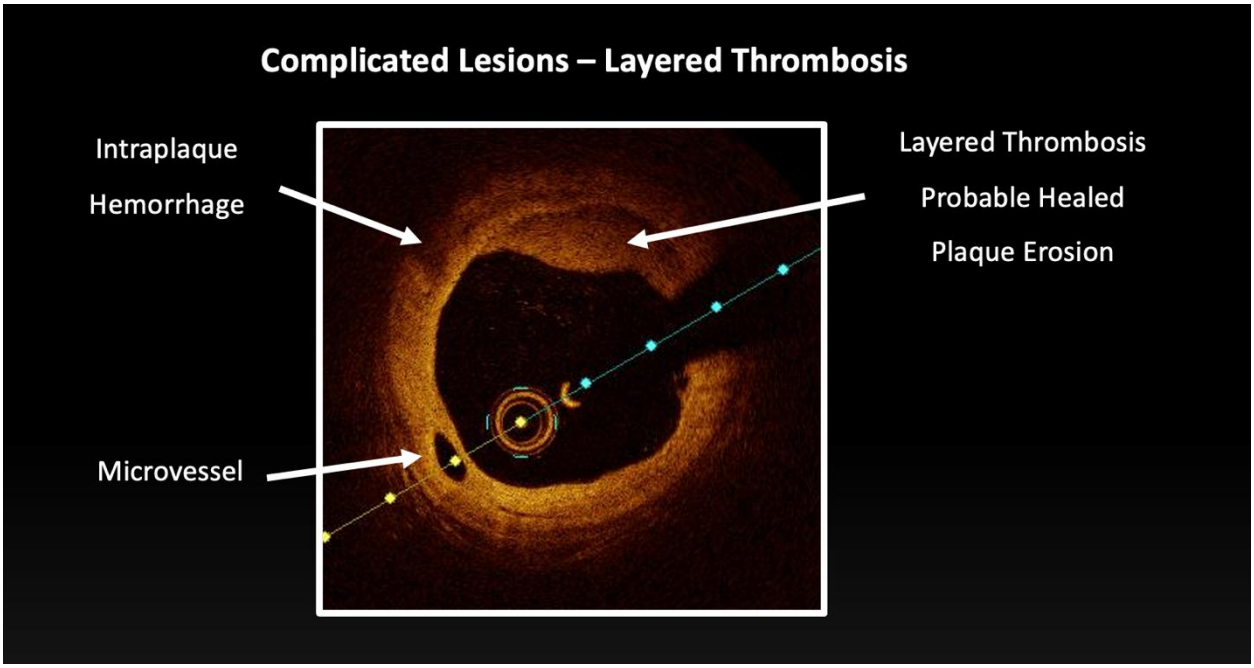

Vulnerability - TCFA
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm
> 90⁰ lipidic infiltration
Cholesterol
Crystal
Extensive
Lipidic Plaque

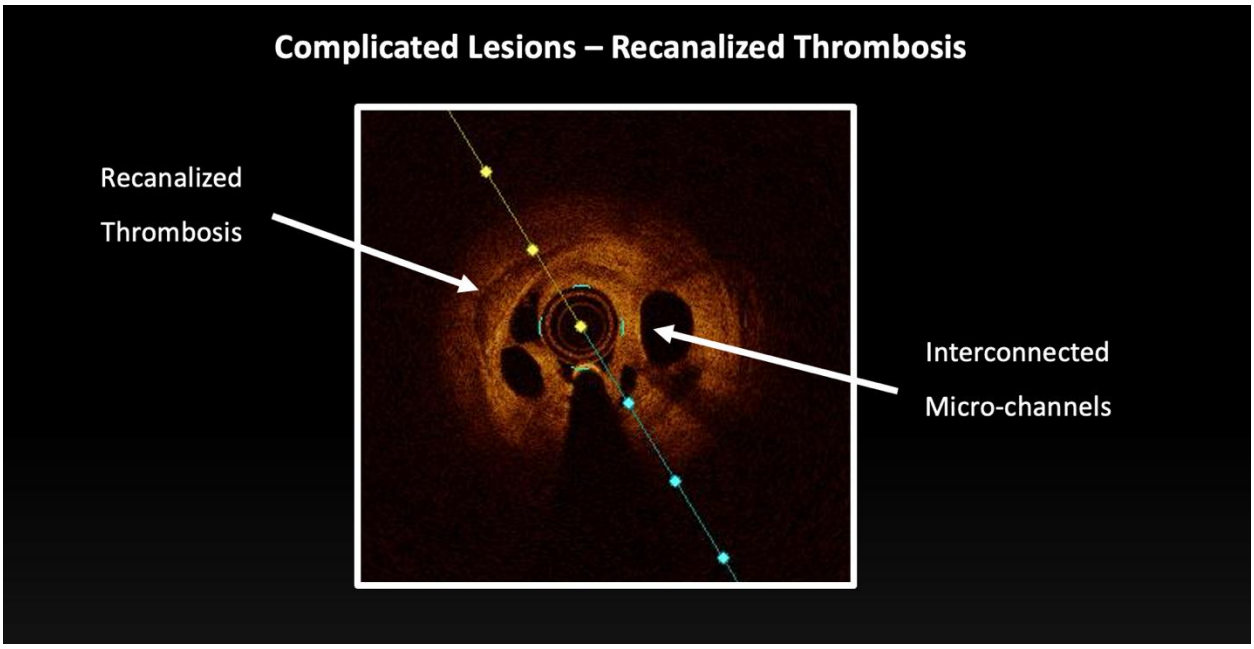

Vulnerability - TCFA
Extensive
Lipidic Plaque
Microvessel
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm
> 90⁰ lipidic infiltration

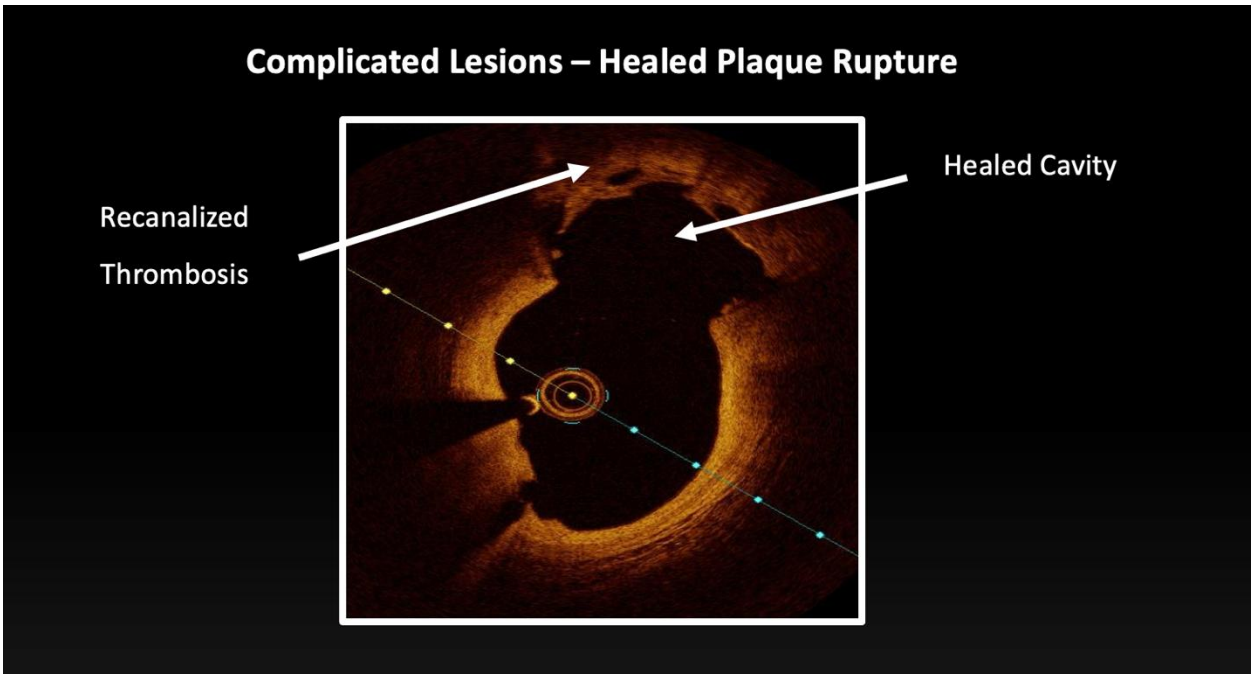

Vulnerability - TCFA
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm
> 90⁰ lipidic infiltration
Microvessels
Extensive
Lipidic Plaque

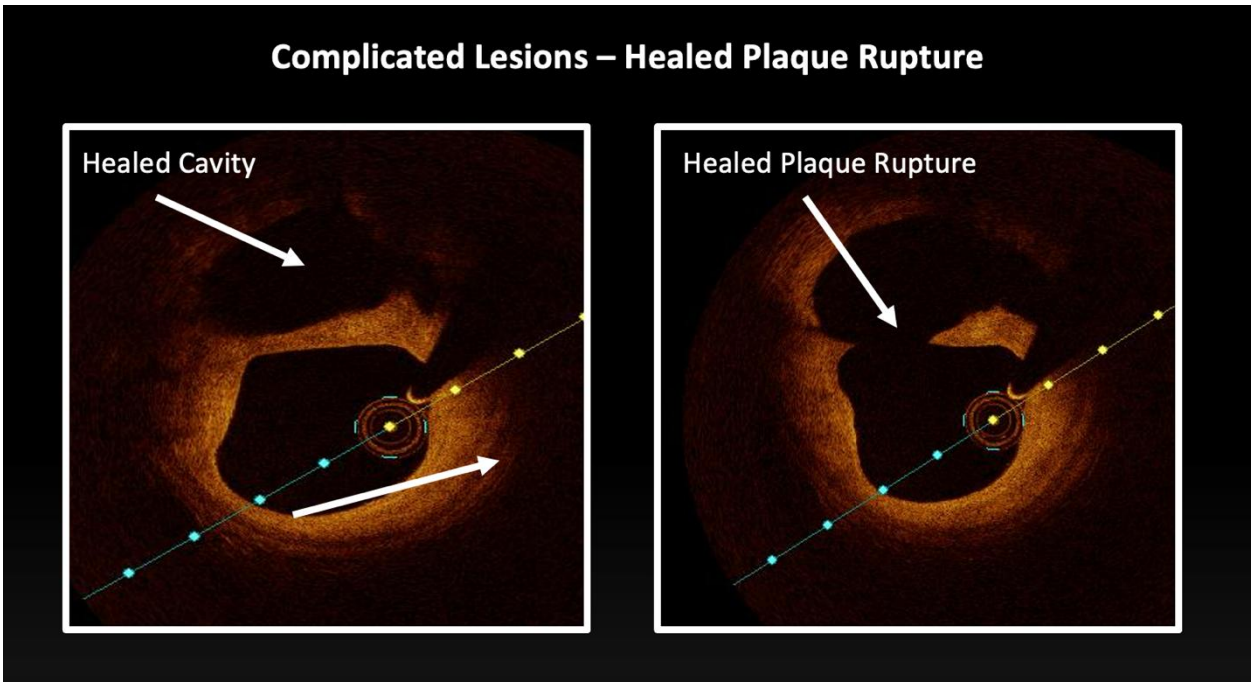

Vulnerability - TCFA
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm
> 90⁰ lipidic infiltration
Extensive
Lipidic Plaque
360º

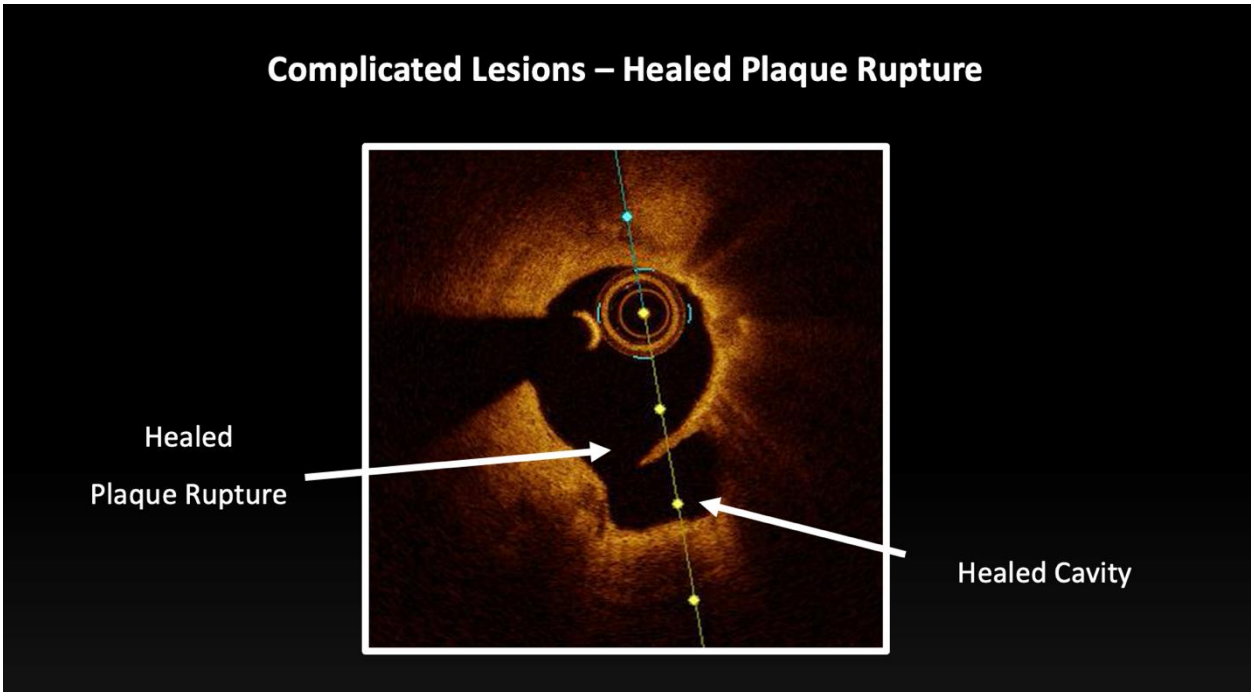

Complicated Lesions – Layered Thrombosis
Microvessel
Layered Thrombosis
Probable Healed
Plaque Erosion

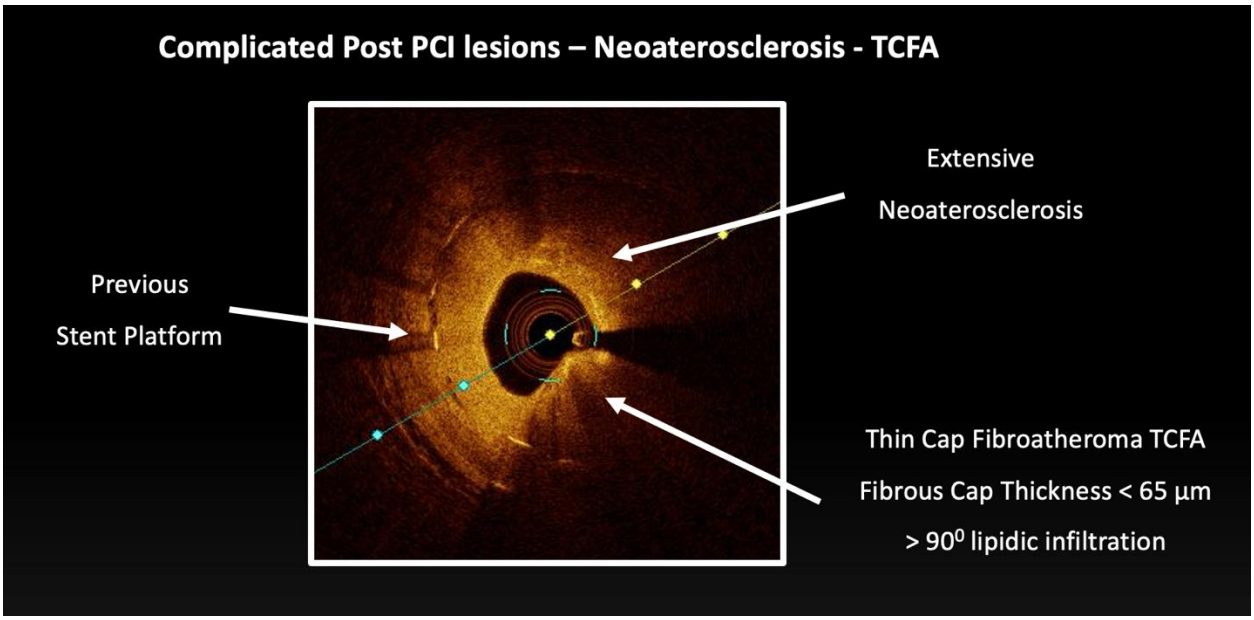

Complicated Lesions – Layered Thrombosis
Intraplaque
Hemorrhage
Microvessel
Layered Thrombosis
Probable Healed
Plaque Erosion

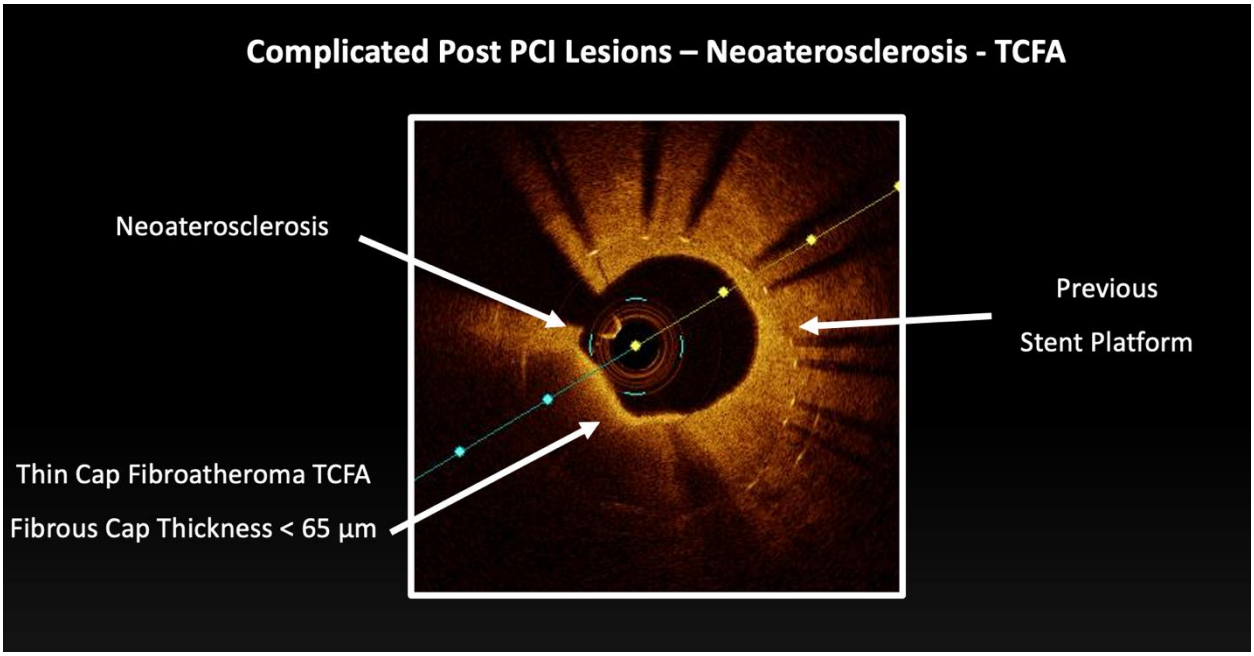

Complicated Lesions – Recanalized Thrombosis
Recanalized
Thrombosis
Interconnected
Micro-channels


Complicated Lesions – Healed Plaque Rupture
Recanalized
Thrombosis
Healed Cavity


Complicated Lesions – Healed Plaque Rupture
Healed Cavity
Healed Plaque Rupture


Complicated Lesions – Healed Plaque Rupture
Healed
Plaque Rupture
Healed Cavity


Complicated Post PCI lesions – Neoaterosclerosis - TCFA
Extensive
Neoaterosclerosis
Previous
Stent Platform
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm
> 90⁰ lipidic infiltration


Complicated Post PCI Lesions – Neoaterosclerosis - TCFA
Neoaterosclerosis
Previous
Stent Platform
Thin Cap Fibroatheroma TCFA
Fibrous Cap Thickness < 65 µm

8 PART V. PUBLICATIONS LIST

8.1 Publication 1.

Complete Revascularization with Multivessel PCI for Myocardial Infarction

N Engl J Med. 2019 Oct 10;381(15):1411-1421.

The COMPLETE trial is a multinational, randomized trial evaluating a strategy of complete revascularization, consisting of angiography-guided PCI of all suitable non-culprit-lesions versus a strategy of culprit-lesion-only PCI (optimal medical therapy alone), in 4,041 patients from 140 centres in 31 countries undergoing pPCI for acute STEMI. Complete revascularization, defined by the angiographic core laboratory as successful treatment of all target lesions, was achieved in 99.1% of patients randomized to this arm of the trial.

At a median follow-up of 3 years, complete revascularization reduced the first co-primary outcome of CV death or new MI by 26% compared with the culprit-lesion only strategy (HR 0.74; 95% CI 0.60-0.91; P=0.004). The second co-primary outcome of CV death, new MI or ischemia-driven revascularization was reduced by 49% with complete revascularization (HR 0.51; 95% CI 0.43-0.61; P<0.001). For both coprimary outcomes, the benefit of complete revascularization was consistently observed regardless of the intended timing of nonculprit-lesion PCI (P = 0.62 and P = 0.27 for interaction for the first and second coprimary outcomes, respectively).

The COMPLETE trial concluded that among patients with STEMI and MVD, complete revascularization was superior to culprit-lesion-only PCI in reducing the risk of cardiovascular death or myocardial infarction, as well as the risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularization.

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Complete Revascularization with Multivessel PCI for Myocardial Infarction

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ABSTRACT

BACKGROUND

In patients with ST-segment elevation myocardial infarction (STEMI), percutaneous coronary intervention (PCI) of the culprit lesion reduces the risk of cardiovascular death or myocardial infarction. Whether PCI of nonculprit lesions further reduces the risk of such events is unclear.

METHODS

We randomly assigned patients with STEMI and multivessel coronary artery disease who had undergone successful culprit-lesion PCI to a strategy of either complete revascularization with PCI of angiographically significant nonculprit lesions or no further revascularization. Randomization was stratified according to the intended timing of nonculprit-lesion PCI (either during or after the index hospitalization). The first coprimary outcome was the composite of cardiovascular death or myocardial infarction; the second coprimary outcome was the composite of cardiovascular death, myocardial infarction, or ischemia-driven revascularization.

RESULTS

At a median follow-up of 3 years, the first coprimary outcome had occurred in 158 of the 2016 patients (7.8%) in the complete-revascularization group as compared with 213 of the 2025 patients (10.5%) in the culprit-lesion-only PCI group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.91; P=0.004). The second coprimary outcome had occurred in 179 patients (8.9%) in the complete-revascularization group as compared with 339 patients (16.7%) in the culprit-lesion-only PCI group (hazard ratio, 0.51; 95% CI, 0.43 to 0.61; P<0.001). For both coprimary outcomes, the benefit of complete revascularization was consistently observed regardless of the intended timing of nonculprit-lesion PCI (P=0.62 and P=0.27 for interaction for the first and second coprimary outcomes, respectively).

CONCLUSIONS

Among patients with STEMI and multivessel coronary artery disease, complete revascularization was superior to culprit-lesion-only PCI in reducing the risk of cardiovascular death or myocardial infarction, as well as the risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularization. (Funded by the Canadian Institutes of Health Research and others; COMPLETE ClinicalTrials.gov number, NCT01740479.)

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*A complete list of the COMPLETE trial steering committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

A Quick Take is available at NEJM.org

Primary percutaneous coronary intervention (PCI) is the preferred method of reperfusion for patients with ST-segment elevation myocardial infarction (STEMI).[1-4] These patients often have multivessel coronary artery disease, with additional angiographically significant lesions in locations separate from that of the culprit lesion that caused the acute event.[5] Whether to routinely revascularize these nonculprit lesions or to manage them conservatively with guideline-based medical therapy alone is a common dilemma.[6-8] Nonculprit lesions, which are usually discovered incidentally at the time of primary PCI, may represent stable coronary artery plaques, for which additional revascularization may not offer additional benefit.[9] However, if nonculprit lesions have morphologic features consistent with unstable plaques, which confer an increased risk of future cardiovascular events, there may be a benefit of routine nonculprit-lesion PCI.[10,11]

Although observational studies have suggested a possible reduction in clinical events with staged nonculprit-lesion PCI,[12,13] these studies are limited by selection bias and confounding. Randomized trials have shown reductions in the risk of composite outcomes with nonculprit-lesion PCI, with results driven predominantly by the decreased risk of subsequent revascularization with that strategy.[14-17] Meta-analyses suggest a reduction in the risk of death from cardiovascular causes or myocardial infarction with nonculprit-lesion PCI,[18-20] but previous individual trials have not had the power to examine this clinically important outcome. The Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial was designed to address this evidence gap.

Methods

Trial Design and Oversight

The COMPLETE trial was a multinational, randomized trial that evaluated a strategy of complete revascularization (consisting of PCI of all suitable nonculprit lesions) as compared with a strategy of no further revascularization in patients with STEMI and multivessel coronary artery disease who had undergone successful culprit-lesion PCI.[21] The executive committee designed the protocol, which is available with the full text of this article at NEJM.org, and was responsible for the conduct and oversight of the trial. The trial was coordinated and sponsored by the Population Health Research Institute of Hamilton Health Sciences and McMaster University. The trial was funded by the Canadian Institutes of Health Research. AstraZeneca and Boston Scientific provided additional funding. These companies had no role in the trial design; collection, analysis, or interpretation of the data; or writing of the manuscript. The protocol was approved by institutional review boards at all trial centers. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Eligibility

Patients who presented to the hospital with STEMI were considered for inclusion in the trial if they could undergo randomization within 72 hours after successful culprit-lesion PCI. Eligible patients were required to have multivessel coronary artery disease, defined as the presence of at least one angiographically significant non–infarct-related (nonculprit) lesion that was amenable to successful treatment with PCI and was located in a vessel with a diameter of at least 2.5 mm that was not stented as part of the index culprit-lesion PCI. Nonculprit lesions were deemed angiographically significant if they were associated with at least 70% stenosis of the vessel diameter on visual estimation or with 50 to 69% stenosis accompanied by a fractional flow reserve (FFR) measurement of 0.80 or less. The main exclusion criteria were an intention before randomization to revascularize a nonculprit lesion, a planned surgical revascularization, or previous coronary-artery bypass grafting surgery. Details regarding inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. Written informed consent was obtained from all the patients.

Randomization and Trial Treatments

Eligible patients were randomly assigned to undergo either complete revascularization or culprit-lesion-only revascularization according to a computer-generated randomization list with the use of randomly permuted blocks and with blinding to trial center. Randomization was stratified according to center and the intended timing of nonculprit-lesion PCI (if the patient were to be assigned to the complete-revascularization group). Randomization was performed as soon as possible (no later than 72 hours) after the index PCI.

Patients who were randomly assigned to the complete-revascularization strategy were to have routine staged PCI (i.e., PCI during a procedure separate from the index PCI procedure for STEMI) of all suitable nonculprit lesions, regardless of whether there were clinical symptoms or there was evidence of ischemia. Investigators specified before randomization whether they intended to perform nonculprit-lesion PCI during the index hospitalization or after hospital discharge (no later than 45 days after randomization). Everolimus-eluting stents were strongly recommended for all PCI procedures. It was recommended that PCI of chronic total occlusions be attempted only by operators who had experience in treating chronic total occlusions and only when there was a high likelihood of successful PCI.

Patients who were randomly assigned to the culprit-lesion-only PCI strategy received guideline-based medical therapy with no further revascularization, regardless of whether there was evidence of ischemia on noninvasive testing. Protocol-specified criteria for crossover to the complete-revascularization strategy are provided in the Supplementary Appendix.

All coronary angiograms obtained during the trial were forwarded to an angiographic core laboratory located at the Population Health Research Institute for detailed assessment.[21] After initial hospital discharge, routine follow-up occurred at 6 weeks, 6 months, 1 year, and yearly thereafter up to the final follow-up visit.

RECOMMENDED MEDICAL THERAPY

Guideline-based medical therapy was recommended in both treatment groups. Dual antiplatelet therapy with aspirin and ticagrelor for at least 1 year was recommended.[22] Beyond 1 year, aspirin was recommended for all patients, and ticagrelor (60 mg twice daily) was recommended for patients who were not at high risk for bleeding.[23] High-dose statin therapy, angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers, mineralocorticoid-receptor antagonists, and beta-blockers were recommended.[21]

OUTCOMES

The first coprimary outcome was the composite of death from cardiovascular causes or new myocardial infarction; the second coprimary outcome was the composite of death from cardiovascular causes, new myocardial infarction, or ischemia-driven revascularization. Safety outcomes included major bleeding and contrast-associated acute kidney injury. Secondary outcomes are described in the Supplementary Appendix; detailed definitions of all outcomes are provided in Table S2 in the Supplementary Appendix. Myocardial infarction was defined according to the third universal definition and was subclassified according to type.[24] An event-adjudication committee, which consisted of clinicians who were unaware of the treatment assignments, adjudicated primary, secondary, and safety outcome events.

STATISTICAL ANALYSIS

We estimated that a sample of 4000 patients would give the trial 80% power to detect a 22% lower risk of the composite of cardiovascular death or myocardial infarction in the complete-revascularization group than in the culprit-lesion-only PCI group, assuming an event rate of 5% per year in the culprit-lesion-only PCI group. To preserve the overall type I error rate of 5% for the testing of both coprimary outcomes, the first coprimary outcome was tested at a P value of 0.045 and the second at a P value of 0.0119.[21] One interim analysis was performed. Because a very conservative monitoring boundary was used for this analysis, no adjustment of the type I error threshold was applied. Details regarding these analyses are provided in the Supplementary Appendix.

All patients who underwent randomization were included in the analysis according to the treatment group to which they were assigned, regardless of the treatment they actually received (intention-to-treat principle). The coprimary outcomes were analyzed with the use of a time-to-first-event approach. Estimates of the hazard ratios and 95% confidence intervals were calculated with the use of Cox proportional-hazards models, with treatment group as an independent variable and with stratification according to the intended timing of nonculprit-lesion PCI. Confidence intervals for secondary and exploratory efficacy outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. The two treatment groups were compared with the use of the stratified log-rank test. Cumulative incidence was estimated with the Kaplan–Meier method. A sensitivity analysis was performed with a Fine–Gray model to account for the competing risk of death from noncardiovascular causes.[25]

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Complete Revascularization (N=2016)	Culprit-Lesion-Only PCI (N=2025)
Age — yr	61.6±10.7	62.4±10.7
Male sex — no. (%)	1623 (80.5)	1602 (79.1)
Diabetes — no. (%)	385 (19.1)	402 (19.9)
Chronic renal insufficiency — no./total no. (%)	37/1884 (2.0)	44/1903 (2.3)
Previous myocardial infarction — no. (%)	148 (7.3)	154 (7.6)
Current smoker — no. (%)	819 (40.6)	787 (38.9)
Hypertension — no. (%)	982 (48.7)	1027 (50.7)
Dyslipidemia — no. (%)	764 (37.9)	797 (39.4)
Previous PCI — no. (%)	142 (7.0)	141 (7.0)
Previous stroke — no. (%)	64 (3.2)	62 (3.1)
Time from symptom onset to index PCI — no./total no. (%)		
<6 hr	1383/1994 (69.4)	1341/2000 (67.0)
6 to 12 hr	322/1994 (16.1)	354/2000 (17.7)
>12 hr	289/1994 (14.5)	305/2000 (15.2)
Killip class ≥II — no./total no. (%)	212/1995 (10.6)	218/1996 (10.9)
Glycated hemoglobin — %	6.3±1.6	6.3±1.6
Low-density lipoprotein cholesterol — mmol/liter	3.1±1.2	3.1±1.2
Peak creatinine — μmol/liter	84.7±30.8	85.2±26.8
Medications at discharge — no. (%)		
Aspirin	2011 (99.8)	2015 (99.5)
$P2Y_{12}$ inhibitor		
Any	2003 (99.4)	2018 (99.7)
Ticagrelor	1298 (64.4)	1281 (63.3)
Prasugrel	193 (9.6)	169 (8.3)
Clopidogrel	516 (25.6)	572 (28.2)
Beta-blocker	1776 (88.1)	1804 (89.1)
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	1723 (85.5)	1714 (84.6)
Statin	1980 (98.2)	1968 (97.2)

* Plus–minus values are means ±SD. To convert the values for low-density lipoprotein cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. PCI denotes percutaneous coronary intervention.

RESULTS

PATIENTS, TREATMENT, AND FOLLOW-UP

From February 1, 2013, through March 6, 2017, a total of 4041 patients from 140 centers in 31 countries underwent randomization: 2016 were assigned to the complete-revascularization group and 2025 to the culprit-lesion-only PCI group. Baseline and procedural characteristics are shown in Tables 1 and 2, respectively. Details are provided in Table S3 and Figure S1 in the Supplementary Appendix.

Among the patients who underwent complete revascularization, the median time from randomization to nonculprit-lesion PCI was 1 day (interquartile range, 1 to 3) among the 1285 patients for whom the intended timing of nonculprit-lesion PCI was during the index hospitalization and 23 days (interquartile range, 12.5 to 33.5) among the 596 patients for whom the in-

Table 2. Procedural Characteristics.*

Characteristic	Complete Revascularization (N=2016)	Culprit-Lesion-Only PCI (N=2025)
Index procedure for STEMI — no. (%)		
Primary PCI	1853 (91.9)	1885 (93.1)
Pharmacoinvasive PCI	64 (3.2)	61 (3.0)
Rescue PCI	99 (4.9)	79 (3.9)
Radial access — no. (%)	1629 (80.8)	1634 (80.7)
Thrombus aspiration — no./total no. (%)	451/1864 (24.2)	481/1875 (25.7)
SYNTAX score†‡		
Culprit lesion–specific score	8.8±5.3	8.6±5.3
Nonculprit lesion–specific score	4.6±2.8	4.6±2.7
Baseline score, including culprit lesion	16.3±6.8	16.0±6.6
Residual score, after index PCI	7.2±4.9	7.0±4.7
Location of culprit lesion — no./total no. (%)†		
Left main coronary artery	3/1918 (0.2)	4/1940 (0.2)
Left anterior descending artery	660/1918 (34.4)	657/1940 (33.9)
Circumflex artery	346/1918 (18.0)	307/1940 (15.8)
Right coronary artery	909/1918 (47.4)	972/1940 (50.1)
No. of residual diseased vessels — no./total no. (%)†		
1	1458/1917 (76.1)	1492/1934 (77.1)
≥2	459/1917 (23.9)	442/1934 (22.9)
Location of nonculprit lesions — no./total no. of lesions (%)†		
Left main coronary artery	10/2731 (0.4)	3/2624 (0.1)
Left anterior descending artery	1037/2731 (38.0)	1080/2624 (41.2)
Proximal	267/2731 (9.8)	274/2624 (10.4)
Middle	592/2731 (21.7)	621/2624 (23.7)
Circumflex artery	993/2731 (36.4)	933/2624 (35.6)
Proximal left circumflex artery, obtuse marginal branch, and ramus intermedius artery	744/2731 (27.2)	697/2624 (26.6)
Distal left circumflex artery and posterior left ventricular branch	249/2731 (9.1)	236/2624 (9.0)
Right coronary artery	691/2731 (25.3)	608/2624 (23.2)
Diameter of vessel with nonculprit lesion — mm†	2.8±0.5	2.9±0.6
Nonculprit-lesion stenosis on visual estimation		
%	79.3±8.1	78.7±7.9
No./total no. of lesions (%)		
50–69%, with fractional flow reserve <0.80	21/2612 (0.8)	16/2576 (0.6)
70–79%	1078/2612 (41.3)	1162/2576 (45.1)
80–89%	875/2612 (33.5)	839/2576 (32.6)
90–99%	583/2612 (22.3)	508/2576 (19.7)
100%	55/2612 (2.1)	51/2576 (2.0)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. STEMI denotes ST-segment elevation myocardial infarction.
† Data were obtained at the angiographic core laboratory.
‡ The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score is used to describe the degree of angiographic complexity; a score of 0 indicates no angiographically significant disease, and higher scores indicate more extensive and complex coronary artery disease.

tended timing of nonculprit-lesion PCI was after hospital discharge. Within the first 45 days, crossover from the culprit-lesion-only PCI group to the complete-revascularization group occurred in 96 patients (4.7%), and crossover from the complete-revascularization group to the culprit-lesion-only PCI group occurred in 78 patients (3.9%). After nonculprit-lesion PCI, 90.1% of the patients in the complete-revascularization group had a SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score of 0, indicating no angiographically significant disease (i.e., complete revascularization).

Outcome events were assessed up to the date of each patient's final follow-up visit, which ranged from September 1, 2018, to June 7, 2019, when the database was locked. The mean follow-up time was 36.2 months, and the median follow-up time was 35.8 months (interquartile range, 27.6 to 44.3). Data on vital status were complete for 99.1% and 99.3% of the patients in the complete-revascularization and culprit-lesion-only PCI groups, respectively. Data on concomitant medication use at hospital discharge and throughout follow-up are provided in Table S4 in the Supplementary Appendix.

PRIMARY AND SECONDARY OUTCOMES

At a median follow-up of 3 years, death from cardiovascular causes or new myocardial infarction (the first coprimary composite outcome) had occurred in 158 patients (7.8%) in the complete-revascularization group as compared with 213 patients (10.5%) in the culprit-lesion-only PCI group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.91; P=0.004) (Table 3 and Fig. 1A). This result was driven by the lower incidence of new myocardial infarction in the complete-revascularization group than in the culprit-lesion-only PCI group (5.4% vs. 7.9%; hazard ratio, 0.68; 95% CI, 0.53 to 0.86); the incidence of death from cardiovascular causes was 2.9% and 3.2%, respectively (hazard ratio, 0.93; 95% CI, 0.65 to 1.32). Specifically, the following types of myocardial infarction occurred less frequently in the complete-revascularization group than in the culprit-lesion-only PCI group: non-STEMI (66 events vs. 105 events), new STEMI (43 vs. 53), and predominantly, myocardial infarction type 1 (63 vs. 128) (Table S5 in the Supplementary Appendix).

Death from cardiovascular causes, new myocardial infarction, or ischemia-driven revascularization (the second coprimary composite outcome) occurred in 179 patients (8.9%) in the complete-revascularization group as compared with 339 patients (16.7%) in the culprit-lesion-only PCI group (hazard ratio, 0.51; 95% CI, 0.43 to 0.61; P<0.001) (Table 3 and Fig. 1B). The results of competing-risk analyses with respect to the two coprimary outcomes were consistent with the results of the primary analyses (Table S6 in the Supplementary Appendix).

Death from cardiovascular causes, new myocardial infarction, ischemia-driven revascularization, unstable angina, or New York Heart Association class IV heart failure (the key secondary outcome) occurred in 272 patients (13.5%) in the complete-revascularization group as compared with 426 patients (21.0%) in the culprit-lesion-only PCI group (hazard ratio, 0.62; 95% CI, 0.53 to 0.72). Results for other secondary outcomes are shown in Table 3.

SUBGROUP ANALYSES AND TIMING OF NONCULPRIT-LESION PCI

For the coprimary outcomes, there was no differential treatment effect in prespecified subgroups (Fig. 2). The benefit of complete revascularization was consistently observed among patients for whom the intended timing of nonculprit-lesion PCI was during the index hospitalization and those for whom the intended timing was after hospital discharge (P=0.62 and P=0.27 for interaction for the first and second coprimary outcomes, respectively). In 87.1% of the patients in the complete-revascularization group, the actual timing of nonculprit-lesion PCI corresponded to the intended timing specified by the investigator before randomization. The hazard ratio for the first coprimary outcome with a complete-revascularization strategy as compared with a culprit-lesion-only PCI strategy was 0.77 (95% CI, 0.59 to 1.00) in the subgroup for which in-hospital nonculprit-lesion PCI was intended and 0.69 (95% CI, 0.49 to 0.97) in the subgroup for which postdischarge nonculprit-lesion PCI was intended.

SAFETY AND OTHER OUTCOMES

There was no significant difference between the two treatment groups in the risk of major bleeding, stroke, or stent thrombosis (Table 3). Results for specific types of stent thrombosis are shown in Table S7 in the Supplementary Appendix. Contrast-associated acute kidney injury oc-

Table 3. Efficacy and Safety Outcomes.*

Outcome	Complete Revascularization (N=2016)		Culprit-Lesion-Only PCI (N=2025)		Hazard Ratio (95% CI)	P Value
	no. (%)	*% per person-yr*	*no. (%)*	*% per person-yr*		
Coprimary outcomes						
Cardiovascular death or myocardial infarction	158 (7.8)	2.7	213 (10.5)	3.7	0.74 (0.60–0.91)	0.004
Cardiovascular death, myocardial infarction, or ischemia-driven revascularization	179 (8.9)	3.1	339 (16.7)	6.2	0.51 (0.43–0.61)	<0.001
Key secondary outcome						
Cardiovascular death, myocardial infarction, ischemia-driven revascularization, unstable angina, or NYHA class IV heart failure	272 (13.5)	4.9	426 (21.0)	8.1	0.62 (0.53–0.72)	
Other secondary outcomes						
Myocardial infarction	109 (5.4)	1.9	160 (7.9)	2.8	0.68 (0.53–0.86)	
Ischemia-driven revascularization	29 (1.4)	0.5	160 (7.9)	2.8	0.18 (0.12–0.26)	
Unstable angina	70 (3.5)	1.2	130 (6.4)	2.2	0.53 (0.40–0.71)	
Death from cardiovascular causes	59 (2.9)	1.0	64 (3.2)	1.0	0.93 (0.65–1.32)	
Death from any cause	96 (4.8)	1.6	106 (5.2)	1.7	0.91 (0.69–1.20)	
Other outcomes						
Stroke	38 (1.9)	0.6	29 (1.4)	0.5	1.31 (0.81–2.13)	
NYHA class IV heart failure	58 (2.9)	1.0	56 (2.8)	0.9	1.04 (0.72–1.50)	
Stent thrombosis	26 (1.3)	0.4	19 (0.9)	0.3	1.38 (0.76–2.49)	
Safety outcomes						
Major bleeding	58 (2.9)	1.0	44 (2.2)	0.7	1.33 (0.90–1.97)	0.15
Contrast-associated acute kidney injury†	30 (1.5)	—	19 (0.9)	—	1.59 (0.89–2.84)	0.11

* P values were calculated with the use of the stratified log-rank test. Confidence intervals for secondary and exploratory efficacy outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. NYHA denotes New York Heart Association.
† Contrast-associated acute kidney injury was treated as a binary outcome. Shown are an odds ratio (instead of a hazard ratio), 95% confidence interval, and P value that were calculated with stratified logistic regression.

curred in 30 patients in the complete-revascularization group as compared with 19 patients in the culprit-lesion-only PCI group (odds ratio, 1.59; 95% CI, 0.89 to 2.84; P=0.11). This event was attributed to the nonculprit-lesion PCI procedure in 7 patients in the complete-revascularization group as compared with none (in accordance with the protocol) in the culprit-lesion-only PCI group. For those 7 patients, the intended timing of nonculprit-lesion PCI was during the index hospitalization.

DISCUSSION

The COMPLETE trial showed that, among patients with STEMI and multivessel coronary artery disease, a strategy of staged nonculprit-lesion PCI with the goal of complete revascularization resulted in a 26% lower risk of a composite of death from cardiovascular causes or new myocardial infarction at a median follow-up of 3 years than did a strategy of culprit-lesion-only PCI. This benefit was driven by the 32% lower risk of new, nonfatal myocardial infarction in the complete-revascularization group than in the culprit-lesion-only PCI group; the incidence of death from cardiovascular causes was similar in the two groups. For the second coprimary outcome, which included ischemia-driven revascularization in addition to the other two events, the risk with a complete-revascularization strategy was approximately half the risk with a culprit-lesion-only PCI strategy. There was no significant difference between the two groups in the risk of

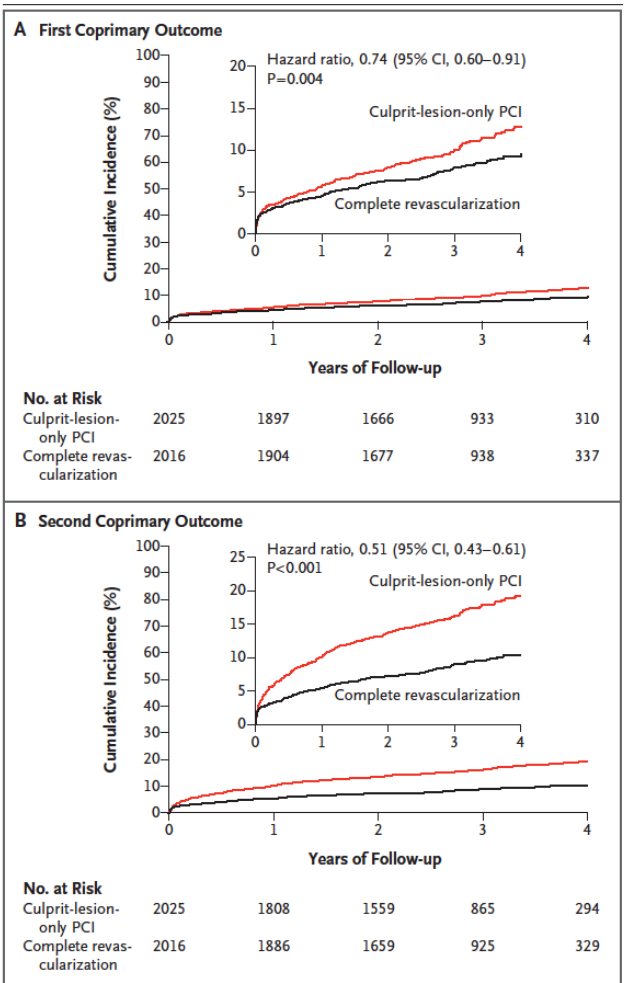


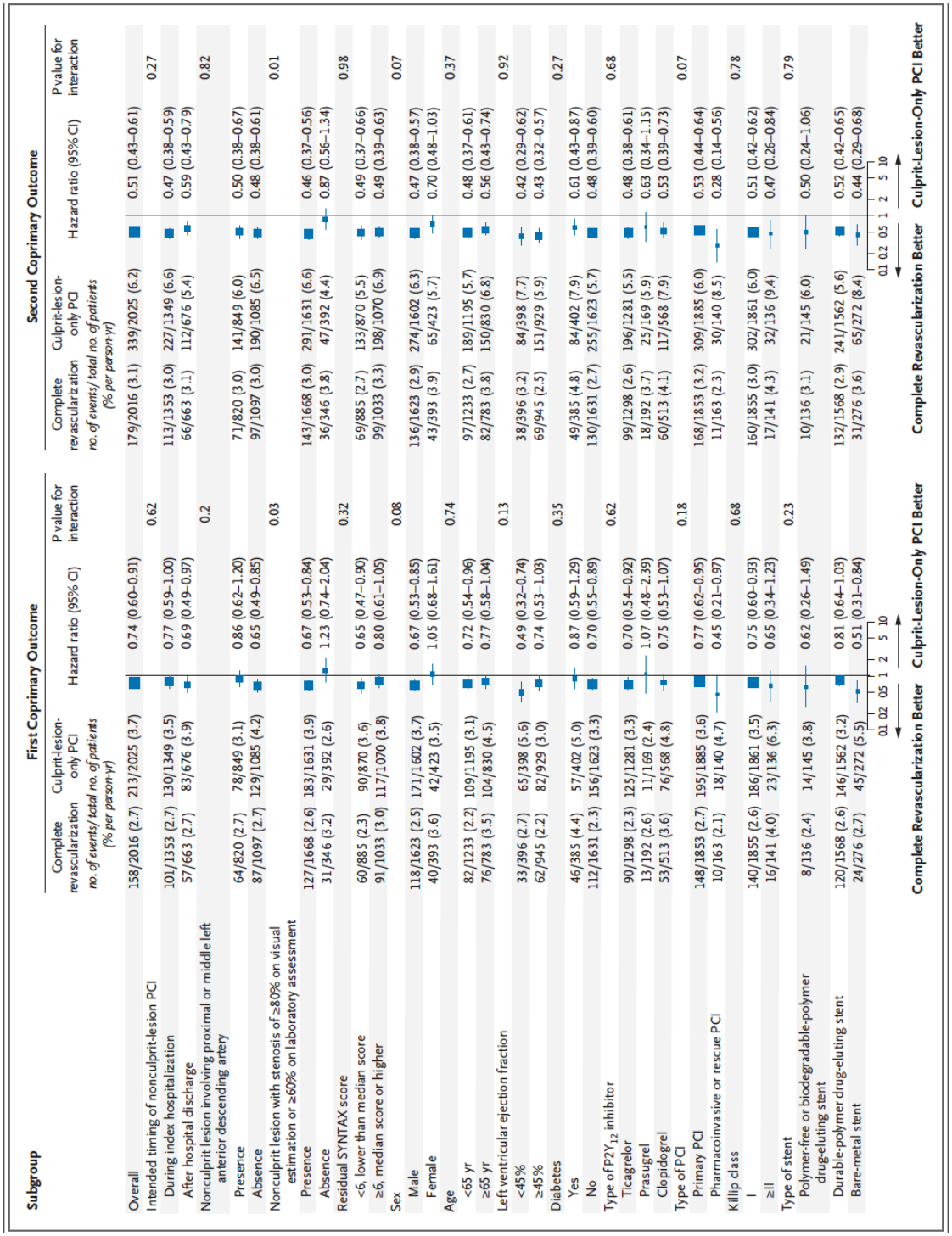
Figure 1. Cumulative Incidence of the First and Second Coprimary Outcomes.
Panels A and B show Kaplan–Meier estimates of the cumulative incidence of the first coprimary outcome (death from cardiovascular causes or new myocardial infarction) and the second coprimary outcome (death from cardiovascular causes, new myocardial infarction, or ischemia-driven revascularization), respectively. Insets show the same data on an enlarged y axis. PCI denotes percutaneous coronary intervention.

Figure 2 (facing page). Subgroup Analyses of the First and Second Coprimary Outcomes.
P values for interaction have not been adjusted for multiple comparisons. The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score is used to describe the degree of angiographic complexity; a score of 0 indicates no angiographically significant disease, and higher scores indicate more extensive and complex coronary artery disease.

major bleeding or stroke. The benefit of complete revascularization was consistently observed regardless of whether nonculprit-lesion PCI was to be performed during the index hospitalization or several weeks after discharge from the hospital.

We designed the trial to have sufficient power to determine whether a complete-revascularization strategy would lead to a meaningful reduction in the risk of the clinically important outcome of cardiovascular death or new myocardial infarction. Previous trials that evaluated a complete-revascularization strategy in patients with STEMI were smaller and included revascularization as part of the composite primary outcome.[14-17] In the absence of a reduction in irreversible events such as cardiovascular death or new myocardial infarction, the clinical relevance of performing early nonculprit-lesion PCI in all patients with multivessel coronary artery disease to prevent later PCI in a smaller number of those patients is debatable. We have now found that routine nonculprit-lesion PCI with the goal of complete revascularization confers a reduction in the long-term risk of cardiovascular death or myocardial infarction. Over a period of 3 years, the number needed to treat to prevent cardiovascular death or myocardial infarction from occurring in 1 patient is 37 patients, and the number needed to treat to prevent cardiovascular death, myocardial infarction, or ischemia-driven revascularization from occurring in 1 patient is 13 patients.

At least 70% stenosis in coronary arteries on visual estimation is routinely reported to be a standard criterion used in coronary angiography to establish the presence of angiographically significant coronary artery disease. Evidence of ischemia in the form of an FFR measurement of 0.80 or less was required only in patients with moderate stenosis (50 to 69%), and only a small number of such patients were enrolled in the trial. Although it is possible that an FFR-based approach to guide nonculprit-lesion PCI could have reduced the number of PCI procedures among the patients included in the complete-revascularization group, it is unclear how this strategy might have influenced the effect on hard clinical outcomes. It is possible that angiographically significant lesions associated with an FFR measurement



Subgroup	First Coprimary Outcome				Second Coprimary Outcome			
	Complete revascularization	Culprit-lesion-only PCI	Hazard ratio (95% CI)	P value for interaction	Complete revascularization	Culprit-lesion-only PCI	Hazard ratio (95% CI)	P value for interaction
	no. of events/ total no. of patients (% per person-yr)				*no. of events/ total no. of patients (% per person-yr)*			
Overall	158/2016 (2.7)	213/2025 (3.7)	0.74 (0.60–0.91)		179/2016 (3.1)	339/2025 (6.2)	0.51 (0.43–0.61)	
Intended timing of nonculprit-lesion PCI				0.62				0.27
During index hospitalization	101/1353 (2.7)	130/1349 (3.5)	0.77 (0.59–1.00)		113/1353 (3.0)	227/1349 (6.6)	0.47 (0.38–0.59)	
After hospital discharge	57/663 (2.7)	83/676 (3.9)	0.69 (0.49–0.97)		66/663 (3.1)	112/676 (5.4)	0.59 (0.43–0.79)	
Nonculprit lesion involving proximal or middle left anterior descending artery				0.2				0.82
Presence	64/820 (2.7)	78/849 (3.1)	0.86 (0.62–1.20)		71/820 (3.0)	141/849 (6.0)	0.50 (0.38–0.67)	
Absence	87/1097 (2.7)	129/1085 (4.2)	0.65 (0.49–0.85)		97/1097 (3.0)	190/1085 (6.5)	0.48 (0.38–0.61)	
Nonculprit lesion with stenosis of ≥80% on visual estimation or ≥60% on laboratory assessment				0.03				0.01
Presence	127/1668 (2.6)	183/1631 (3.9)	0.67 (0.53–0.84)		143/1668 (3.0)	291/1631 (6.6)	0.46 (0.37–0.56)	
Absence	31/346 (3.2)	29/392 (2.6)	1.23 (0.74–2.04)		36/346 (3.8)	47/392 (4.4)	0.87 (0.56–1.34)	
Residual SYNTAX score				0.32				0.98
<6, lower than median score	60/885 (2.3)	90/870 (3.6)	0.65 (0.47–0.90)		69/885 (2.7)	133/870 (5.5)	0.49 (0.37–0.66)	
≥6, median score or higher	91/1033 (3.0)	117/1070 (3.8)	0.80 (0.61–1.05)		99/1033 (3.3)	198/1070 (6.9)	0.49 (0.39–0.63)	
Sex				0.08				0.07
Male	118/1623 (2.5)	171/1602 (3.7)	0.67 (0.53–0.85)		136/1623 (2.9)	274/1602 (6.3)	0.47 (0.38–0.57)	
Female	40/393 (3.6)	42/423 (3.5)	1.05 (0.68–1.61)		43/393 (3.9)	65/423 (5.7)	0.70 (0.48–1.03)	
Age				0.74				0.37
<65 yr	82/1233 (2.2)	109/1195 (3.1)	0.72 (0.54–0.96)		97/1233 (2.7)	189/1195 (5.7)	0.48 (0.37–0.61)	
≥65 yr	76/783 (3.5)	104/830 (4.5)	0.77 (0.58–1.04)		82/783 (3.8)	150/830 (6.8)	0.56 (0.43–0.74)	
Left ventricular ejection fraction				0.13				0.92
<45%	33/396 (2.7)	65/398 (5.6)	0.49 (0.32–0.74)		38/396 (3.2)	84/398 (7.7)	0.42 (0.29–0.62)	
≥45%	62/945 (2.2)	82/929 (3.0)	0.74 (0.53–1.03)		69/945 (2.5)	151/929 (5.9)	0.43 (0.32–0.57)	
Diabetes				0.35				0.27
Yes	46/385 (4.4)	57/402 (5.0)	0.87 (0.59–1.29)		49/385 (4.8)	84/402 (7.9)	0.61 (0.43–0.87)	
No	112/1631 (2.3)	156/1623 (3.3)	0.70 (0.55–0.89)		130/1631 (2.7)	255/1623 (5.7)	0.48 (0.39–0.60)	
Type of $P2Y_{12}$ inhibitor				0.62				0.68
Ticagrelor	90/1298 (2.3)	125/1281 (3.3)	0.70 (0.54–0.92)		99/1298 (2.6)	196/1281 (5.5)	0.48 (0.38–0.61)	
Prasugrel	13/192 (2.6)	11/169 (2.4)	1.07 (0.48–2.39)		18/192 (3.7)	25/169 (5.9)	0.63 (0.34–1.15)	
Clopidogrel	53/513 (3.6)	76/568 (4.8)	0.75 (0.53–1.07)		60/513 (4.1)	117/568 (7.9)	0.53 (0.39–0.73)	
Type of PCI				0.18				0.07
Primary PCI	148/1853 (2.7)	195/1885 (3.6)	0.77 (0.62–0.95)		168/1853 (3.2)	309/1885 (6.0)	0.53 (0.44–0.64)	
Pharmacoinvasive or rescue PCI	10/163 (2.1)	18/140 (4.7)	0.45 (0.21–0.97)		11/163 (2.3)	30/140 (8.5)	0.28 (0.14–0.56)	
Killip class				0.68				0.78
I	140/1855 (2.6)	186/1861 (3.5)	0.75 (0.60–0.93)		160/1855 (3.0)	302/1861 (6.0)	0.51 (0.42–0.62)	
≥II	16/141 (4.0)	23/136 (6.3)	0.65 (0.34–1.23)		17/141 (4.3)	32/136 (9.4)	0.47 (0.26–0.84)	
Type of stent				0.23				0.79
Polymer-free or biodegradable-polymer drug-eluting stent	8/136 (2.4)	14/145 (3.8)	0.62 (0.26–1.49)		10/136 (3.1)	21/145 (6.0)	0.50 (0.24–1.06)	
Durable-polymer drug-eluting stent	120/1568 (2.6)	146/1562 (3.2)	0.81 (0.64–1.03)		132/1568 (2.9)	241/1562 (5.6)	0.52 (0.42–0.65)	
Bare-metal stent	24/276 (2.7)	45/272 (5.5)	0.51 (0.31–0.84)		31/276 (3.6)	65/272 (8.4)	0.44 (0.29–0.68)	

0.1 0.2 0.5 1 2 5 10

Complete Revascularization Better — Culprit-Lesion-Only PCI Better

0.1 0.2 0.5 1 2 5 10

Complete Revascularization Better — Culprit-Lesion-Only PCI Better

of more than 0.80 may still contain morphologic features consistent with unstable plaques, which confer an increased risk of recurrent events. At least two trials involving patients with STEMI and multivessel coronary artery disease that evaluated an FFR-based approach to guide nonculprit-lesion PCI did not show a reduction in the risk of cardiovascular death or myocardial infarction, although neither trial was powered for this outcome.[16,17]

In the COMPLETE trial, randomization was stratified according to the intended timing of nonculprit-lesion PCI. Investigators had to specify before randomization whether they intended to perform nonculprit-lesion PCI during the index hospitalization or after hospital discharge (within 45 days) if the patient were to be assigned to the complete-revascularization group. We found a consistent benefit of complete revascularization regardless of whether nonculprit-lesion PCI was performed earlier, during the index hospitalization, or later, several weeks after discharge. During the early period after STEMI, events related to the index infarction and culprit-lesion PCI probably accounted for a substantial proportion of the events that occurred in both treatment groups. The benefit of complete revascularization seems to have emerged over the long term, with continued divergence of the Kaplan–Meier curves for several years.

Limitations of our trial should be considered. We did not evaluate nonculprit-lesion PCI that was performed during the same procedure as that for the index culprit-lesion PCI for STEMI. Although cardiogenic shock was not an exclusion criterion, no patients with cardiogenic shock were enrolled in the trial and the results should not be extrapolated to such patients. Complete revascularization was attained in more than 90% of the patients in the complete-revascularization group, and crossover to the nonculprit-lesion PCI strategy occurred in only 4.7% of the patients in the culprit-lesion-only PCI group. It is unclear whether the trial results would have been similar if complete revascularization had been observed in fewer patients or if the crossover criteria in the culprit-lesion-only PCI group had been more liberal.

In conclusion, the COMPLETE trial showed that, among patients with STEMI and multivessel coronary artery disease, a strategy of routine nonculprit-lesion PCI with the goal of complete revascularization, performed either during the index hospitalization or soon after discharge, was superior to a strategy of culprit-lesion-only PCI in reducing the risk of death from cardiovascular causes or new myocardial infarction, as well as the risk of death from cardiovascular causes, new myocardial infarction, or ischemia-driven revascularization, at a median follow-up of 3 years.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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8.2 Publication 2.

Nonculprit Lesion Plaque Morphology in Patients With ST-Segment–Elevation Myocardial Infarction. ***Results From the COMPLETE Trial Optical Coherence Tomography Substudy***

Circ Cardiovasc Interv. 2020 Jul;13(7):e008768. doi:10.1161/CIRCINTERVENTIONS.119.008768.

The COMPLETE- OCT is an imaging sub study of the COMPLETE trial. In a prospective design, optical coherence tomography of at least 2 coronary arteries before non-culprit lesion percutaneous coronary intervention was performed in 93 patients with ST-segment–elevation myocardial infarction and multivessel disease; and the ST-segment–elevation myocardial infarction culprit vessel if there was unstented segment amenable to imaging. Non-culprit lesions were categorized as obstructive (≥70% stenosis by visual angiographic assessment) or nonobstructive, and as thin-cap fibroatheroma (TCFA) or non-TCFA by optical coherence tomography criteria. TCFA was defined as a lesion with mean fibrous cap thickness <65 μm overlying a lipid arc >90°.

COMPLETE-OCT demonstrated that lipid plaque with TCFA morphology was commonly found in patients with STEMI and multivessel disease. Lesions that had >70% diameter stenosis by angiographic evaluation were more likely to be a TCFA than lesions that were <70% (35% vs. 23%). However, due to the larger number of <70% lesions present, the absolute number of TCFA with stenosis severity <70% was greater than those with stenosis severity >70% (74 vs. 58

TCFA lesions). PCI of >70% lesions in the COMPLETE trial reduced MI and death by 26%. Nevertheless, even in the complete revascularization arm, approximately 3/4ths of MIs were not prevented. It is likely that <70% stenoses contributed to many of these events.

COMPLETE-OCT concluded that among patients who underwent optical coherence tomography imaging in the COMPLETE trial, nearly 50% had at least one obstructive non-culprit lesion containing complex vulnerable plaque. Obstructive lesions more commonly harbored vulnerable plaque morphology than nonobstructive lesions. This may help explain the benefit of routine percutaneous coronary intervention of obstructive non-culprit lesions in patients with ST-segment–elevation myocardial infarction and multivessel disease.

Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Nonculprit Lesion Plaque Morphology in Patients With ST-Segment–Elevation Myocardial Infarction

Results From the COMPLETE Trial Optical Coherence Tomography Substudy

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BACKGROUND: Complete revascularization with routine percutaneous coronary intervention of nonculprit lesions after primary percutaneous coronary intervention improves outcomes in ST-segment–elevation myocardial infarction. Whether this benefit is associated with nonculprit lesion vulnerability is unknown.

METHODS: In a prospective substudy of the COMPLETE trial (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI), we performed optical coherence tomography of at least 2 coronary arteries before nonculprit lesion percutaneous coronary intervention in 93 patients with ST-segment–elevation myocardial infarction and multivessel disease; and the ST-segment–elevation myocardial infarction culprit vessel if there was unstented segment amenable to imaging. Nonculprit lesions were categorized as obstructive (≥70% stenosis by visual angiographic assessment) or nonobstructive, and as thin-cap fibroatheroma (TCFA) or non-TCFA by optical coherence tomography criteria. TCFA was defined as a lesion with mean fibrous cap thickness <65 μm overlying a lipid arc >90°.

RESULTS: On a patient level, at least one obstructive TCFA was observed in 44/93 (47%) of patients. On a lesion level, there were 58 TCFAs among 150 obstructive nonculprit lesions compared with 74 TCFAs among 275 nonculprit lesions (adjusted TCFA prevalence: 35.4% versus 23.2%, P=0.022). Compared with obstructive non-TCFAs, obstructive TCFAs had similar lesion length (23.1 versus 20.8 mm, P=0.16) but higher lipid quadrants (55.2 versus 19.2, P<0.001), greater mean lipid arc (203.8° versus 84.5°, P<0.001), and more macrophages (97.1% versus 54.4%, P<0.001) and cholesterol crystals (85.8% versus 44.3%, P<0.001). For nonobstructive lesions, TCFA lesions had similar lesion length (16.7 versus 14.6 mm, P=0.11), but more lipid quadrants (36.4 versus 13.5, P<0.001), and greater mean lipid arc (191.8° versus 84.2°, P<0.001) compared with non-TCFA.

CONCLUSIONS: Among patients who underwent optical coherence tomography imaging in the COMPLETE trial, nearly 50% had at least one obstructive nonculprit lesion containing complex vulnerable plaque. Obstructive lesions more commonly harbored vulnerable plaque morphology than nonobstructive lesions. This may help explain the benefit of routine percutaneous coronary intervention of obstructive nonculprit lesions in patients with ST-segment–elevation myocardial infarction and multivessel disease.

REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01740479.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: coronary artery disease ■ fibroatheroma ■ ST-segment–elevation myocardial infarction ■ tomography, optical coherence

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For Sources of Funding and Disclosures, see page 8.

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WHAT IS KNOWN

- The COMPLETE trial (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI) demonstrated that routine staged angiography-guided percutaneous coronary intervention of obstructive nonculprit lesions after ST-segment–elevation myocardial infarction reduced the composite of cardiovascular death or new myocardial infarction by about 26% (P=0.004).
- Thin-cap fibroatheroma is a well-recognized feature of vulnerable plaque and a precursor for plaque rupture.

WHAT THE STUDY ADDS

- Obstructive nonculprit lesions (>70% visual diameter stenosis) in ST-segment–elevation myocardial infarction population more commonly have increased lipid content and other plaque features of vulnerability compared with nonobstructive lesions.
- Almost half of patients undergoing multivessel optical coherence tomography imaging had at least one obstructive nonculprit lesion containing vulnerable plaque morphology.
- This may help explain the benefit of routine percutaneous coronary intervention of obstructive nonculprit lesions in patients with ST-segment–elevation myocardial infarction and multivessel disease.

Nonstandard Abbreviations and Acronyms

FCT	fibrous cap thickness
FFR	fractional flow reserve
IVUS	intravascular ultrasound
LDL	low-density lipoprotein
MLA	minimum lumen area
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
STEMI	ST-segment–elevation myocardial infarction
TCFA	thin-cap fibroatheroma

The COMPLETE trial (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI) demonstrated that a strategy of complete revascularization with routine nonculprit lesion percutaneous coronary intervention (PCI) reduced the composite of cardiovascular death or new myocardial infarction (MI) by 26% (P=0.004) at 3 years, compared with a strategy of PCI of the culprit lesion only.[1,2] Approximately 50% of patients presenting with ST-segment–elevation myocardial infarction (STEMI) have multivessel disease, with lesions in nonculprit vessels, in addition to the culprit lesion.[3–5] Whether the benefit of complete revascularization is due to PCI of lesions with morphological features consistent with unstable plaques, which confer an increased risk of future cardiovascular events, is unknown.

Optical coherence tomography (OCT) is an intracoronary imaging modality that can identify thin-cap fibroatheroma (TCFA), the primary morphology defining a vulnerable plaque.[6] In this prospective substudy of the COMPLETE trial, we sought to determine the prevalence of TCFA by OCT in obstructive and nonobstructive nonculprit lesions among patients randomized to nonculprit lesion PCI in the COMPLETE trial.

METHODS

The COMPLETE trial enrolled 4041 patients with STEMI who had successful PCI of the culprit lesion and one or more nonculprit lesions with either ≥70% angiographic severity or, in a small minority, 50% to 69% angiographic severity associated with fractional flow reserve (FFR) ≤0.80. COMPLETE-OCT was an observational intravascular imaging substudy of the main trial, conducted at 6 centers in Canada between January 18, 2016, to November 20, 2017. Patients randomized to the complete revascularization arm were eligible for the study if they had a target nonculprit lesion suitable for OCT imaging, plus at least one additional coronary artery amenable for OCT imaging with or without an angiographically significant lesion.

The substudy was designed by the principal investigators and funded by Hamilton Health Sciences, Population Health Research Institute and Abbott Vascular. It was approved by the local human research ethics committees of the recruiting hospitals. Informed consent was provided by all patients enrolled. The data, analytic methods, and study materials are proprietary to the Population Health Research Institute and at this time are not available to nonstudy participants.

A suitable artery for OCT imaging was defined as a vessel with >2 mm in diameter with at least 50 mm of unstented native artery available for image evaluation. Arteries unsuitable for imaging were those in which passage of the OCT catheter was unlikely to be successful due to either severe calcification (multiple persisting opacifications of the coronary wall visible in >1 projection surrounding the complete lumen of the coronary artery proximal to or at the site of the lesion) or marked tortuosity (defined as one or more bends of 90° or more, or 3 or more bends of 45° to 90°), or chronic total occlusions. Patients with an estimated glomerular filtration rate <35 mL/min per 1.73 m^2 were excluded.

OCT Procedure

Dragonfly Duo and Dragonfly Optis imaging catheters, and Optis Mobile System (Abbott Vascular, Westford, MA) were used. During PCI, a guidewire was advanced, and the radiopaque distal marker of the OCT catheter was positioned distally in the vessel and, while flushing with intracoronary contrast, 54 or 75 mm automatic pullback was recorded depending on the available catheter technology. If the OCT catheter was unable to traverse the nonculprit lesion, balloon dilatation was allowed with a maximum 2.0 mm diameter compliant balloon up to 10 atms. The same procedure was followed for the second and third coronary arteries if applicable.

OCT Image Analysis

An OCT core laboratory (Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada) performed the OCT image analysis. Two experienced intravascular imaging investigators (Drs Pinilla-Echeverri and Sheth) analyzed the OCT raw data using Offline Review Workstation software version E.4.1 (Abbott Vascular).

A lesion was quantitatively defined by any cross-sectional frame containing ≥1 diseased quadrant. In diffuse diseased segments, lesions separated by at least a single frame with ≥3 quadrants of normal 3-layer artery appearance without any lipid quadrants were considered distinct lesions. Plaque composition was analyzed in each quadrant at 1 mm intervals throughout the lesion. Plaques were classified as lipidic, fibrous, or calcific using standard definitions.[5] Lesion length was defined as the number of contiguous millimeters with >1 diseased quadrant. The minimum lumen area (MLA) was defined as the tightest area along the lesion and was automatically calculated from the lumen profile tool on the OCT review software. Fibrous cap thickness (FCT) was measured at its thinnest part in 3 different cross-sectional images, and the average value was calculated; importantly, in cases with predilatation, measurements were performed in images without disruption of the fibrous cap. Lipid arc was measured at every 1 mm interval throughout the lesion, and the average value was calculated.

Qualitative analysis was performed as per standard definitions.[5] TCFA was defined as a lesion with a mean FCT <65 µm overlying a lipidic plaque (lipid arc >90°). Microvessels were characterized by a black hole or tubular structure within a lesion with a diameter of 50 to 300 µm that was seen on at least 3 consecutive frames. Macrophage accumulation was characterized by increased signal intensity within the lesion, accompanied by heterogeneous backward shadows. Cholesterol crystals were characterized by the presence of linear and highly reflecting structures within the lesion.

Obstructive lesions were defined as those with >70% diameter stenosis by visual estimation of the site. Any lesion that was not identified as >70% by visual estimation was considered nonobstructive. Combining angiographic stenosis severity and TCFA criteria by OCT, lesions were classified into 4 groups: obstructive TCFA, obstructive non-TCFA, nonobstructive TCFA, and nonobstructive non-TCFA.

Outcomes

The primary outcome was the comparative prevalence of TCFA in obstructive and nonobstructive nonculprit lesions. Other complex lesion features (lipid content, macrophages, microvessels, and cholesterol crystals) were identified.

Statistical Analysis

Baseline and procedural characteristics were reported as mean/SD for continuous variables and proportion of prevalence for categorical variables. To account for the potential underlying correlation among multiple lesions in the same patient, the primary outcome was analyzed using a logistic mixed-effects model with patient as a random effect. Imaging findings were analyzed using a linear mixed model for continuous variables, a negative binomial mixed model for count variables and a logistic mixed model for categorical variables. All the reported means with 95% CI for continuous/count variables and prevalence for categorical variables were adjusted for multiple lesions per patient. Continuous variables that violated the normality assumption based on residual analysis were transformed to achieve normality, and the adjusted means were thereafter back-transformed to the original scale. The intraclass (patient) correlation coefficient, which evaluates the correlation among lesions within the same patient, was reported for each imaging parameter except for count variables as there is no generally accepted method for calculating intraclass (patient) correlation coefficient in a negative binomial mixed model. Statistical analyses were conducted with the use of SAS 9.4 software (SAS Institute, Inc, Cary, NC). All *P* values were 2-sided with significance level at $P<0.05$. Considering the exploratory nature of the study, we did not adjust for multiple comparisons.

RESULTS

A total of 129 patients were screened for the COMPLETE-OCT substudy during the recruitment period, 25 patients were ineligible, and 5 eligible patients did not have OCT imaging performed. Of the 99 patients that underwent OCT imaging, 6 had nonassessable morphology of the nonculprit lesions randomized to PCI due to either inadequate blood clearance (n=5) or significant disruption of the underlying plaque (n=1). Overall, 93 patients had diagnostic OCT images that were included in the analysis. Patient baseline characteristics are shown in Table 1, and PCI data are shown in Table 2. Reasons for patient exclusion from recruitment and analysis (Table I in the Data Supplement); baseline (Table II in the Data Supplement) and procedure characteristics (Table III in the Data Supplement) in patients undergoing OCT compared with those without OCT imaging in the complete revascularization arm are shown in Appendix in the Data Supplement.

Staged nonculprit lesion PCI in the COMPLETE-OCT substudy was performed with a mean timing of 2.9±4.8 days from index culprit lesion PCI. OCT imaging was performed in at least 2 vessels in all patients, with mean of 2.82±0.95 OCT pullbacks per patient. Mean unstented coronary length

Table 1. Patient Baseline Characteristics

	All (N=93)
Age (y), mean±SD	61.2±10.0
Sex (male), n (%)	77 (82.8)
Diabetes mellitus, n (%)	12 (12.9)
Chronic renal insufficiency, n (%)	1 (1.1)
Prior myocardial infarction, n (%)	8 (8.6)
Current smoker, n/total number (%)	35/91 (38.5)
Hypertension, n (%)	39 (41.9)
Dyslipidemia, n (%)	40 (43.0)
Prior stroke, n (%)	1 (1.1)
Body mass index, kg/m^2, mean±SD	29.8±5.8
Hemoglobin A1C (%), median (IQR)	5.7 (5.4–6.2)
LDL cholesterol, mmol/L, mean±SD	2.9±1.0
Peak creatinine, µmol/L, mean±SD	82.0±18.0

LDL indicates low-density lipoprotein.

Table 2. Procedure Characteristics

	All (N=93)
Radial access, n (%)	86 (92.5)
No. of residual diseased vessels (core lab), n/total number (%)	
1	55/86 (64.0)
≥2	31/86 (36.0)
Nonculprit lesion location (core lab), n/total lesions (%)	
Left main	0 (0.0)
LAD	55/134 (41.0)
Proximal LAD	14/134 (10.4)
Mid LAD	33/134 (24.6)
Apical LAD	2/134 (1.5)
Diagonals	6/134 (4.5)
Circumflex	43/134 (32.1)
Prox LCX and OM/ramus	31/134 (23.1)
Distal LCX and PLV	12/134 (9.0)
RCA	36/134 (26.9)
RCA before the Crux	34/134 (25.4)
RCA beyond the Crux	2/134 (1.5)
Nonculprit lesion diameter stenosis (visual), n/total lesions (%)	
70%–79%	50/123 (40.7)
80%–89%	39/123 (31.7)
90%–99%	33/123 (26.8)
100%	1/123 (0.8)
Nonculprit lesion diameter stenosis (visual), mean±SD	79.3±8.4
Nonculprit lesion reference diameter (core lab), mean±SD	2.8±0.4

LAD indicates left anterior descending; LCX, left circumflex artery; OM, obtuse marginal; PLV, posterior left ventricular; and RCA, right coronary artery.

imaged per patient was 152.5±53.9 mm. Balloon dilatation was performed before OCT intracoronary imaging in 7 obstructive TCFA lesions (12.1%) and 21 obstructive non-TCFA lesions (22.8%). A sensitivity analysis that excluded all predilated lesions demonstrated similar results, with no heterogeneity (Table IV in the Data Supplement).

Primary Outcome

For the primary outcome of TCFA frequency in obstructive and nonobstructive nonculprit lesions, there were 58 TCFAs among 150 obstructive nonculprit lesions compared with 74 TCFAs among 275 nonobstructive lesions (adjusted TCFA prevalence: 35.4% versus 23.2%, P=0.022; Figure 1).

Obstructive Lesions

Obstructive TCFA and obstructive non-TCFA had similar lesion length (23.1 versus 20.8 mm, P=0.16) and MLA (1.9 versus 1.7 mm^2, P=0.52); however, obstructive TCFA lesions had a higher number of lipid quadrants (55.2 versus 19.2, P<0.001) and greater mean lipid arc (203.8° versus 84.5°,

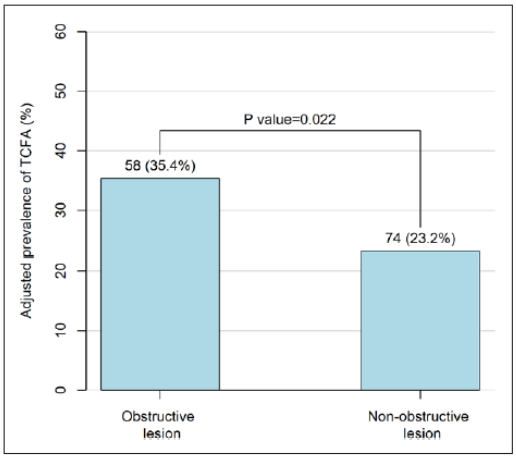

Figure 1. Adjusted* prevalence of thin-cap fibroatheroma (TCFA) in obstructive and nonobstructive lesions.
TCFA frequency in obstructive and nonobstructive nonculprit lesions. Fifty-eight TCFAs were detected among 150 obstructive nonculprit lesions compared with 74 TCFAs among 275 nonobstructive lesions (adjusted TCFA prevalence: 35.4% vs 23.2%, P=0.022).
*Prevalence of TCFA was adjusted for multiple lesions per patient using logistic mixed-effects model.

P<0.001) compared with obstructive non-TCFA lesions which were predominantly fibrotic and calcific in composition (Table 3). Obstructive TCFA lesions also showed lower mean FCT (54.5 versus 152.2 µm, P<0.001) and higher frequencies of macrophages (97.1% versus 54.4%, P<0.001) and cholesterol crystals (85.8% versus 44.3%, P<0.001) compared with the obstructive non-TCFA. A scatterplot of number of lipid quadrants by MLA for obstructive TCFA and non-TCFA lesions is shown in Figure 2. An MLA>2 mm^2 was observed in 31% of the obstructive TCFA lesions and 25% of obstructive non-TCFA lesions.

Nonobstructive Lesions

There were 275 nonobstructive lesions of which 74 (27%) were nonobstructive TCFA and 201 (73%) were nonobstructive non-TCFA lesions. These lesions showed similar lesion lengths (16.7 versus 14.6 mm, P=0.11) that were shorter than obstructive lesions. Nonobstructive TCFA had a higher number of lipid quadrants (36.4 versus 13.5, P<0.001) and greater mean lipid arc (191.8° versus 84.2°, P<0.001) compared with nonobstructive non-TCFA lesions.

TCFA Lesions

Obstructive TCFA and nonobstructive TCFA lesions had similar percentage of lipidic (78.4% versus 76.8%, P=0.73), fibrotic (16.9% versus 16.2%, P=0.88) and calcific (4.1% versus 7%, P=0.39) plaque, similar mean FCT (54.5 versus 54.5 µm, P=0.98) and mean lipid arc

Table 3. OCT Imaging Findings by Lesions

					P Value for Pairwise Comparison			
	Group 1: Obstructive TCFA (N=58)	Group 2: Nonobstructive TCFA (N=74)	Group 3: Obstructive Non-TCFA (N=92)	Group 4: Nonobstructive Non-TCFA (N=201)	Group 1 vs 2	Group 1 vs 3	Group 2 vs 4	ICC
	Adjusted mean (95% CI)	Adjusted mean (95% CI)	Adjusted mean (95% CI)	Adjusted mean (95% CI)				
Lesion length, mm	23.1 (20.4–25.7)	16.7 (14.2–19.1)	20.8 (18.7–22.9)	14.6 (12.9–16.3)	<0.001	0.16	0.11	0.242
Plaque type by quadrant								
Lipid								
No. of quadrants	55.2 (39.9–76.2)	36.4 (27.2–48.7)	19.2 (14.8–25.0)	13.5 (11.1–16.4)	0.05	<0.001	<0.001	...
% of quadrants	78.4 (70.6–86.2)	76.8 (69.6–83.9)	36.5 (30.2–42.9)	35.8 (30.8–40.8)	0.73	<0.001	<0.001	0.254
Fibrous								
No. of quadrants	9.4 (7.2–12.1)	7.1 (5.6–9.0)	21.2 (17.3–26.0)	14.2 (12.1–16.6)	0.10	<0.001	<0.001	...
% of quadrants	16.9 (9.6–24.3)	16.2 (9.5–22.9)	43.7 (37.8–49.6)	45.5 (41.0–50.1)	0.88	<0.001	<0.001	0.180
Calcified								
No. of quadrants	2.5 (1.5–4.3)	1.7 (1.0–2.8)	9.8 (6.4–15.0)	5.4 (3.8–7.6)	0.26	<0.001	<0.001	...
% of quadrants	4.1 (0.0–9.5)	7.0 (2.0–12.0)	20.1 (15.7–24.6)	19.0 (15.4–22.5)	0.39	<0.001	<0.001	0.257
Maximum lipid arc	342.2 (312.0–372.3)	304.0 (276.6–331.4)	212.5 (188.4–236.6)	170.2 (152.5–188.0)	0.06	<0.001	<0.001	0.101
Mean lipid arc	203.8 (183.9–223.7)	191.8 (173.5–210.0)	84.5 (68.4–100.5)	84.2 (71.8–96.6)	0.34	<0.001	<0.001	0.191
Mean FCT, µm	54.5 (51.3–57.9)	54.5 (51.6–57.6)	152.2 (141.0–164.3)	143.9 (136.6–151.6)	0.98	<0.001	<0.001	0.098
Minimum lumen area	1.9 (1.4–2.4)	4.8 (4.4–5.2)	1.7 (1.3–2.1)	4.1 (3.9–4.4)	<0.001	0.52	0.009	0.017
	Event no. (adjusted prevalence [%])	Event no. (adjusted prevalence [%])	Event no. (adjusted prevalence [%])	Event no. (adjusted prevalence [%])				
Macrophages	55 (97.1)	65 (93.7)	48 (54.4)	93 (47.8)	0.28	<0.001	<0.001	0.325
Microvessels	19 (32.0)	23 (30.6)	28 (29.8)	44 (21.4)	0.86	0.77	0.12	0.032
Cholesterol crystals	48 (85.8)	29 (37.6)	42 (44.3)	58 (25.8)	<0.001	<0.001	0.09	0.149

FCT indicates fibrous cap thickness; ICC, intraclass (patient) correlation coefficient; OCT, optical coherence tomography; and TCFA, thin-cap fibroatheroma.

(203.8° versus 191.8°, *P*=0.34). However, obstructive TCFA lesions were longer (23.1 versus 16.7 mm, *P*<0.001) and had a smaller mean MLA (1.9 versus 4.8 mm^2, *P*<0.001).

On a per-patient basis, obstructive TCFA with or without nonobstructive TCFA was observed in 47.3% of patients, nonobstructive TCFA only in 20.4%, and no TCFA in 32.3% (Figure 3). Baseline characteristics between patients who had at least 1 TCFA and patients with no TCFA are shown in Table V in the Data Supplement. Levels of LDL (low-density lipoprotein) cholesterol were significantly higher in patients with at least 1 TCFA versus patients with no TCFA (3.1 versus 2.5 mmol/L, *P*=0.025).

Examples illustrating the 4 plaque types are shown in Figure 4.

DISCUSSION

In this prospective OCT substudy, we evaluated nonculprit lesions in patients after STEMI who were randomized to nonculprit lesion PCI in the COMPLETE trial and demonstrated that[1] obstructive lesions more commonly contained vulnerable plaque morphology compared with nonobstructive lesions,[2] obstructive TCFAs had increased lipid content and other plaque features of vulnerability compared with obstructive non-TCFA lesions[3] obstructive TCFAs in these STEMI patients with multivessel disease were common, with about 47% of patients having at least one obstructive nonculprit lesion TCFA.

Obstructive TCFA lesions demonstrated extensive lipid infiltration, small MLA, and vulnerable plaque features. Such lesions may carry a high risk of subsequent cardiovascular events. In the PROSPECT study (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), the risk of future cardiac events associated with TCFA was 3.35-fold higher than non-TCFA lesions.[7] Similarly, in the ATHEROREMO-IVUS (The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis - Intravascular Ultrasound) study risk of future cardiac events was 2.51-fold higher when virtual histology-intravascular ultrasound (IVUS) derived TCFA was detected.[8] Recently, the lipid-rich plaque study showed the ability to predict future nonculprit segment related major adverse cardiovascular events by detecting vulnerable plaque with near-infrared spectroscopy-IVUS.[9] Increased plaque lipid content on OCT is a predictor of nonculprit lesion progression with a predicted rate of events that is 3 times that of nonlipid

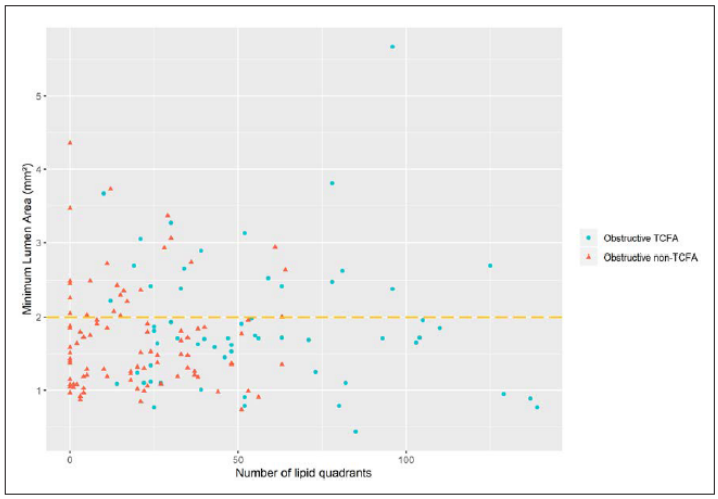

Figure 2. Scatter plot of minimum lumen area vs number of lipid quadrants for obstructive thin-cap fibroatheroma (TCFA; blue) and obstructive non-TCFA (orange). Number of lipid quadrants by minimum lumen area (MLA) for obstructive TCFA and non-TCFA lesions. An MLA>2 mm² was seen in 31% of obstructive TCFA and 25% of obstructive non-TCFA lesions.

rich plaques.[10] Macrophages and cholesterol crystals are OCT detected features of plaque instability.[10–13] Consistent with prior reports,[11,12] we found these lesion characteristics more commonly in obstructive TCFA compared with obstructive non-TCFA lesions.

TCFA is as a precursor lesion for plaque rupture.[13] Optimal medical therapy with high-intensity statin improves clinical outcomes in patients with coronary atherosclerosis and induces plaque level changes detectable by imaging.[14] A meta-analysis by Ozaki et al[15] showed that statin therapy induced a significant increase in FCT as assessed by OCT. A recent multimodality imaging study in noninfarct related arteries in the STEMI population found a significant increase in minimum FCT, reduction in macrophage accumulation, and frequent regression of TCFAs to other plaque phenotypes in nonculprit lesions of patients with STEMI treated with high-intensity statin therapy.[16]

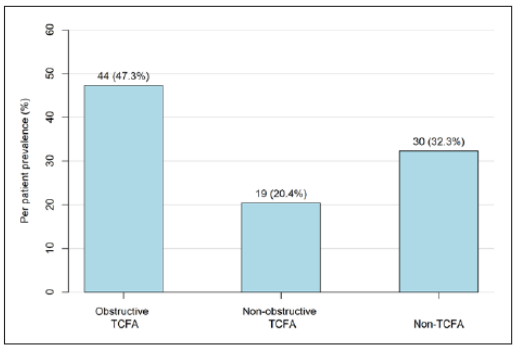

Figure 3. Per-patient prevalence of thin-cap fibroatheroma (TCFA).
Lesions were ranked from high risk to low risk as obstructive TCFA>nonobstructive TCFA>no TCFA, and each patient was classified into one of these 3 categories based on highest-risk lesion. Obstructive TCFA with or without nonobstructive TCFA was seen in 47.3% of patients, nonobstructive TCFA only in 20.4%, and no TCFA in 32.3%.

Recently, we have demonstrated in the COMPLETE trial that angiography-guided PCI of nonculprit lesions was associated with a reduction in subsequent cardiovascular events. Most patients in the COMPLETE trial, including those in this substudy, did not have FFR evaluation of the nonculprit lesion. We observed an MLA of >2 mm² in 31% of obstructive TCFA lesions, a value that often represents FFR negative lesions.[17,18] In FFR-guided nonculprit lesion PCI, 30% to 45% of lesions identified as obstructive on angiography are deferred after FFR.[19,20] Therefore, it is possible that an FFR-guided nonculprit lesion PCI strategy would lead to deferral of lesions that, despite being FFR negative, still have high-risk morphological features for future cardiovascular events. To the extent that future events are driven by plaque vulnerability, the potential benefit of an FFR-guided strategy may be attenuated by deferring intervention on such lesions. The recently published FORZA study (Fractional Flow Reserve or Optical Coherence Tomography Guidance to Revascularize Intermediate Coronary Stenosis Using Angioplasty), recruited patients with angiographically intermediate coronary lesions to undergo either FFR or OCT-guided PCI and showed that OCT guidance was associated with lower composite of major adverse cardiac events or significant angina at 13 months follow-up and FFR-guidance was associated with higher rate of deferred PCI and medical management.[21]

Nonobstructive TCFAs were more numerous than obstructive TCFAs but had fewer features of lesion complexity. This finding is consistent with prior observations that TCFAs with <70% stenosis are more frequent than TCFAs with >70% stenosis but have lower plaque burden by IVUS and fewer features of plaque vulnerability by OCT.[22] The small plaque burden of nonobstructive TCFAs

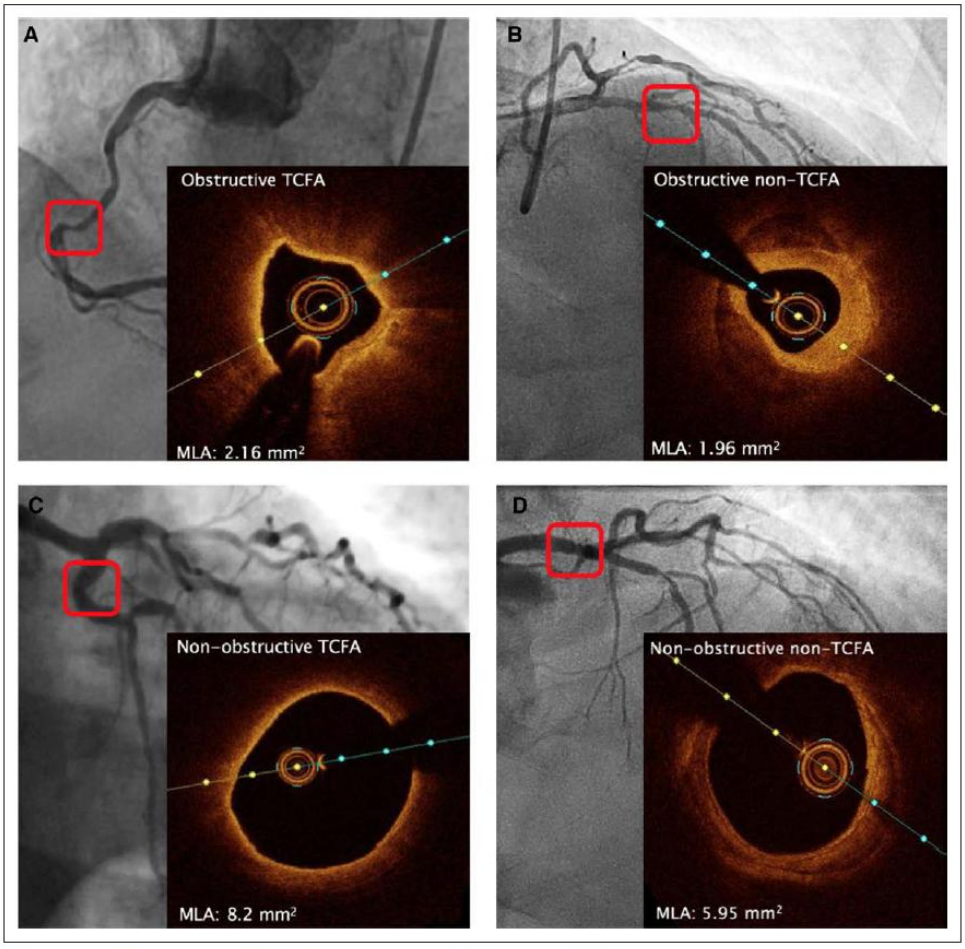

Figure 4. Representative angiographic and optical coherence tomography (OCT) images.
A, Obstructive thin-cap fibroatheroma (TCFA); mid right coronary artery, minimum lumen area (MLA) 2.16 mm², circumferential lipid, macrophages, and cholesterol crystals. **B**, Obstructive non-TCFA; mid left anterior descending, MLA 1.96 mm², fibrotic and deep calcific plaque. **C**, Non-obstructive TCFA; proximal left circumflex artery, MLA 8.2 mm², lipidic plaque with superficial calcification. **D**, Non-obstructive non-TCFA; left main, MLA 5.95 mm², circumferential calcium.

is associated with recurrent cardiac events only over the long-term, whereas short-term events (<6 months) are predicted by the presence of large plaque TCFA burden.[8] There are 2 ongoing randomized studies of optimal medical therapy alone versus PCI examining if preventive coronary intervention on functionally insignificant vulnerable coronary stenosis can reduce the incidence of the future major adverse cardiovascular events: PROSPECT II and PROSPECT ABSORB (A Multicenter Prospective Natural History Study Using Multimodality Imaging in Patients With Acute Coronary Syndromes - PROSPECT II [Natural History Study] Combined With a Randomized, Controlled, Intervention Study; URL: https://www.clinicaltrials.gov. Unique identifier: NCT02171065) using imaging with near-infrared spectroscopy-IVUS; and PREVENT (The Preventive Coronary Intervention on Stenosis With Functionally Insignificant Stenosis With Vulnerable Plaque Characteristics; URL: https://www.clinicaltrials.gov. Unique identifier: NCT02316886) using multimodality imaging (near-infrared spectroscopy, OCT, virtual histology-IVUS, and IVUS).

At least one nonculprit obstructive TCFA was found in 47% of patients in the COMPLETE-OCT substudy. This finding is consistent with other studies, highlighting the increased frequency of additional vulnerable plaques in acute coronary syndrome compared with stable angina patients.[23] The reduction of future events observed with complete revascularization in the COMPLETE trial

suggests that nonculprit lesion PCI may effectively pacify these lesions.

Limitations

OCT was performed in a subset of patients randomized to complete revascularization in the COMPLETE trial. The findings apply to this subgroup of patients and may not be generalizable to all patients with STEMI and multivessel disease. The COMPLETE-OCT substudy was observational and designed to better understand nonculprit lesion plaque morphology, it was not powered to link clinical events to plaque morphology. The requirement for angiographically suitable arteries for OCT imaging may have excluded certain plaque types; however, angiographic severity was similar to the lesions of patients in overall trial. A very small proportion of OCT acquisitions could not be interpreted due to inadequate blood clearance, a known limitation of OCT imaging. To optimize blood clearance, predilation was required in some severely stenosed obstructive lesions; because OCT imaging was performed only after angioplasty in these lesions, the MLA may have been overestimated in these cases. However, in a sensitivity analysis that excluded all predilated lesions, the results were similar to the overall data, with no heterogeneity.

Conclusions

Among patients who underwent OCT imaging in the COMPLETE trial, nearly 50% had at least one obstructive nonculprit lesion containing complex vulnerable plaque morphology. Obstructive lesions more commonly harbored vulnerable plaque morphology than nonobstructive lesions. This may help explain the benefit of routine PCI of obstructive nonculprit lesions in patients with STEMI and multivessel disease.

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Disclosures

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8.3 Publication 3.

Nonculprit Lesion Severity and Outcome of Revascularization in Patients With STEMI and Multivessel Coronary Disease

J Am Coll Cardiol. 2020 Sep 15;76(11):1277-1286. doi: 10.1016/j.jacc.2020.07.034.

In the COMPLETE (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) trial, angiography-guided percutaneous coronary intervention of non-culprit lesions with the aim of complete revascularization reduced major cardiovascular events in patients with ST-segment elevation myocardial infarction and multivessel coronary artery disease. The purpose of this specific analysis was to determine the effect of non-culprit lesion stenosis severity measured by quantitative coronary angiography on the benefit of complete revascularization.

Among 4.041 patients randomized in the COMPLETE trial, non-culprit lesion stenosis severity was measured using QCA in the angiographic core laboratory in 3,851 patients with 5,355 non-culprit lesions. In pre-specified analyses, the treatment effect in patients with QCA stenosis ≥60% versus <60% on the first coprimary outcome of CV death or new MI and the second co-primary outcome of CV death, new MI, or ischemia-driven revascularization was determined.

The first coprimary outcome was reduced with complete revascularization in the 2,479 patients with QCA stenosis ≥60% (2.5%/year vs. 4.2%/year; hazard ratio [HR]: 0.61; 95% confidence

interval [CI]: 0.47 to 0.79), but not in the 1,372 patients with QCA stenosis <60% (3.0%/year vs. 2.9%/year; HR: 1.04; 95% CI: 0.72 to 1.50; interaction p ¼ 0.02). The second coprimary outcome was reduced in patients with QCA stenosis ≥60% (2.9%/year vs. 6.9%/year; HR: 0.43; 95% CI: 0.34 to 0.54) to a greater extent than patients with QCA stenosis <60% (3.3%/year vs. 5.2%/year; HR: 0.65; 95% CI: 0.47 to 0.89; interaction p ¼ 0.04).

This analysis concluded that among patients with ST-segment elevation MI and multivessel coronary artery disease, complete revascularization reduced major CV outcomes to a greater extent in patients with stenosis severity of ≥60% compared with <60%, as determined by quantitative coronary angiography.

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ORIGINAL INVESTIGATIONS

Nonculprit Lesion Severity and Outcome of Revascularization in Patients With STEMI and Multivessel Coronary Disease

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ABSTRACT

BACKGROUND In the COMPLETE (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) trial, angiography-guided percutaneous coronary intervention (PCI) of nonculprit lesions with the aim of complete revascularization reduced major cardiovascular (CV) events in patients with ST-segment elevation myocardial infarction (MI) and multivessel coronary artery disease.

OBJECTIVES The purpose of this study was to determine the effect of nonculprit-lesion stenosis severity measured by quantitative coronary angiography (QCA) on the benefit of complete revascularization.

METHODS Among 4,041 patients randomized in the COMPLETE trial, nonculprit lesion stenosis severity was measured using QCA in the angiographic core laboratory in 3,851 patients with 5,355 nonculprit lesions. In pre-specified analyses, the treatment effect in patients with QCA stenosis ≥60% versus <60% on the first coprimary outcome of CV death or new MI and the second co-primary outcome of CV death, new MI, or ischemia-driven revascularization was determined.

RESULTS The first coprimary outcome was reduced with complete revascularization in the 2,479 patients with QCA stenosis ≥60% (2.5%/year vs. 4.2%/year; hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.47 to 0.79), but not in the 1,372 patients with QCA stenosis <60% (3.0%/year vs. 2.9%/year; HR: 1.04; 95% CI: 0.72 to 1.50; interaction p = 0.02). The second coprimary outcome was reduced in patients with QCA stenosis ≥60% (2.9%/year vs. 6.9%/year; HR: 0.43; 95% CI: 0.34 to 0.54) to a greater extent than patients with QCA stenosis <60% (3.3%/year vs. 5.2%/year; HR: 0.65; 95% CI: 0.47 to 0.89; interaction p = 0.04).

CONCLUSIONS Among patients with ST-segment elevation MI and multivessel coronary artery disease, complete revascularization reduced major CV outcomes to a greater extent in patients with stenosis severity of ≥60% compared with <60%, as determined by quantitative coronary angiography. (J Am Coll Cardiol 2020;76:1277–86)

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CV = cardiovascular

FFR = fractional flow reserve

IDR = ischemia-driven revascularization

MI = myocardial infarction

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiography

STEMI = ST-segment elevation myocardial infarction

Among patients with ST-segment elevation myocardial infarction (STEMI), approximately 30% to 50% have multivessel coronary artery disease with additional angiographically significant nonculprit lesions remote from the culprit lesion (1). Recently, the COMPLETE (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) randomized trial demonstrated that routine angiography-guided percutaneous coronary intervention (PCI) of nonculprit lesions with visual stenosis ≥70% reduced the composite of cardiovascular (CV) death or new myocardial infarction (MI) by 26%, compared with PCI confined to culprit lesions only (2). Although visual estimation of stenosis severity is practical at the point of care, prior studies have established quantitative coronary angiography (QCA) performed in a core laboratory as the gold standard for assessment of diameter stenosis severity (3). Visual evaluation tends to overestimate diameter stenosis compared with QCA for moderate-to-severe lesions (4); QCA values typically range from 50% to 70% for visually estimated stenoses of ≥70%. For the present analysis of data from the COMPLETE trial, we pre-specified a cutpoint of 60% stenosis by QCA to identify subgroups with severe versus moderate stenoses. The objective was to evaluate the effect of QCA stenosis severity (≥60% vs. <60%) on the comparison of complete revascularization versus culprit-lesion-only PCI with respect to the coprimary outcomes of: 1) CV death or MI; and 2) CV death, MI, or ischemia-driven revascularization (IDR).

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METHODS

COMPLETE was a multinational, randomized trial that evaluated a strategy of complete revascularization (PCI of all suitable nonculprit lesions) compared with a strategy of culprit-only PCI in patients with STEMI and multivessel coronary artery disease. The study design and main results have been previously published (2,5). Briefly, following PCI of the culprit

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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TABLE 1 Baseline Characteristics According to QCA Severity

	QCA ≥60%			QCA <60%			
	All (N = 2,479)	Complete (n = 1,238)	Culprit-Only (n = 1,241)	All (N = 1,372)	Complete (n = 679)	Culprit-Only (n = 693)	p Value*
Age, yrs	62.1 ± 10.8	61.5 ± 10.8	62.6 ± 10.8	61.8 ± 10.5	61.9 ± 10.5	61.8 ± 10.4	0.47
Male	1,964 (79.2)	994 (80.3)	970 (78.2)	1,109 (80.8)	550 (81.0)	559 (80.7)	0.23
Diabetes	487 (19.6)	234 (18.9)	253 (20.4)	247 (18.0)	118 (17.4)	129 (18.6)	0.21
Chronic renal insufficiency	50/2,301 (2.2)	22/1,152 (1.9)	28/1,149 (2.4)	25/1,302 (1.9)	12/639 (1.9)	13/663 (2.0)	0.61
Prior myocardial infarction	195 (7.9)	95 (7.7)	100 (8.1)	94 (6.9)	45 (6.6)	49 (7.1)	0.25
Current smoker	931 (37.6)	485 (39.2)	446 (35.9)	594 (43.3)	289 (42.6)	305 (44.0)	<0.001
Hypertension	1,267 (51.1)	621 (50.2)	646 (52.1)	635 (46.3)	311 (45.8)	324 (46.8)	0.004
Dyslipidemia	1,020 (41.1)	509 (41.1)	511 (41.2)	483 (35.2)	221 (32.5)	262 (37.8)	<0.001
Prior PCI	179 (7.2)	91 (7.4)	88 (7.1)	94 (6.9)	46 (6.8)	48 (6.9)	0.67
Prior stroke	87 (3.5)	42 (3.4)	45 (3.6)	37 (2.7)	21 (3.1)	16 (2.3)	0.17
Body mass index, kg/m^2	28.6 ± 5.7	28.8 ± 6.4	28.3 ± 4.9	27.9 ± 4.9	28.0 ± 5.0	27.9 ± 4.8	<0.001
Time from symptom onset to primary PCI							0.10
<6 h	1,665/2,447 (68.0)	855/1,222 (70.0)	810/1,225 (66.1)	957/1,361 (70.3)	476/676 (70.4)	481/685 (70.2)	
6 to 12 h	401/2,447 (16.4)	187/1,222 (15.3)	214/1,225 (17.5)	227/1,361 (16.7)	113/676 (16.7)	114/685 (16.6)	
>12 h	381/2,447 (15.6)	180/1,222 (14.7)	201/1,225 (16.4)	177/1,361 (13.0)	87/676 (12.9)	90/685 (13.1)	
Killip class ≥2	260/2,445 (10.6)	132/1,224 (10.8)	128/1,221 (10.5)	144/1,356 (10.6)	69/672 (10.3)	75/684 (11.0)	0.99
Medications at discharge							
ASA	2,472 (99.7)	1,237 (99.9)	1,235 (99.5)	1,367 (99.6)	677 (99.7)	690 (99.6)	0.76
$P2Y_{12}$ inhibitor (any)	2,469 (99.6)	1,232 (99.5)	1,237 (99.7)	1,367 (99.6)	675 (99.4)	692 (99.9)	0.85
Ticagrelor	1,647 (66.4)	830 (67.0)	817 (65.8)	867 (63.2)	437 (64.4)	430 (62.0)	0.043
Prasugrel	218 (8.8)	119 (9.6)	99 (8.0)	133 (9.7)	70 (10.3)	63 (9.1)	0.35
Clopidogrel	610 (24.6)	285 (23.0)	325 (26.2)	368 (26.8)	169 (24.9)	199 (28.7)	0.13
Beta-blocker	2,223 (89.7)	1,108 (89.5)	1,115 (89.8)	1,210 (88.2)	593 (87.3)	617 (89.0)	0.16
ACE inhibitor/ARB	2,113 (85.2)	1,066 (86.1)	1,047 (84.4)	1,183 (86.2)	587 (86.5)	596 (86.0)	0.40
Statin	2,427 (97.9)	1,218 (98.4)	1,209 (97.4)	1,342 (97.8)	667 (98.2)	675 (97.4)	0.85
Hemoglobin A1C, %	5.8 (5.5–6.4)	5.8 (5.5–6.4)	5.8 (5.5–6.4)	5.8 (5.4–6.2)	5.8 (5.4–6.2)	5.8 (5.5–6.2)	0.20
LDL cholesterol, mmol/l	3.1 ± 1.2	3.1 ± 1.2	3.1 ± 1.2	3.1 ± 1.2	3.1 ± 1.2	3.1 ± 1.2	0.56
Peak creatinine, μmol/l	85.2 ± 29.7	84.4 ± 31.6	86.0 ± 27.6	84.0 ± 27.1	84.3 ± 28.3	83.7 ± 25.9	0.21

Values are mean ± SD, n (%), n/N (%), or median (interquartile range). *QCA ≥60% vs. QCA <60%.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography.

lesion, 4,041 patients were randomized to either additional staged PCI of angiographically significant nonculprit lesions or to no further revascularization. The angiographic threshold for inclusion was ≥70% severity by visual assessment (or fractional flow reserve [FFR] <0.80 when visual estimation of stenosis was 50% to 70%; accounting for <1% of treated lesions). The COMPLETE trial received ethics committee approval from the Hamilton Integrated Research Ethics Board and ethics committee approval from each participating study center.

ANGIOGRAPHIC ANALYSIS. All angiograms, including the index PCI for STEMI, nonculprit study PCI, and any unplanned PCIs or coronary angiograms, were anonymized and sent to the central angiographic core laboratory located at McMaster University and Hamilton Health Sciences. QCA was performed on all randomized nonculprit lesions using QAngio XA (Medis, Leiden, the Netherlands). The stenosis severity was equal to 1 – the minimum lumen diameter divided by the average of the proximal and distal reference vessel diameters. A protocol-specified subgroup analysis was based on a combination of visual and QCA results where the maximum stenosis severity of any lesion by either method was used to classify the patient as severe or not (i.e., ≥80% visual and/or ≥60% QCA) (2). In the present analysis, only QCA measurements were used. For patients with more than 1 nonculprit lesion, the mean stenosis severity of all nonculprit lesions was used, so that all randomized lesions contributed to the stenosis severity weighting. The subgroups analyzed were QCA diameter stenosis ≥60% versus <60%. PCI procedural outcome was classified for culprit and nonculprit PCI procedures by the angiographic core laboratory as: 1) PCI success; 2) PCI partial success; or 3) PCI failure. Details of the QCA

TABLE 2 Procedure Characteristics According to QCA Severity

	QCA ≥60%			QCA <60%			
	All (N = 2,479)	Complete (n = 1,238)	Culprit-Only (n = 1,241)	All (N = 1,372)	Complete (n = 679)	Culprit-Only (n = 693)	p Value*
Index procedure for STEMI							
Primary PCI	2,294 (92.5)	1,147 (92.6)	1,147 (92.4)	1,268 (92.4)	618 (91.0)	650 (93.8)	0.89
Pharmaco-invasive PCI	77 (3.1)	34 (2.7)	43 (3.5)	44 (3.2)	27 (4.0)	17 (2.5)	0.86
Rescue PCI	108 (4.4)	57 (4.6)	51 (4.1)	60 (4.4)	34 (5.0)	26 (3.8)	0.98
Radial access	1,991 (80.3)	991 (80.0)	1,000 (80.6)	1,146 (83.5)	573 (84.4)	573 (82.7)	0.014
Thrombus aspiration	573/2,263 (25.3)	278/1,130 (24.6)	295/1,133 (26.0)	316/1,296 (24.4)	149/642 (23.2)	167/654 (25.5)	0.53
SYNTAX score (angiographic core laboratory)							
STEMI culprit lesion-specific score	8.6 ± 5.3	8.7 ± 5.3	8.6 ± 5.3	8.8 ± 5.3	8.9 ± 5.4	8.7 ± 5.3	0.38
Nonculprit lesion-specific score	4.7 ± 2.8	4.7 ± 2.8	4.7 ± 2.8	4.4 ± 2.6	4.4 ± 2.6	4.4 ± 2.5	<0.001
Baseline (including STEMI culprit)	16.3 ± 6.8	16.5 ± 6.9	16.1 ± 6.8	15.9 ± 6.5	16.0 ± 6.5	15.8 ± 6.4	0.06
Residual (after index PCI)	7.3 ± 4.9	7.4 ± 5.1	7.2 ± 4.8	6.7 ± 4.5	6.7 ± 4.6	6.7 ± 4.5	<0.001
Culprit lesion location (core laboratory)							
Left main	5 (0.2)	2 (0.2)	3 (0.2)	2 (0.1)	1 (0.1)	1 (0.1)	>0.99
Left anterior descending	833 (33.6)	413 (33.4)	420 (33.8)	481 (35.1)	247 (36.4)	234 (33.8)	0.36
Circumflex	385 (15.5)	209 (16.9)	176 (14.2)	267 (19.5)	136 (20.0)	131 (18.9)	0.002
Right coronary artery	1,256 (50.7)	614 (49.6)	642 (51.7)	622 (45.3)	295 (43.4)	327 (47.2)	0.002
Number of residual diseased vessels (core laboratory)							
1	1,878 (75.8)	928 (75.0)	950 (76.6)	1,072 (78.1)	530 (78.1)	542 (78.2)	0.10
≥2	601 (24.2)	310 (25.0)	291 (23.4)	300 (21.9)	149 (21.9)	151 (21.8)	0.10
Nonculprit lesion location (core laboratory)							
Left main	3/3,472 (0.1)	2/1,773 (0.1)	1/1,699 (0.1)	10/1,883 (0.5)	8/958 (0.8)	2/925 (0.2)	0.39
Left anterior descending	1,352/3,472 (38.9)	666/1,773 (37.6)	686/1,699 (40.4)	765/1,883 (40.6)	371/958 (38.7)	394/925 (42.6)	0.23
Proximal left anterior descending	336/3,472 (9.7)	168/1,773 (9.5)	168/1,699 (9.9)	205/1,883 (10.9)	99/958 (10.3)	106/925 (11.5)	0.61
Mid left anterior descending	758/3,472 (21.8)	377/1,773 (21.3)	381/1,699 (22.4)	455/1,883 (24.2)	215/958 (22.4)	240/925 (25.9)	0.05
Circumflex	1,349/3,472 (38.9)	696/1,773 (39.3)	653/1,699 (38.4)	577/1,883 (30.6)	297/958 (31.0)	280/925 (30.3)	<0.001
Proximal left circumflex and obtuse marginal/ramus	1,016/3,472 (29.3)	523/1,773 (29.5)	493/1,699 (29.0)	425/1,883 (22.6)	221/958 (23.1)	204/925 (22.1)	<0.001
Distal left circumflex and posterior lateral ventricular	333/3,472 (9.6)	173/1,773 (9.8)	160/1,699 (9.4)	152/1,883 (8.1)	76/958 (7.9)	76/925 (8.2)	0.52
Right coronary artery	768/3,472 (22.1)	409/1,773 (23.1)	359/1,699 (21.1)	531/1,883 (28.2)	282/958 (29.4)	249/925 (26.9)	<0.001
Nonculprit lesion reference diameter (core laboratory)	2.8 ± 0.5	2.8 ± 0.5	2.9 ± 0.5	2.9 ± 0.6	2.8 ± 0.5	2.9 ± 0.6	0.003
Nonculprit lesion diameter stenosis (core laboratory)	70.3 ± 13.0	70.1 ± 10.2	70.5 ± 15.4	54.4 ± 6.5	54.4 ± 7.0	54.3 ± 6.0	<0.001
Nonculprit lesion diameter stenosis (visual)	80.6 ± 8.7	80.8 ± 8.7	80.4 ± 8.6	76.2 ± 6.6	76.5 ± 6.6	75.8 ± 6.6	<0.001
Nonculprit lesion diameter stenosis (visual)							<0.001
50%–69%	14/3,207 (0.4)	10/1,620 (0.6)	4/1,587 (0.3)	22/1,741 (1.3)	11/869 (1.3)	11/872 (1.3)	
70%–79%	1,145/3,207 (35.7)	547/1,620 (33.8)	598/1,587 (37.7)	983/1,741 (56.5)	469/869 (54.0)	514/872 (58.9)	
80%–89%	1,103/3,207 (34.4)	572/1,620 (35.3)	531/1,587 (33.5)	524/1,741 (30.1)	268/869 (30.8)	256/872 (29.4)	
90%–99%	846/3,207 (26.4)	440/1,620 (27.2)	406/1,587 (25.6)	210/1,741 (12.1)	121/869 (13.9)	89/872 (10.2)	
100%	99/3,207 (3.1)	51/1,620 (3.1)	48/1,587 (3.0)	2/1,741 (0.1)	0/869 (0.0)	2/872 (0.2)	
Index PCI							0.90
Success	2,258 (91.1)	1,129 (91.2)	1,129 (91.0)	1,245 (90.7)	618 (91.0)	627 (90.5)	
Partial	212 (8.6)	105 (8.5)	107 (8.6)	121 (8.8)	60 (8.8)	61 (8.8)	
Failure	9 (0.4)	4 (0.3)	5 (0.4)	6 (0.4)	1 (0.1)	5 (0.7)	
Nonculprit PCI							0.025
Success	–	1,537/1,588 (96.8)	–	–	800/814 (98.3)	–	
Partial	–	34/1,588 (2.1)	–	–	13/814 (1.6)	–	
Failure	–	17/1,588 (1.1)	–	–	1/814 (0.1)	–	

Values are n (%), n/N (%), or mean ± SD. *QCA ≥60% versus QCA <60%.
STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

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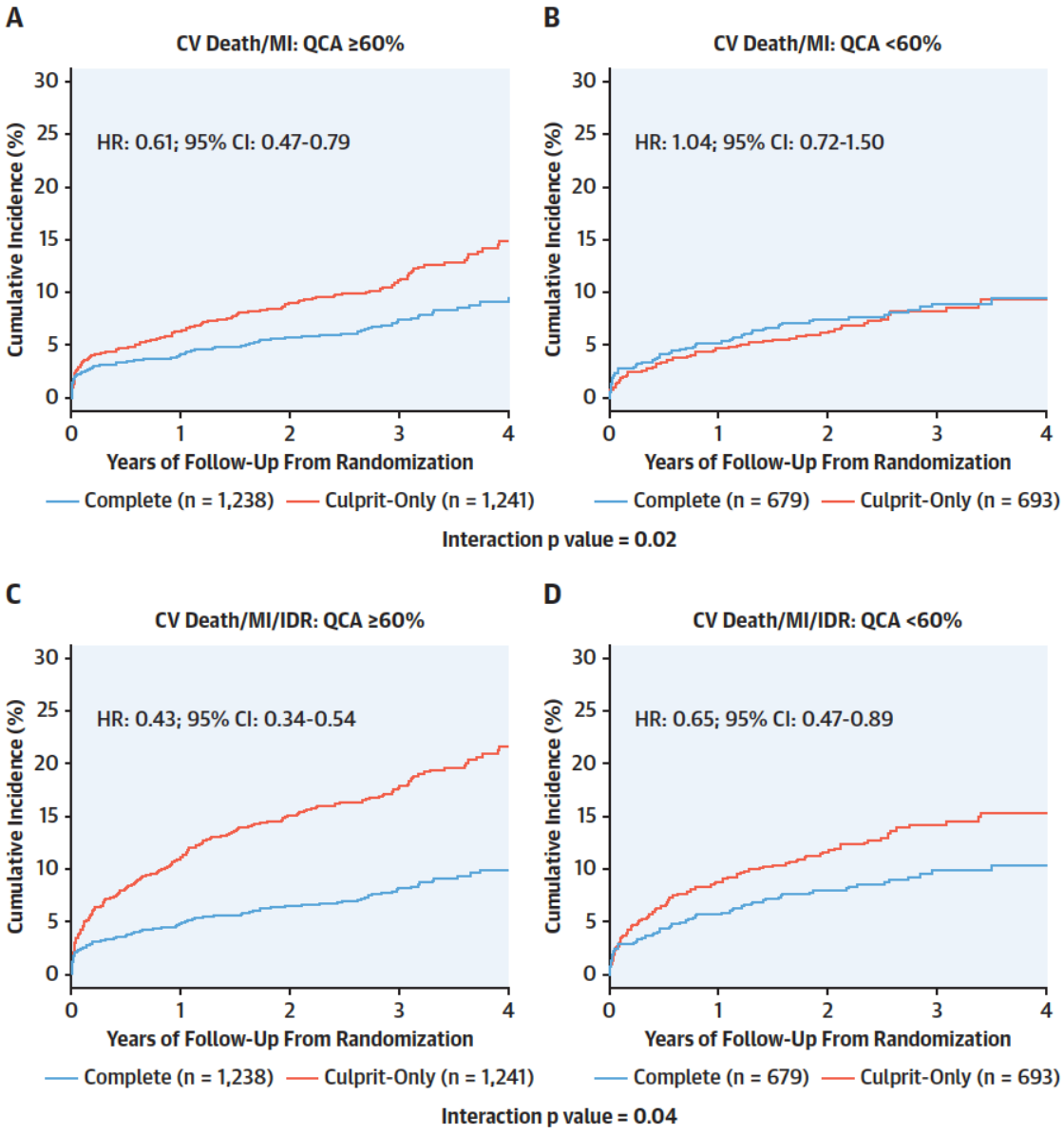
CENTRAL ILLUSTRATION Cumulative Incidence of the Coprimary Outcomes by Stenosis Severity

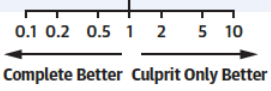


Sheth, T. et al. J Am Coll Cardiol. 2020;76(11):1277-86.

Kaplan-Meier estimates of the cumulative incidence of **(A)** cardiovascular (CV) death and new myocardial infarction (MI) for quantitative coronary angiography (QCA) stenosis ≥60%; **(B)** CV death and new MI for QCA stenosis <60%; **(C)** CV death, new MI, and ischemia-driven revascularization (IDR) for QCA stenosis ≥60%; and **(D)** CV death, new MI, and IDR for QCA stenosis <60%. These major CV outcomes were reduced by complete revascularization to a greater extent in patients with QCA nonculprit-lesion severity ≥60% compared with <60%. CI = confidence interval; HR = hazard ratio.

FIGURE 1 Subgroup Analysis of Clinical Outcomes in QCA ≥60% Versus <60% Group

Subgroup	Complete *no. of events/total no. (% per person-yr)*	Culprit Only *no. of events/total no. (% per person-yr)*	Hazard Ratio (95% CI)	p Value for Interaction
Co-Primary outcomes				
Cardiovascular death or MI				0.02
QCA ≥60%	94/1,238 (2.5)	151/1,241 (4.2)	0.61 (0.47-0.79)	
QCA <60%	57/679 (3.0)	56/693 (2.9)	1.04 (0.72-1.50)	
Cardiovascular death, MI, or IDR				0.04
QCA ≥60%	105/1,238 (2.9)	234/1,241 (6.9)	0.43 (0.34-0.54)	
QCA <60%	63/679 (3.3)	97/693 (5.2)	0.65 (0.47-0.89)	
Key secondary outcomes				
CV death, MI, IDR, unstable angina, or class IV HF				0.12
QCA ≥60%	170/1,238 (4.9)	296/1,241 (9.1)	0.55 (0.45-0.66)	
QCA <60%	85/679 (4.6)	118/693 (6.5)	0.72 (0.54-0.95)	
Other secondary outcomes				
MI				0.02
QCA ≥60%	65/1,238 (1.8)	114/1,241 (3.2)	0.56 (0.41-0.76)	
QCA <60%	42/679 (2.2)	41/693 (2.1)	1.04 (0.68-1.61)	
IDR				0.6
QCA ≥60%	18/1,238 (0.5)	103/1,241 (2.9)	0.17 (0.10-0.28)	
QCA <60%	7/679 (0.4)	53/693 (2.8)	0.13 (0.06-0.29)	
Unstable angina				0.31
QCA ≥60%	48/1,238 (1.3)	86/1,241 (2.4)	0.55 (0.39-0.78)	
QCA <60%	15/679 (0.8)	39/693 (2.0)	0.39 (0.21-0.70)	
Cardiovascular death				0.26
QCA ≥60%	35/1,238 (0.9)	46/1,241 (1.2)	0.76 (0.49-1.18)	
QCA <60%	19/679 (1.0)	16/693 (0.8)	1.21 (0.62-2.35)	
All-cause death				0.86
QCA ≥60%	61/1,238 (1.6)	72/1,241 (1.9)	0.85 (0.60-1.19)	
QCA <60%	28/679 (1.4)	32/693 (1.6)	0.89 (0.54-1.48)	
Other outcomes				
Stroke				0.32
QCA ≥60%	23/1,238 (0.6)	22/1,241 (0.6)	1.05 (0.58-1.88)	
QCA <60%	11/679 (0.6)	6/693 (0.3)	1.86 (0.69-5.04)	
NYHA functional class IV HF				0.02
QCA ≥60%	35/1,238 (0.9)	46/1,241 (1.2)	0.76 (0.49-1.18)	
QCA <60%	21/679 (1.1)	10/693 (0.5)	2.14 (1.01-4.55)	
Stent thrombosis				0.03
QCA ≥60%	15/1,238 (0.4)	16/1,241 (0.4)	0.94 (0.46-1.90)	
QCA <60%	10/679 (0.5)	2/693 (0.1)	5.12 (1.12-23.40)	
Safety outcomes				
Clinically significant bleeding, stroke, stent thrombosis or contrast-associated AKI*				0.2
QCA ≥60%	96/1,238 (2.7)	83/1,241 (2.3)	1.17 (0.87-1.57)	
QCA <60%	58/679 (3.1)	37/693 (1.9)	1.63 (1.08-2.46)	
Clinically significant bleeding				0.68
QCA ≥60%	52/1,238 (1.4)	44/1,241 (1.2)	1.19 (0.80-1.78)	
QCA <60%	33/679 (1.7)	25/693 (1.3)	1.36 (0.81-2.29)	
Contrast associated AKI				0.16
QCA ≥60%	14/1,238 (0.4)	13/1,241 (0.3)	1.08 (0.51-2.30)	
QCA <60%	11/679 (0.6)	4/693 (0.2)	2.82 (0.90-8.86)	



A forest plot demonstrating the hazard ratios (HRs) and 95% confidence intervals (CIs) for complete versus culprit-only revascularization on coprimary outcomes, key secondary outcomes, and other secondary outcomes. In addition to the first and second primary outcomes, significant interaction ($p < 0.05$) was also detected for myocardial infarction (MI), heart failure (HF), and stent thrombosis. *Composite safety outcome was defined post hoc. AKI = acute kidney injury; IDR = ischemia-driven revascularization; NYHA = New York Heart Association; QCA = quantitative coronary angiography.

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technique and PCI outcome definitions are provided in the Supplemental Appendix.

OUTCOMES. Detailed definitions of all efficacy and safety outcomes have been previously published (2). Deaths were classified as CV or non-CV. An event adjudication committee of clinicians who were masked to treatment allocation adjudicated primary and secondary efficacy outcomes as well as bleeding events. The outcome of IDR required all of the following criteria: 1) ischemic symptoms consistent with Canadian Cardiovascular Society class ≥2 angina despite optimal medical therapy; 2) PCI or CABG of either the culprit lesion (within 5 mm of the stented segment) associated with the index PCI or a non-culprit lesion that led to enrollment into the trial; and 3) at least 1 of the following: positive noninvasive function study demonstrating reversible ischemia, new ischemic electrocardiographic changes at rest or with exertion, or an FFR ≤0.80.

STATISTICAL ANALYSIS. Randomized patients with available angiographic core laboratory data were included in the analysis following intention-to-treat principles. Baseline and procedural characteristics between these 2 groups were compared using the 2-sample Student's *t*-test for normally distributed variables, Wilcoxon rank-sum test for non-normally distributed variables, and chi-square test for categorical variables.

The effect of complete versus culprit-lesion-only PCI on the 2 coprimary outcomes, secondary outcomes, and a post hoc defined composite safety outcome was estimated separately for each subgroup of stenosis severity using Cox proportional hazards models. Interaction effects of allocated therapy and QCA stenosis severity were assessed with a likelihood ratio test. The cumulative incidences of the 2 coprimary outcomes were plotted using the Kaplan-Meier method. To evaluate the robustness of the primary results, we conducted a sensitivity analysis using different cut-offs of QCA stenosis severity. In addition, a propensity score matching strategy was implemented to control for potential confounding effects in subgroup analysis due to the differences in baseline characteristics between the QCA stenosis ≥60% and <60% subgroups. Propensity score for QCA stenosis was constructed using logistic regression with the following baseline and procedural variables: age, sex, diabetes, renal insufficiency, prior MI, prior stroke, current smoker, hypertension, dyslipidemia, body mass index, prior PCI, radial access, residual syntax score after index PCI, and culprit lesion location. Each patient with QCA stenosis <60% was matched with up to 2 patients with QCA stenosis ≥60% by logit of propensity score. Quality of matching was evaluated by standardized difference (6). Subgroup analysis was repeated on the matched population. All statistical analyses were conducted with the use of SAS 9.4 software (SAS Institute, Inc., Cary, North Carolina). All tests of significance were 2-sided with an alpha level of 0.05. Considering the exploratory nature of the study, we did not adjust for multiple testing.

RESULTS

PATIENT CHARACTERISTICS. Of the 4,041 patients randomized in the COMPLETE trial, QCA was performed by the angiographic core laboratory in 3,851 patients with 5,355 nonculprit lesions. One nonculprit lesion was present in 2,627 patients, and ≥2 nonculprit lesions were present in 1,224 patients. QCA stenosis severity ≥60% was present in 2,479 patients, and QCA stenosis severity <60% was present in 1,372 patients. Baseline and procedural characteristics are shown in Tables 1 and 2. Patients with QCA stenosis ≥60% were less likely to be current smokers, but were more likely to be hypertensive, dyslipidemic, or have elevated body mass index. They had slightly higher mean nonculprit-lesion-specific SYNTAX scores and residual SYNTAX scores after index PCI. However, there was no difference in the proportion of patients with ≥2 diseased nonculprit vessels. Nonculprit lesion location in the circumflex was more common and right coronary artery was less common in patients with QCA stenosis ≥60%. Mean diameter stenosis was slightly greater by visual assessment and substantially greater by QCA in this group. No obvious imbalance in patient characteristics between treatment arms within each subgroup of stenosis severity was detected. PCI success rate for culprit lesion and nonculprit lesion PCI was high in both QCA subgroups.

OUTCOMES. CV death or MI. There was a significant interaction for the effect of stenosis severity on the outcome of CV death or MI ($p = 0.02$). Among the 2,479 patients with QCA stenosis ≥60%, the incidence of the first coprimary outcome of CV death or MI was 2.5%/year in patients randomized to complete revascularization versus 4.2%/year in patients randomized to culprit-lesion-only PCI (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.47 to 0.79) (Central Illustration A). Among the 1,372 patients with QCA stenosis <60%, the incidence of the first coprimary outcome of CV death or MI was 3.0%/year in

patients randomized to complete revascularization versus 2.9%/year in patients randomized to culprit-lesion-only PCI (HR: 1.04; 95% CI: 0.72 to 1.50) (Central Illustration B).

CV death, MI, or IDR. There was a significant interaction for the effect of stenosis severity on the outcome of CV death, MI, or IDR ($p = 0.04$). Among the 2,479 patients with QCA stenosis ≥60%, the incidence of the second coprimary outcome of CV death, MI, or IDR was 2.9%/year in patients randomized to complete revascularization versus 6.9%/year in patients randomized to culprit-lesion-only PCI (HR: 0.43; 95% CI: 0.34 to 0.54) (Central Illustration C). Among the 1,372 patients with QCA stenosis <60%, the incidence of the second coprimary outcome of CV death, MI, or IDR was 3.3%/year in patients randomized to complete revascularization versus 5.2%/year in patients randomized to culprit-lesion-only PCI (HR: 0.65; 95% CI: 0.47 to 0.89) (Central Illustration D).

OTHER CLINICAL OUTCOMES. The HRs for components of the primary outcomes, secondary outcomes, and a post hoc-defined composite safety outcome in QCA <60% versus ≥60% groups are shown in Figure 1. In addition to the first and second primary outcomes, a significant interaction ($p < 0.05$) was also detected for MI ($p = 0.02$), heart failure ($p = 0.02$), and stent thrombosis ($p = 0.03$). In the case of stent thrombosis, this observation is based on only 12 events and could be due to play of chance. There were no significant interactions with stroke ($p = 0.32$), clinically significant bleeding ($p = 0.68$), or contrast-induced acute kidney injury ($p = 0.16$), The risk of an exploratory, post hoc-defined composite safety outcome (clinically significant bleeding, stroke, stent thrombosis, or contrast-associated acute kidney injury) was more frequent in the complete arm than in the culprit-only arm in the QCA <60% subgroup (HR: 1.63; 95% CI: 1.08 to 2.46) but was similar between the 2 arms in the QCA ≥60% subgroup (HR: 1.17; 95% CI: 0.87 to 1.57; interaction $p = 0.20$).

SENSITIVITY ANALYSES. We performed a sensitivity analysis at different cut-offs of QCA stenosis severity (Supplemental Table 1). For the first coprimary outcome, a reduction of events in the complete arm was seen for QCA stenosis ≥80%, 70% to <80%, and 60% to <70%, but not for <60% (interaction $p = 0.07$). A treatment effect was seen in all categories for the second coprimary outcome (interaction $p = 0.13$). Using the propensity score, we matched 1,225 patients with QCA stenosis <60% to 2,137 patients with QCA stenosis ≥60%. All baseline and procedural characteristics between the 2 matched groups were well balanced as demonstrated by the small standardized differences (<0.1) (Supplemental Table 2). Similar results to the primary subgroup analysis were observed using the matched population (Supplemental Figure 1).

DISCUSSION

In this study, we performed QCA of nonculprit lesions in patients with STEMI and multivessel disease and showed that complete revascularization reduced major CV outcomes to a greater extent in patients with QCA-determined nonculprit-lesion stenosis severity ≥60% compared with <60%.

These data provide insight into the impact of nonculprit-lesion stenosis severity on the treatment effect of PCI in patients with STEMI and multivessel disease. The comparative likelihood of future MI between lesions of mild-moderate versus severe stenosis is controversial. Recent studies using CT coronary angiography have suggested that most subsequent acute coronary syndrome events are observed in the setting of mild stenosis at baseline (7,8). The prognosis of patients with multivessel nonobstructive CAD was similar to those with limited obstructive CAD (9), suggesting that severe lesions may simply be a marker for the extent of CAD rather than contributing to prognosis directly. Conversely, pathology and imaging studies show that patients with sudden cardiac death or acute MI usually have culprit lesions that are severely stenosed and have large plaque burden (10–13). The present QCA analysis of the COMPLETE trial demonstrated that the risk of future MI and CV death by nonculprit PCI death was substantially reduced by performance of PCI in patients with QCA stenosis ≥60%. These data provide compelling evidence for the causal role of severe stenoses in future MI in this population. For the second coprimary outcome that included IDR, benefit was seen in both subgroups, although the hazard reduction was greater in the subgroup with stenosis ≥60%.

The mechanistic basis for the risk of MI associated with severe nonculprit lesions is uncertain. Angiographically severe stenoses may be more likely to have features of vulnerable plaque. The frequency of thin cap fibroatheroma (TCFA), as defined by optical coherence tomography, is increased when the lesion severity is ≥70% compared with <70% (14,15). Specifically in the setting of STEMI and multivessel disease, 47% of patients have at least 1 TCFA at a nonculprit lesion site (15). Prospective studies have previously shown

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that TCFA lesions and small residual lumen area are risk factors for progression at the lesion level (16,17). Conversely, the concept of vulnerable plaque has been questioned (18,19) by observations that TCFAs may be multiple and may persist for years without causing a clinical event. In addition, plaque rupture, for which TCFA is a precursor, may be declining as a cause of acute coronary syndromes, whereas superficial erosion appears to be on the rise, possibly due to more widespread use of statin therapy. Imaging techniques such as near-infrared spectroscopy, intravascular ultrasound, and optical coherence tomography can identify features of vulnerable plaques, and several trials are exploring the role of using plaque morphology on imaging to guide PCI (20). These studies will provide randomized comparisons of PCI of TCFA-containing lesions versus medical therapy of such lesions on hard clinical outcomes and help to more fully test the vulnerable plaque hypothesis.

Whether the identification of nonculprit lesions for PCI should be performed by means other than visual estimation is uncertain. Angiographically severe lesions are more likely to also be physiologically significant. Although angiographic lesion severity has only a moderate negative correlation with FFR (−0.56) overall (21), among lesions with visual assessment of stenosis from 71% to 90% and >90%, positive FFR was observed in 80% and 96% of such lesions, respectively (22). Several trials have explored the role of FFR-guided PCI in patients with STEMI and multivessel disease (23,24), and a meta-analysis of FFR guidance that included these trials showed a reduction in cardiac death and MI, predominantly driven by reduced MI (25). The advantage of a physiology-guided approach is that it may reduce number of nonculprit-lesion PCI procedures by targeting PCI to only functionally significant lesions and may reduce the safety outcomes, including bleeding, stent thrombosis, restenosis, contrast-induced nephropathy, bleeding, and periprocedural MI. There may be potential long-term cost savings due to reduced need for additional stents and future procedures. The limitations of a physiology-guided approach are that its efficacy in the setting of ACS is uncertain because recurrent events may be more closely linked to plaque morphology rather than physiology. Thus, physiologically deferred lesions containing unstable plaque morphology may drive recurrent events. There is increased procedural cost associated with pressure wire use that needs to be balanced against savings from fewer PCIs and safety events. The advantage of an angiography-guided approach is that it is the current standard of care as established by the COMPLETE trial, is simple and widely used, and is the only strategy proven to reduce CV death or new MI. The limitations of an angiography-guided approach is that it is an all-encompassing approach to PCI that may increase the number of unnecessary PCIs, and this increase in procedures may lead to more procedure-related safety events such as bleeding, stent thrombosis, contrast-induced nephropathy, and stroke. Comparative studies are needed between these 2 approaches.

STUDY LIMITATIONS. Not all patients had angiograms submitted for core laboratory evaluation; therefore, the QCA results were not available in approximately 5% of randomized patients. The selection of 60% cutoff for QCA was pre-specified but arbitrary. Subgroup analyses have well-known limitations including false negatives due to inadequate power and false positives due to multiple testing. Although potential confounding effects from observed risk factors were controlled for in the study using a propensity-score matching approach, the ability to make causal inference may still be limited by residual confounding from differences in baseline characteristics between subgroups.

CONCLUSIONS

Among patients with STEMI and multivessel coronary artery disease, complete revascularization reduced major CV outcomes to a greater extent in patients with QCA-determined nonculprit lesion stenosis severity ≥60% compared with <60%. Although visual estimation to identify nonculprit lesions is a safe and effective strategy, future investigation of alternate methods of selecting nonculprit lesions for treatment is warranted.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with STEMI and multivessel coronary disease, those with more severe (>60%) stenosis of nonculprit lesions gain the greatest benefit from complete revascularization in terms of reductions in reinfarction and CV mortality.

TRANSLATIONAL OUTLOOK: Clinical trials are needed to compare the outcomes of angiographically versus physiologically guided assessments of nonculprit coronary lesions in patients with STEMI and multivessel coronary artery disease undergoing PCI.

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KEY WORDS percutaneous coronary intervention, quantitative coronary angiography, ST-segment elevation myocardial infarction

APPENDIX For a supplemental figure and tables, please see the online version of this paper.

8.4 Publication 4.

Using Optical Coherence Tomography to Identify Lipid and Its Impact on Interventions and Clinical Events — A Scoping Review —

Circ J. 2021 Oct 25;85(11):2053-2062. doi: 10.1253/circj.CJ-21-0377. Epub 2021 Jul 22.

Optical coherence tomographic imaging is a high-resolution intracoronary imaging technique that has enabled the identification of lipid, with increasing interest in how it may affect coronary interventions and clinical outcomes. This review summarizes the available evidence around OCT identification of lipid and its effect on interventions, clinical events, and the natural history of coronary disease.

A scoping review was conducted in Medline, HealthStar, and Embase databases for articles published between 1996 and 2021. 1,194 articles were screened and 51 identified for inclusion in this study. The literature supports a common OCT definition of lipid as low-signal regions with diffuse borders, validated against histology and other imaging modalities with acceptable intra- and inter-rater reliability.

There is evidence that OCT-identified lipid at the site of stent implantation increases the risk of edge dissection, incomplete stent apposition, in-stent tissue protrusion, decreased coronary flow after stenting, side branch occlusion, and post-procedural cardiac biomarker increases. In

mostly retrospective studies, lipid indices measured at non-stented sites are associated with plaque progression and the development of recurrent ischemic events.

This analysis concluded that there is extensive literature supporting the ability of OCT to identify lipid and demonstrating a substantial impact of lipid on percutaneous coronary intervention outcomes. Future work to prospectively evaluate the effect of the characteristics of lipid rich plaques on long-term clinical outcomes is needed.

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ORIGINAL ARTICLE
Imaging

Using Optical Coherence Tomography to Identify Lipid and Its Impact on Interventions and Clinical Events

— A Scoping Review —

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Background: Optical coherence tomographic (OCT) imaging has enabled identification of lipid, with increasing interest in how it may affect coronary interventions and clinical outcomes. This review summarizes the available evidence around OCT identification of lipid and its effect on interventions, clinical events, and the natural history of coronary disease.

Methods and Results: We conducted a scoping review using the Medline, HealthStar, and Embase databases for articles published between 1996 and 2021. We screened 1,194 articles and identified 51 for inclusion in this study, summarizing the key findings. The literature supports a common OCT definition of lipid as low-signal regions with diffuse borders, validated against histology and other imaging modalities with acceptable intra- and inter-rater reliability. There is evidence that OCT-identified lipid at the site of stent implantation increases the risk of edge dissection, incomplete stent apposition, in-stent tissue protrusion, decreased coronary flow after stenting, side branch occlusion, and post-procedural cardiac biomarker increases. In mostly retrospective studies, lipid indices measured at non-stented sites are associated with plaque progression and the development of recurrent ischemic events.

Conclusions: There is extensive literature supporting the ability of OCT to identify lipid and demonstrating a substantial impact of lipid on percutaneous coronary intervention outcomes. Future work to prospectively evaluate the effect of the characteristics of lipid-rich plaques on long-term clinical outcomes is needed.

Key Words: Lipid rich plaque; Optical coherence tomography; Thin cap fibroatheroma

Plaque morphology is recognized as an important factor in the outcome of percutaneous coronary intervention (PCI)[1,2] and the natural history of coronary disease.[3–5] Although the role of calcified plaque in PCI has received much attention, there has been a relatively limited focus on lipidic plaque. Optical coherence tomographic (OCT) imaging has enabled identification of lipid, and a growing literature base has explored how it may affect the procedural outcomes of PCI, as well as longer-term clinical outcomes.[6] To assist the practicing interventionalist in applying this evidence base, we conducted a literature review to summarize the available evidence regarding OCT identification of lipid and its consequences. Our objectives were to review: (1) the reliability and validity of lipid identification by OCT compared with histopathology and other detection modalities; (2) the impact of lipid on in-laboratory and post-laboratory PCI outcomes; and (3) the effect of lipid on recurrent ischemic events in natural history studies of coronary disease.

Methods

To explore the breadth and depth of the literature around the OCT identification of lipid and its consequences, we selected a scoping review methodology.[7] This allowed us to summarize the diversity of the literature available and to identify key evidence and gaps without being limited to samples and datasets that can be easily aggregated using more conventional systematic review approaches.[8]

Search Strategy

With the aid of a librarian, we conducted an OVID search of the Medline, HealthStar, and Embase databases for article published between 1996 and February 2021 using the following keywords: tomography, optical OR tomography, optical coherence/ AND (lipid OR thin cap fibroatheroma OR TCFA). We excluded ophthalmologic studies, non-human studies, studies not published in English and duplicates.

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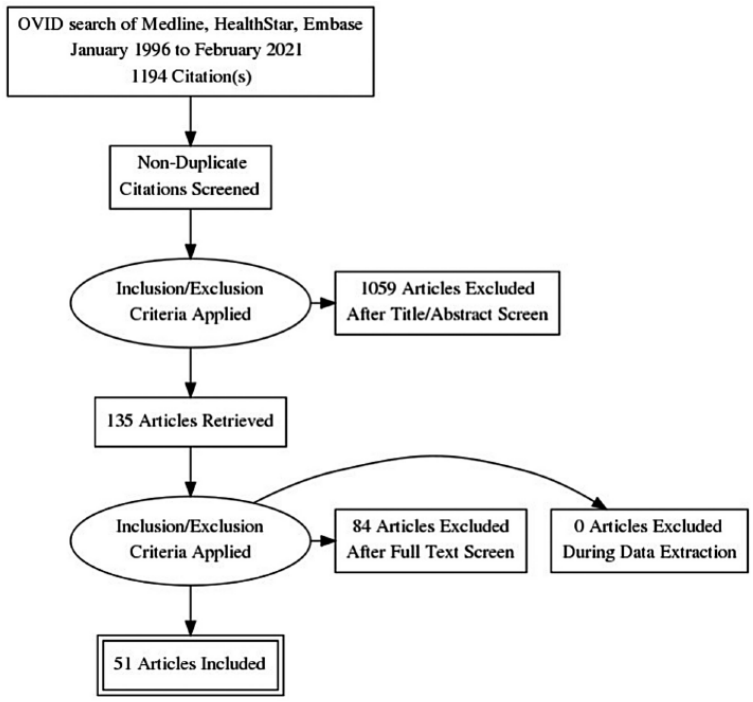

Figure 1. Flow diagram of the scoping review methodology.

Screening

Articles were screened in duplicate using titles and abstracts by 4 reviewers (M.S., M.A., J.C., G.D.) using an online systematic review platform (https://rayyan.qcri.org/). All reviewers trained on a common set of 50 articles to ensure consistency in inclusion and exclusion criteria. We included empirical data (including case series, cross-sectional, cohort, controlled trials, randomized data, systematic reviews, expert consensus statements, and meta-analyses) pertaining to OCT-identified lipid for the purposes of defining or validating lipid pools, correlating lipid pools with intraprocedural, periprocedural, and long-term clinical outcomes. We excluded intravascular imaging studies without OCT comparison, studies with data only relating to differences in lipid pools based on demographics or clinical variables, studies related to the impact of pharmacologic intervention on lipid pools, studies related to neoatherosclerosis, case reports, review articles, expert consensus, commentaries, animal studies, basic science studies including ex vivo models and computational modeling, and studies related to bioabsorbable scaffolds. In all, 274 articles were screened in triplicate because at least 1 reviewer was undecided; 17 conflicts were resolved through discussion.

Eligibility and Data Extraction

The full text of articles meeting the screening criteria were assessed by 2 reviewers (two of M.S., M.A., J.C., G.D.) for inclusion, with disagreements resolved through consensus. Data were extracted from the full text into 3 predefined tables for reliability and validity evidence and intra- and post-procedural outcomes by a single reviewer (one of M.A., J.C., G.D.) and verified by a second (M.S.).

IRB Information

Ethics approval was not applicable for this study because the data collected were from previously published studies.

Results

The results of the literature search are presented in **Figure 1**. In all, 1,194 articles were identified, 920 of which were screened in duplicate and 274 were screened in triplicate because at least 1 reviewer was undecided. Seventeen conflicts were resolved through discussion. Of the 135 articles that underwent full text review, 51 met the criteria for inclusion in the present study.

Reliability and Validity of Lipid and TCFA Detection by OCT

Lipid was consistently defined in OCT imaging as plaque with low signal intensity regions with diffuse borders.[6,9–13] Reports suggest good intraobserver (κ=0.75–0.97) and interobserver (κ=0.76–0.93) agreement,[12,14–18] with improvement documented in 1 paper after training on artifacts and lipid mimics[14] (see **Table 1**). Interobserver agreement on maximal lipid arc was similarly good (intraclass correlation coefficient [ICC] 0.82–0.90).[14,16,19] OCT detection of

Table 1. Inter- and Intrarater Reliability of Lipid-Rich Plaque and Thin Cap Fibroatheroma

Study	Year	No. raters	Lipid-rich plaque			Thin cap fibroatheroma		
			Definition	Intrarater reliability (κ)	Inter-rater reliability (κ)	Definition	Intrarater reliability (κ)	Inter-rater reliability (κ)
Brown et al[16]	2015	Not reported	Signal-poor region with a minimum lipid arc of ≥90°	0.85	0.66	Lipid-rich plaque with a fibrous cap thickness <85 μm	0.64	0.66
Di Vito et al[15]	2017	2	Signal-poor region diffusely bordered by overlying signal-rich bands	0.97	0.93			
Fujii et al[25]	2015	Not reported				Lipid content >1 quadrant with fibrous cap measuring <65 μm	0.92	0.81
Habara et al[12]	2017	2	Signal-poor regions without sharp borders	0.83	0.76			
Kini et al[14]	2015	3	Signal-poor region with poorly delineated borders, little or no signal backscattering, and an overlying signal-rich layer spanning >90° in any cross-section		0.66 (improving with training to 0.75–0.87)	Lipid-rich plaque with minimal fibrous cap thickness <65 mm		0.43 (improving with training to 0.83–0.88)
Lee et al[17]	2011	2	More than 2 quadrants of signal-poor plaque	0.90	0.83	Lipid-rich plaque with a fibrous cap thickness <70 μm	0.83	0.77
Lee et al[18]	2011	2	More than 2 quadrants of signal-poor plaque	0.86	0.78	Lipid-rich plaque with a fibrous cap thickness <70 μm	0.82	0.80
Lee et al[24]	2015	2	Low-signal region with a diffuse border >90°			Lipid-rich plaque with a fibrous cap thickness <80 μm	0.86	0.90
Paoletti et al[22]	2016	Not reported	Signal-poor region diffusely bordered by overlying signal-rich bands			Lipid plaque with a cap thickness <80 μm	R=0.93	R=0.92
Phipps et al[26]	2016	Not reported				Fibrous cap <65 μm overlying a lipid core		0.83
Radu et al[23]	2016	2				Fibroatheroma with minimum fibrous cap thickness<65 μm	0.50 (improving to 1.0 with semiautomatic assessment)	0.23 (improving to 1.0 with semiautomatic assessment)
Roleder et al[19]	2014	Not reported				Lipid-rich plaque with fibrous cap thickness <65 μm		0.84
Yabushita et al[21]	2002	Not reported	Diffusely bordered signal-poor regions with overlying signal-rich bands	0.88	0.91			

lipid was sensitive 89–94%, but less specific 70–92%, based on comparisons with near-infrared spectroscopy (NIRS; sensitivity 86–90%, specificity 70–90%),[15,20] histologic examination of direct atherectomy (sensitivity 89%, specificity 75%),[12] and pathology specimens (sensitivity 90–94%, specificity 90–92%;[21] **Table 2**). Reasons for false positives based on histologic comparisons include macrophages, foam cells, red thrombus, and collagen-poor extracellular matrix.[12,21] Detecting lipid in patients presenting with acute coronary syndromes, especially in ST-elevation myocardial infarction, may be limited by red thrombus, which both obscures lipid and may share similar optical characteristics with lipid.[4]

TCFA was most frequently defined as a lipid-rich plaque with a minimum fibrous cap thickness of <65 μm.[6,14] Interobserver agreement of cap thickness (ICC 0.52–0.91) and TCFA (κ=66–0.93)[14,16–19,22–24] was fair to good, improving with training to identify macrophages and calcification,[14] and with semi-automated detection of fibrous cap.[23] Although OCT detection of TCFA was sensitive (87–100%) and specific (92–97%) in histopathology studies, positive predictive values are lower (41–47%), with microcalcifications, macrophages, foam cells, hemosiderin, fibrin, and loose connective tissue contributing to false posi-

Table 2. Comparison of OCT-Detected Lipid and Thin Cap Fibroatheroma With Other Modalities

Study	Year	No. patients	Comparative standard	OCT criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Presence of lipid								
Di Vito et al[15]	2017	43	NIRS	Signal-poor region diffusely bordered by overlying signal-rich bands	86	70	59	90
Yonetsu et al[20]*	2014	17	NIRS	Diffusely bordered signal-poor region with signal attenuation by the overlying signal-rich layer	90	60	90	60
Habara et al[12]	2018	25	Directional atherectomy	Signal-poor regions without sharp borders	89	75	67	92
Yabushita et al[21]	2002	90	Autopsy	Diffusely bordered signal-poor regions with overlying signal-rich bands	90–94	90–92	74–75	97–98
Thin cap fibroatheroma								
Fujii et al[25]	2015	60	Autopsy	Lipid content >1 quadrant with fibrous cap measuring < 65 μm	100	97	41	100
Miyamoto et al[28]*	2011	81	Integrated backscatter IVUS >55% lipid pool	Thin fibrous cap <65 μm overlying a lipid-rich plaque >90°	95	88	88	94
Phipps et al[26]	2016	10	Autopsy	Fibrous cap <65 μm overlying a lipid core	87	92	37	99

*Data calculated based on numbers provided. IVUS, intravascular ultrasound; NIRS, near-infrared spectroscopy; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value.

tives.[12,25,26] Macrophages, foam cells, and microcalcifications are hypothesized to result in extensive scattering of light, resulting in signal attenuation that mimics lipid.[25,26]

Measurements of OCT lipid (greater angle and thinner cap) were associated with higher maximum lipid core burden index by NIRS.[19,27] Detection of lipid by OCT was more sensitive than with intravascular ultrasound (IVUS), even when IVUS was performed with enhanced integrated backscatter.[28] Lipid and TCFA are more common in plaques with higher grades of stenosis.[4,29] Lipid arc and cap are correlated with atheroma volume.[10] Lipid is more commonly found in the main branch side of bifurcations, with TCFA more frequently opposite the flow divider.[11,30] TCFA is more common in the proximal and mid-left anterior descending artery and proximal circumflex artery,[30] particularly around the obtuse marginal bifurcation,[31] with broader distribution in the right coronary artery clustered around the mid-vessel and distal bifurcation.[30,31]

Effect of Lipid on In-Laboratory Outcomes

Stenting lipid is associated with in-stent plaque prolapse,[32,33] intra-stent thrombus,[32,34,35] and incomplete stent apposition[36] (**Table 3**). Fibrous cap thickness is inversely correlated with in-stent plaque prolapse.[37] Landing a stent in lipid was associated with edge dissections,[38] both proximal[39] and distal,[40] and edge restenosis.[41] Lipid opposite a side branch ostium was associated with angiographic stenosis of the side branch origin after provisional stenting.[42]

In patients undergoing elective stenting, the presence of lipid plaque was associated with a reduction in Thrombolysis in Myocardial Infarction (TIMI) flow.[32,43] In patients undergoing primary PCI, the extent of lipid was associated with no-reflow[44] and no-reflow with filter device use.[45] One study identified an association between lipid and incomplete stent apposition in a primary PCI cohort, where malapposition was also associated with the presence of thrombus and larger proximal vessel diameters.[36] The impact of lipid on stenting is summarized in **Figure 2**.

Effect of Lipid on Post-Laboratory Outcomes

Lipid was associated with post-procedural increases in cardiac biomarkers in elective stenting,[17,18,24,46–52] which was related to landing the stent in lipid proximally,[46] the lipid arc,[23,24] lipid length,[18,24,47] and the presence of TCFA.[18,24,37,47,49] In patients undergoing primary PCI, the extent of lipid was related to the lack of prompt resolution of stent thrombosis[53] and higher increases in enzymes.[53] In patients with acute coronary syndromes, fibrous cap thickness was inversely correlated with microvascular obstruction identified by magnetic resonance imaging.[54]

The impact of lipid on stent healing is less clear, with reports of greater neointimal hyperplasia of struts overlying lipid at OCT imaging follow-up at 3 and 9 months,[55,56] and greater persistence of malapposition of stented lipid plaques at 8 months.[57] The presence of fibrous cap disruption and a necrotic core with macrophages in an acute culprit before stenting were independent predictors of the composite of cardiovascular death, non-fatal myocardial infarction and clinically driven revascularization at 1 year in a retrospective cohort of 209 patients.[58]

Effect of Lipid on Clinical Outcomes

In a natural history study of 1,000 patients, half of whom had an left anterior descending (LAD) culprit, lipid arc >180° and TCFA were both associated with the composite of cardiac death and target vessel LAD segment myocar-

Table 3. Association Between OCT-Detected Lipid and Procedural Outcomes

Study	Year	Population	No. patients	Association
Edge dissections				
Antonsen et al[38]	2016	NSTEMI	97	Edge dissection associated with thick-fibroatheroma (P<0.001)
Gonzalo et al[40]	2010	Stable angina and ACS	73	Distal edge dissection associated with plaque type (fibrocalcific 43.8%, lipid rich 37.5%, fibrous 10%; P=0.009)
Zeglin-Sawczuk et al[39]	2013	Stable angina and ACS	203	>90° lipid arc associated with proximal edge dissection (OR 23.6, P<0.01)
Tissue protrusion				
Bryniarski et al[34]	2017	ACS and stable angina	786	Maximal lipid arc (187° vs. 162°; P=0.004), mean lipid arc (138° vs. 119°; P=0.001) and lipid index (P=0.003)
Sugiyama et al[56]	2017	Stable angina and ACS	145	>180° lipid arc (P<0.001)
Feng et al[33]	2011	Unstable Angina	68	Lipid associated with tissue prolapse (P<0.001) and in-stent microthrombosis (P<0.001)
Incomplete apposition				
Bernelli et al[32]	2016	ACS	140	>90° lipid arc (OR 1.3, P=0.04)
Reduced post-stenting flow				
Gamou et al[43]	2014	Stable angina and ACS	141	TCFA <65 μm (HR 12.32, P=0.0005)
Ikenaga et al[53]	2012	STEMI	39	Length of lipid pool >9 mm (P=0.002)
Ozaki et al[54]	2011	ACS	211	TCFA <70 μm (P=0.012)
Soeda et al[44]	2017	STEMI	145	Maximum lipid arc (344° vs. 320°; P=0.032) and lipid index (P<0.001)
SB occlusion >50%				
Kini et al[42]	2017	Stable angina	30	Maximal lipid arc (146° vs. 75°; OR 1.014 per degree, P=0.038), presence of lipid plaque contralateral to SB ostium (OR 8.14, P=0.046)
Periprocedural biomarker elevation				
Imola et al[46]	2013	Stable angina	30	Lipid pool quadrants (P=0.09) and lipid pool arc (P=0.006) with all lipid arc >154°
Kini et al[51]	2015	Stable angina	110	Greater cap thickness (OR 0.90, P<0.001)
Lee et al[18]	2011	Stable and unstable angina	135	≥2 quadrants of lipid (OR 3.49, P=0.003) and plaque cavity (OR 2.92, P<0.017)
Lee et al[24]	2015	Stable angina	206	Lipid arc (178° vs. 160° degrees; OR 1.01 per degree, P=0.018), lipid length (8 vs. 5 mm; OR 1.08 per mm, P=0.008), and TCFA <80 μm (OR 4.5, P<0.001)
Lee et al[52]	2017	NSTEMI	167	TCFA <70 μm (OR 2.88, P=0.011) and lipid length (10 vs. 7 mm; OR 1.12, P=0.02)
Porto et al[37]	2012	NSTEMI and stable angina	50	TCFA < 65 μm (OR 29.7, P=0.008)
Ueda et al[50]	2014	Stable angina	68	Colocalization of lipid and spotty calcification (OR 8.4, P<0.01)
Uzu et al[35]	2017	Stable angina	94	Lipid index (P<0.001)
Yamamoto et al[47]	2013	Stable angina	79	Optimal cut-off values: lipid arc >115°, fibrous cap thickness <110 μm, and lipid length >7.7 mm

ACS, acute coronary syndrome; HR, hazard ratio; NSTEMI, non-ST segment elevation myocardial infarction; OR, odds ratio; SB, side branch; STEMI, ST-elevation myocardial infarction; TCFA, thin cap fibroatheroma. Other abbreviations as in Table 2.

dial infarction at 1 year.[5]

In non-culprit disease, unstented lipid and TCFA were associated with rapid plaque progression based on imaging at 6-month intervals[59] (**Table 4**). In a cohort of 1,378 patients followed prospectively for 6 years, lipid arc >180° and fibrous cap thickness <65 μm were each independently associated with the development of acute coronary syndrome at the plaque level.[60] The hazard ratio was increased when both these variables were present but fewer lesions possessed both characteristics. In receiver operating characteristic curve analysis, fibrous cap thickness <150 μm had the greatest sensitivity (88%) and negative predictive value (99%) to rule out incident acute coronary syndrome; the presence of lipid plaque with a lipid arc >180° in combination with TCFA <65 μm had the greatest specificity (97%) and positive predictive value (33%).[60] Lipid length >5.9 mm, lipid arc >193°, and area stenosis >69% were predictive of the composite of cardiac death, myocardial infarction, and ischemia-drive revascularization among 1,474 patients followed for a median of 2 years.[61]

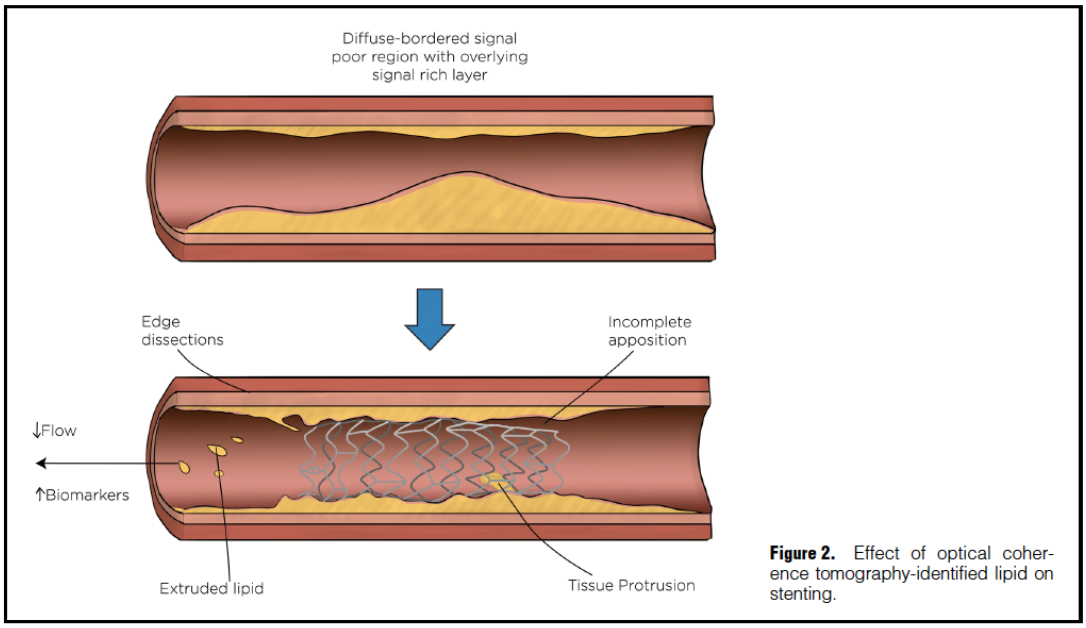

Figure 2. Effect of optical coherence tomography-identified lipid on stenting.

This literature has some limitations. Multivessel imaging was not performed in any of the studies identified. A prospective study design was only used in 1 study (CLIMA: Coronary plaque morphology of the left anterior descending artery and twelve months clinical outcome[5]), whereas the remaining studies were retrospective evaluations of OCT images acquired during image-guided PCI and were confined to the non-stented segment of the PCI target vessel. Only 1 study had exclusively plaque-level endpoints in the study analysis.[57] The imaging parameters associated with events in the current literature are summarized in **Figure 3**.

Discussion

This review identified several key findings: (1) OCT identification of lipid had acceptable reliability, with the potential for improvements with training and automated detection; (2) stenting lipid was associated with plaque prolapse, incomplete apposition, and a reduction in post-intervention coronary flow; (3) stenting lipid was associated with post-procedural increases in cardiac biomarkers and other markers of microvascular obstruction; and (4) unstented lipid has an unfavorable natural history.

The OCT recognition of lipid as a low signal intensity area with diffuse borders is supported by correlative studies using histology and other imaging modalities. However, there is a false positive rate because a minority of plaques with these characteristics are not lipid based on histologic assessment. Operators are encouraged to examine adjacent cross-sections to improve their specificity in identifying lipid. Further, lipid plaque frequently contains micro- and macrocalcifications, and vice versa, making the identification of lipid deep to calcified plaque difficult. Automated approaches hold promise to improve the detection of lipid and to reduce the operator training required to achieve reliable lipid detection. Focal bands of attenuation not found in adjacent cross-sections are characteristic of macrophage infiltration, intraluminal extension with irregular borders is more consistent with red thrombus, and sharply delineated borders in contiguous cross-sections favor calcium. Using a threshold of $<65\,\mu$m, TCFA is accurately diagnosed by OCT in correlative studies. Thresholds for evaluating intra- and interobserver identification of TCFA vary from 65 to $85\,\mu$m with similar results. Semiautomated, machine-based approaches show early promise for improving the consistency of image interpretation of TCFA, and further evaluation of automated detection of lipid plaque is warranted.

Of all plaque types, lipid appears to be the most easily deformed and disrupted. A paucity of supportive fibrous and connective tissues likely contributes to lipid exuding through metallic struts, resulting in intra-stent plaque prolapse and, in some cases, overt mechanical displacement of lipid downstream of the stented segment. Downstream displacement of micro- and macro-lipid plaque components could lead to microvascular obstruction, no-reflow phenomenon, post-procedural increases in enzymes, and leave tissue voids contributing to malapposition. Image guidance during intervention has the advantage of anticipating these potential complications when stenting lipidic lesions. Observation of extensive lipid warrants a focus on appropriate evidence-based systemic lipid therapy.[62]

Despite a diversity of a priori thresholds defining lipid plaque, lipid arc, and TCFA, the associations with stent-elated complications are consistent, with a narrow range of thresholds found. Potential management implications of identifying lipid have not been defined in clinical trials, and there are no established interventional approaches specific to OCT-identified lipid. However, given the observational literature, avoiding ending stents in lipid plaques seems

Table 4. Coronary Disease Natural History Studies Involving Lipid-Related Univariate Predictors of Patient- and Plaque-Level Outcomes

Study	Year	No. patients	Study design	Mean follow-up (months)	Outcomes	Stenosis severity
Iannaccone et al[58]	2018	209	Retrospective, multicenter	12.6	Patient level: composite of death from cardiac causes, non-fatal MI, and clinically driven target vessel revascularization	
Xing et al[61]	2017	1,474	Retrospective multicenter	48	Patient level: composite of cardiac death, acute MI, and ischemia-driven revascularization in non-culprit segment	Area stenosis >69% (HR 6.1, P<0.001; AUC 0.66, P=0.005)
Araki et al[59]	2020	248	Retrospective, single center	7.1	Angiographic: rapid progression (decrease in mean luminal diameter ≥0.4 mm)	
Prati et al[5]	2020	1,003	Prospective, multicenter	12	Patient and vessel level Patient level: composite of cardiac death and target MI in imaged LAD territory	MLA <3.5 mm² (HR 2.07, P=0.032)
Kubo et al[60]	2021	1,378	Retrospective single center	72	Plaque level: ACS in non-culprit imaged segment	MLA <2.9 mm² (HR 4.56, P<0.001)

Study	Lipid extent	Macrophages	Fibrous cap thickness	Plaque rupture
Iannaccone et al[58]	Presence of necrotic core (signal-poor region with poorly delineated borders) with macrophages (HR 3.3, 95% CI 1.6–6.6, P<0.01)		Fibrous cap thickness <65 μm (HR 2.3, 95% CI 1.6–5.4, P=0.04)	Fibrous cap discontinuity (HR 3.7, 95% CI 1.4–9.8, P<0.01)
Xing et al[61]	Lipid arc >193° (HR 2.49, P=0.024; AUC 0.64, P=0.012) Lipid length >5.9 mm (HR 5.69, P=0.001; AUC 0.66, P=0.005)			
Araki et al[59]	Lipid arc >90° (OR 3.1, P<0.001)	Present (OR 2.22, P=0.036)	Fibrous cap thickness <65 μm and lipid arc >90° (OR 4.08, P<0.001)	Fibrous cap discontinuity with cavity formation (OR 2.76, P=0.029)
Prati et al[5]	Lipid arc >180° (HR 2.40, P=0.017)	Present (HR 2.66, P=0.027)	Fibrous cap thickness <75 μm (HR 4.65, P<0.001)	
Kubo et al[60]	Lipid arc >180° (HR 12.6, P<0.001)	Present (HR 4.83, P<0.001)	Fibrous cap thickness <65 μm (HR 10.4, P<0.001)	

AUC, area under the curve; MI, myocardial infarction; MLA, minimum lumen area. Other abbreviations as in Table 3.

justified. Moderating the approach to post-dilation that takes into account the extent of lipid plaque burden would be reasonable. In contrast with the existing literature, which problematizes stent underexpansion with calcified plaque as the principal determinant of restenosis,[63,64] the absence of literature around underexpansion related to lipid is notable.

The presence of lipid-rich plaque is associated with recurrent ischemic events in non-stented segments. However, there were no OCT studies of plaque natural history conducted with a prospective multivessel imaging protocol. In contrast, IVUS plaque characteristics were assessed in 3 large prospective, multivessel imaging studies with adjudication of events at the patient and plaque level.[3,65,66] Patients who have a significant lipid burden frequently have other risk factors for recurrent events, making it important to have enough outcome events in observational studies to allow clinical variables to be adjusted for. When imaging findings are evaluated for predictive value at the patient level, they serve as an overall measure of risk rather than providing insight into plaque-level events. Therefore, the development of a treatment target for lipid-rich plaque will require robust plaque-level data. Adequately powered natural history studies are needed to provide further evidence for the effects of lipid plaque on future events at both the patient and plaque levels. Ideally, these studies would be conducted with reproducible quantification of lipid by automated and computerized approaches, laying the groundwork for a definition of clinically relevant lipid based on predictive ability for future events.

Study Limitations

Several limitations of this study are worth highlighting. The scoping review methodology provides an overview of the available evidence, without formally assessing study quality or aggregating outcomes across studies. Studies that compare OCT with other imaging modalities or histopathologic specimens rely on manual coregistration, which can introduce the possibility of bias, especially because lipid is frequently found colocated and may be mistaken for calcium, and vice versa. Given the observational nature of the data, the results are linked to the specific populations studied and include heterogeneity in the a priori imaging thresholds applied to assess for associations.

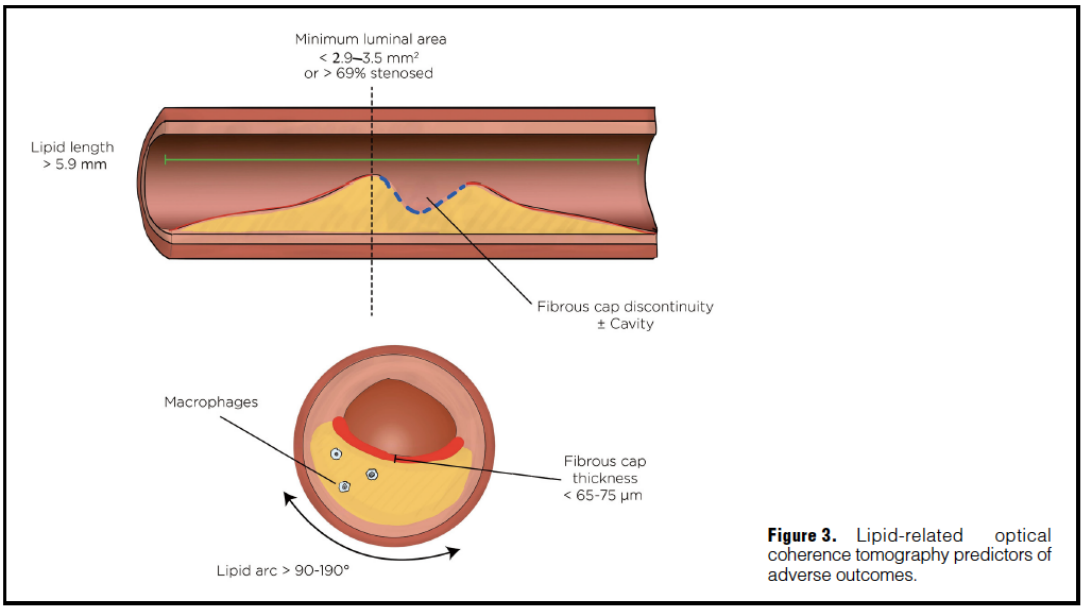

Figure 3. Lipid-related optical coherence tomography predictors of adverse outcomes.

Conclusions

Lipid and TCFA are readily identifiable on OCT with acceptable reliability. Stenting lipid is associated with plaque prolapse, incomplete apposition, a reduction in post-stenting coronary flow, and post-procedural increases in cardiac biomarkers. Characteristics of unstented lipid are linked to rapid plaque progression and recurrent ischemic events and should be investigated further.

Impact on Daily Practice

Lipid is identified as a low signal intensity area with diffuse borders on OCT. Stenting lipid is associated with edge dissections, reduced vessel flow and periprocedural increases in enzymes. It is reasonable to avoid ending stents in lipid and to moderate the approach to post-dilation.

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Data Availability

Not applicable.

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9 PART VI. FINAL REMARKS AND FUTURE DIRECTIONS

MI and SCD are the most common acute manifestation of patients with CAD globally. pPCI is the preferred method of reperfusion in patients with STEMI and has changed the prognosis of this populations once presenting with an ACS. These patients often have multivessel CAD, with residual stenoses in locations separate from the culprit lesion that caused the acute event.

9.1 IS THE FUTURE ISCHEMIA-DRIVEN OR IMAGING-DRIVEN REVASCULARIZATION?

COMPLETE-OCT substudy demonstrated that non-culprit lesions in patients with STEMI and multivessel CAD commonly contain TCFA plaque morphology, with 47% of patients having at least one obstructive non-culprit TCFA, meaning that about half of ACS patients have non-culprit lesions with plaque morphology similar to the culprit lesion that caused the index event (25). This observation is supported by other large scale registry studies, including PROSPECT (97), ATHEROREMO-IVUS (168), and the Lipid-Rich Plaque study (201), demonstrated that lesions with vulnerable plaque morphology were associated with a 2-4 fold increase in cardiovascular events, regardless of physiological significance.

An ischemia-driven PCI strategy is well established in patients with stable CAD and has been shown to be superior to an angiography-guided strategy; but there is uncertainty regarding the use of this strategy in the setting of ACS. Given recent trials; FLOWER-MI and FUTURE, a physiology-guided strategy to guide PCI for non-culprit lesions in STEMI is not superior to angiography alone.

Collectively, these data raise the question of whether a physiology-guided strategy in the setting of ACS will be able to identify all high-risk obstructive lesions, as it does not provide insight into the biology of the plaque composition. On the other hand, the incidence of TCFA increases with lesion severity, so a physiology guided strategy will likely be complimentary to OCT guided imaging in identifying these lesions that require intervention.

9.2 IS THE FUTURE JUST NOVEL MEDICAL THERAPIES?

LRP detection could also be used as a surrogate marker for event reduction with medical therapies such as high-dose statin or PCSK9 inhibitors. One study is investigating the effect of a PCSK9 inhibitor to abolish or reduce LCBI and alter OCT findings; PACMAN-AMI trial (NCT03067844), which aims to examine the effects of the PCSK9-inhibiting antibody alirocumab on coronary atherosclerosis in patients with acute myocardial infarction with NIRS, IVUS, and OCT imaging modalities.

Systemic risk factors modification strategy reduced the incidence of death and myocardial infarction by 30%; however, a subset of patients continued to have recurrent symptoms related to coronary artery disease progression and lesion instability (273-275). Non-invasive imaging and coronary angiography were limited techniques to identify those plaques with a higher propensity for future instability. Thus, focal prophylactic treatment of potentially vulnerable plaques was not performed because PCI of intermediate lesions were shown to have restenosis rates similar to those of PCI for symptom-causing lesions, thereby obviating the potential benefits of a prophylactic strategy (276). With the introduction of drug-eluting stents, capable of reducing restenosis rates to <5%, opened the debate about optimal management of incidental potentially unstable non-target lesions noted during PCI in an acute setting aiming to reduce death and myocardial infarction.

9.3 IS THE FUTURE ABOUT PREVENTIVE PCI?

Can intracoronary imaging provide sufficient risk stratification to warrant PCI of a plaque in the absence of refractory symptoms or negative physiology assessment?

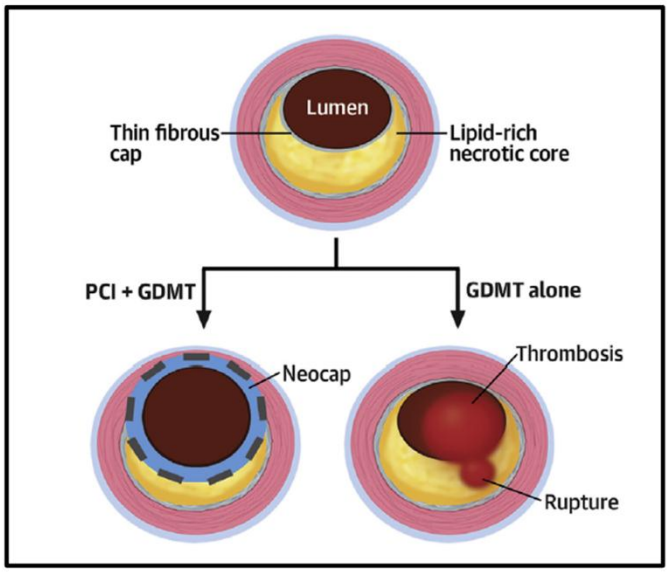
The event rate for medical treatment with FFR > 0.80 varies among different studies, but at worst reaches 1% per year for death or MI related specifically to the interrogated vessel (224, 227, 228, 230). If PCI had no acute risk or long-term complications, then it could be applied almost universally to those no-flow limiting vulnerable plaques. However, despite enormous improvements in device design, implantation technique, and pharmacologic therapy; PCI carries immediate and delayed consequences. Modern stents have a rate of 2% to 3.5%/year. Given the very low event rates in unselected FFR negative lesions, definite imaging criteria that could enrich outcomes remain under investigation; however, there is good evidence of certain vulnerability criteria that are related to future MACE, imaging also has the power to improve outcomes by PCI optimization.

Stone et al. (277) conducted PROSPECT ABSORB. Patients with an angiographically non-obstructive stenosis not intended for PCI but with IVUS plaque burden of >65% were randomized to PCI with bioresorbable vascular scaffold versus guideline-directed medical therapy alone. The primary powered effectiveness endpoint was the IVUS-derived minimum lumen area (MLA) at protocol-driven 25-month follow-up.

High-risk vulnerable plaques might have a benign angiographic appearance, but their presence portends an increased lesion-specific and patient-level risk of unanticipated future MACE despite intensive treatment with guideline-directed medical therapy (97, 167, 168, 201, 203, 278). However, there is not enough evidence to support whether prophylactic revascularization of non–flow-limiting vulnerable plaques might improve patient prognosis.

The background of the PROSPECT ABSORB (277) was based on experimental and observational human studies that supported the concept of fibroatheromas PCI with either metallic stents or bioresorbable vascular scaffolds resulting in neointimal hyperplasia, effectively thickening the fibrous cap and normalizing wall stress (279-283). PCI might thus provide freedom from atherosclerotic progression and clinical events arising from the vulnerable plaque site (25, 284-287).

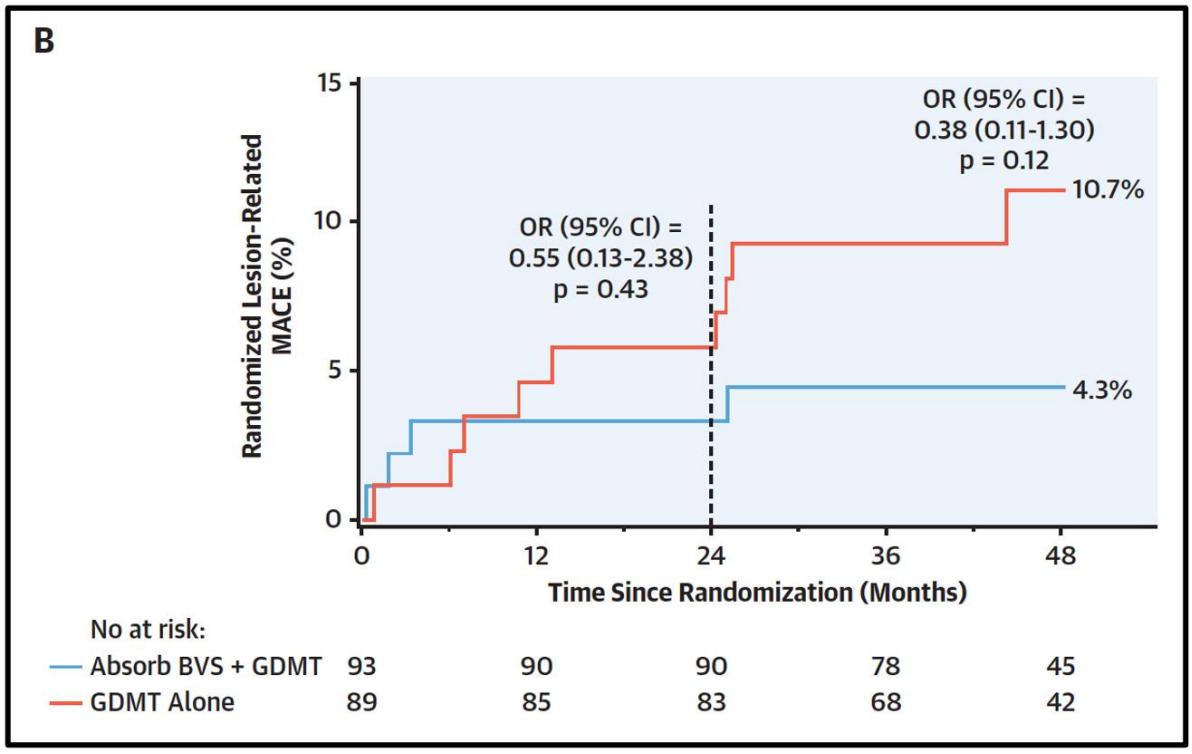
PROSPECT ABSORB. Conceptual framework. High-risk plaque.



Stone, GW et al. J Am Coll Cardiol 2020 Vol. 76 Issue 20 Pages 2289-2301

The secondary major clinical effectiveness endpoint of randomized lesion–related MACE at the latest follow-up occurred in 4.3% of bioresorbable vascular scaffold-treated patients compared with 10.7% of guideline-directed medical therapy alone–treated patients (OR: 0.38; 95% CI: 0.11 to 1.28; p ¼ 0.12).

PROSPECT ABSORB. Lesion-related MACE



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PROSPECT ABSORB (277) concluded that PCI with bioresorbable vascular scaffold implantation in angiographically mild, non–flow-limiting lesions with large plaque burden, small MLA, and high lipid content was safe and substantially enlarged luminal dimensions during follow-up; and was associated with favorable long-term clinical outcomes.

There is an ongoing randomized study; PREVENT (The Preventive Coronary Intervention on Stenosis With Functionally Insignificant Stenosis With Vulnerable Plaque Characteristics; URL: https://www.clinicaltrials. gov. Unique identifier: NCT02316886) using multimodality imaging

(NIRS, OCT, virtual histology-IVUS, and IVUS). The purpose of this study is to determine whether preventive coronary intervention on functionally insignificant coronary stenosis with vulnerable plaque characteristics plus optimal medical therapy reduces the incidence of MACE.

9.4 ARE WE DONE WITH THE NON-CULPRIT LESION REVASCULARIZATION GUIDELINES?

Approximately 50% of patients with STEMI have multivessel disease (5, 288). PCI options for patients with STEMI and multivessel disease include: 1) culprit artery-only primary PCI, with PCI of non-culprit arteries only for spontaneous ischemia or intermediate or high-risk findings on predischarge non-invasive testing; 2) multivessel PCI at the time of primary PCI; or 3) culprit artery-only primary PCI followed by staged PCI of non-culprit arteries.

Initial observational studies, RCTs, and meta-analyses comparing culprit artery-only PCI with multivessel PCI reported conflicting results (13, 289-292), likely because of differing inclusion criteria, study protocols, timing of multivessel PCI, statistical heterogeneity, and variable endpoints. Previous clinical practice guidelines recommended against PCI of non-culprit artery stenoses at the time of primary PCI in hemodynamically stable patients with STEMI (3, 192).

Planning for routine, staged PCI of non-infarct artery stenoses based on the initial angiographic findings was not addressed in these previous guidelines, and non-infarct artery PCI was considered only in the limited context of spontaneous ischemia or high-risk findings on predischarge non-invasive testing. The earlier recommendations were based in part on safety concerns, which included increased risks for procedural complications, longer procedural time, contrast nephropathy, and stent thrombosis in a prothrombotic and proinflammatory state, and in part on the findings from many observational studies and meta-analyses of trends

toward or statistically significant worse outcomes in those who underwent multivessel primary PCI.

Four RCTs the suggested that a strategy of multivessel PCI, either at the time of primary PCI or as a planned, staged procedure, may be beneficial and safe in selected patients with STEMI (14-17). Based on these findings, the prior Class III (Harm) recommendation with regard to multivessel primary PCI in hemodynamically stable patients with STEMI was upgraded and modified to a Class IIb recommendation to include consideration of multivessel PCI, either at the time of primary PCI or as a planned, staged procedure.

2015. ACC/AHA/SCAI. Guidelines on primary PCI for patients with STEMI.

2013 Recommendation	2015 Focused Update Recommendation	Comment
Class III: Harm PCI should not be performed in a noninfarct artery at the time of primary PCI in patients with STEMI who are hemodynamically stable (11-13). (*Level of Evidence: B*)	***Class IIb*** PCI of a noninfarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure (11–24). (*Level of Evidence: B-R*)	Modified recommendation (changed class from "III: Harm" to "IIb" and expanded time frame in which multivessel PCI could be performed).

2018. ESC/EACTS. Guidelines on myocardial revascularization

Primary percutaneous coronary intervention for myocardial reperfusion in ST-elevation myocardial infarction: procedural aspects (strategy and technique)

Recommendations	Class[a]	Level[b]
Strategy		
Routine revascularization of non-IRA lesions should be considered in patients with multivessel disease before hospital discharge.[211–214]	IIa	A
CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.	IIa	C
In cardiogenic shock, routine revascularization of non-IRA lesions is not recommended during primary PCI.[190]	III	B
Technique		
Routine use of thrombus aspiration is not recommended.[223–226,228]	III	A

© ESC 2018

CABG = coronary artery bypass grafting; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

Recently, the Complete vs Culprit-Only Revascularization to Treat Multivessel Disease After Early PCI for STEMI (COMPLETE) study demonstrated that a strategy of complete revascularization with staged PCI of the non-culprit lesion reduced the composite of CV death and new MI (22). Before the COMPLETE trial, guideline recommendations were limited to small sample-size RCTs with lower power to detect differences in CV death or new MI. In addition, most trials included revascularization in the primary composite outcome, which is subject to criticism in an open-label trial. But currently, reasonable conclusions can be made regarding complete revascularization in patients with multivessel disease after STEMI presentation.

The 2021 ACC/AHA/SCAI revascularization guidelines were recently published and for the first-time non-culprit lesion PCI has class of recommendation 1, with level of evidence A. This recommendation is supported by the COMPLETE trial (22).

2021. ACC/AHA/SCAI Guidelines for Coronary Artery Revascularization

Recommendations for Revascularization of the Non-Infarct Artery in Patients With STEMI
Referenced studies that support the recommendations are summarized in Online Data Supplement 8.

COR	LOE	RECOMMENDATIONS
1	A	1. In selected hemodynamically stable patients with STEMI and multivessel disease, after successful primary PCI, staged PCI of a significant non-infarct artery stenosis is recommended to reduce the risk of death or MI (1-4).
2a	C-EO	2. In selected patients with STEMI with complex multivessel non-infarct artery disease, after successful primary PCI, elective CABG is reasonable to reduce the risk of cardiac events.
2b	B-R	3. In selected hemodynamically stable patients with STEMI and low-complexity multivessel disease, PCI of a non-infarct artery stenosis may be considered at the time of primary PCI to reduce cardiac event rates (1,2,5-7).
3: Harm	B-R	4. In patients with STEMI complicated by cardiogenic shock, routine PCI of a non-infarct artery at the time of primary PCI should not be performed because of the higher risk of death or renal failure (8-10).

Despite of the strong evidence about complete revascularization, current guidelines focus exclusively on the importance of ischemia and do not mention the vulnerable plaque (36, 233, 234). Recent studies have provided important insights by showing that ischemia is not the only predictor of future adverse events, and therefore, intravascular imaging and vulnerable plaque detection merits further attention in future guideline drafting (25, 203, 205, 250, 251).

Although there is enough evidence that have suggested multivessel PCI may be associated with better outcomes, questions remain regarding optimal timing of non-culprit vessel PCI and optimal method of evaluating non-culprit lesions; percent of diameter stenosis by angiography-QCA, FFR and/or intracoronary imaging.

9.5 DO WE NEED ANOTHER TRIAL IN NON-CULPRIT LESION PCI?

The COMPLETE trial showed clear benefit of complete revascularization strategy in patients presenting with STEMI and multivessel CAD; however, the decision for revascularization was made on operator assessment of luminal stenosis by angiography (22). Then, the question whether this strategy could be optimized by physiology and/or imaging is unclear. Future trials need to focus on the value that physiology and imaging can add to the decision-making process; acknowledging that this could increase the cost of the assessment/intervention and the risk of PCI related complications and stent failure.

Based on this rationale, there is an urgent need for an adequately powered randomized trial comparing a physiology-guided revascularization strategy to an angiography-guided strategy for non-culprit lesion PCI in patients with STEMI and multivessel CAD with a large OCT imaging substudy supporting the PCI decision-making process in negative-physiology non culprit lesions if vulnerable plaque is present. A non-inferiority trial design is appropriate for this comparison as we hypothesize that a physiology-guided approach may preserve the benefit of an angiography-guided approach on future CV death, MI, and ischemia-driven revascularization, while reducing important additional outcomes of safety and cost. The COMPLETE-2 trial will start recruitment soon and will provide strong insights about the role of both physiology and imaging in patients presenting with STEMI and multivessel CAD.

10 PART VII. PRESENTATIONS AND ACADEMIC COLLABORATIONS

10.1 PRESENTATIONS

1. Coronary Physiology vs. Coronary Imaging in CAD. Canadian Cardiovascular Congress CCC 2021. Canada. Oct 23, 2021.
2. Treatment of non-culprit lesions after STEMI. SICA 2021 Mexico, International Course on Acute Coronary Syndromes, National Institute of Cardiology 'Ignacio Chavez" Sep 13, 2021.
3. Concepts on the Treatment of Complex and Challenging Optical Coherence Tomography (OCT)-Guided Cases Using MLD MAX & Discussion of a Clinical Case. SOLACI-CACI 2021 - Symposium ABBOTT. Argentina. Aug 3, 2021.
4. Introduction to MLD-MAX Algorithm and Light Lab Data. CRT Virtual Fellows Course 2021. United States. Jul 10, 2021.
5. STEMI: Complete Revascularization Vs Culprit Lesion. CARDIOEXCELLENCE USA 2021. United States. Jun 4, 2021.
6. Complex PCI in Coronary Calcified Lesions, the right tools and techniques. Elevate PCI Conclave 2021. India. Jun 11, 2021.
7. Are we safe to defer patients using OCT in ACS?. ACC 2021 Atlanta Session: Invasive Imaging and Physiology Diagnosis and Management of ACS Patients and Plaques. United States. May 15, 2021.
8. Complete Revascularization in AMI: One-stop fix or Wait a Few Days. SCAI 2021 Virtual Scientific Sessions. United States. May 16, 2021.

9. Imaging in PCI. IVUS and OCT in all cases. XII Cardiology and Cardiac Surgery International Symposium. Colombia. May 7, 2021.
10. Revascularization of non-culprit arteries after STEMI: PRO. Mexican Cardiology Congress 2021. Mexico. Mar 19, 2021.
11. My Approach for COMPLETE Revascularization. Best of Both the Worlds: Integrating Physiology with Morphology 2021. India. Jan 23, 2021.
12. ST Segment Elevation Myocardial Infarction. Interventional Cardiology Perspective. Costal Rica Cardiology National Congress 2020. Costa Rica. Dec 4, 2020.
13. Optical Coherence Tomography, new gold standard in the diagnosis and treatment of the coronary artery disease. Cardiolili 2020 XIII Congreso Internacional de Cardiologia. Colombia. Nov 7, 2020.
14. Imaging in Acute Myocardial Infarction. CRT Virtual Imaging and Physiology 2020. United States. Nov 21, 2020.
15. Use of optical coherence tomography in acute coronary syndrome: Lessons learned from the COMPLETE trial. CITIC Digital 2020. Mexico. Nov 25, 2020.
16. OCT basic features in Interventional Cardiology; When, How, What to focus on. XVI Congreso Colombiano De Hemodinamia 2020. Nov 6, 2020.
17. Intravascular Imaging. CAIC-ACCI 2020 Interventional Cardiology / Fellows' Course. Canada. Oct 17, 2020.
18. How to use intravascular imaging to optimize PCI in ACS. Transcatheter Cardiovascular Therapeutics 2020. United States. Oct 18, 2020.
19. Antiplatelet therapy in Acute Coronary Syndrome. Colombian Cardiology Congress 2020. Oct 23, 2020.

20. Spotlight Discussion: Management of multivessel disease in patients with acute coronary syndromes. Intracoronary Guidance in Complex PCI. Spain. Oct 26, 2020.
21. How benign is good enough?. Canadian Coronary Physiology and Invasive Imaging Symposium. CPI 2020. Montreal, Quebec, Canada. Feb 5, 2020.
22. Hybrid imaging cases from novel IVUS/ OCT imaging catheter. Canadian Coronary Physiology and Invasive Imaging Symposium. CPI 2020. Montreal, Quebec, Canada. Feb 5, 2020.
23. Coronary Physiology. When, why and which index? English Session. CALA Kickoff Meeting. Abbott Vascular. 2020. Sao Paulo, Brazil. Feb 17, 2020.
24. Coronary Physiology. When why and which index? Spanish Session. CALA Kickoff Meeting. Abbott Vascular. 2020. Sao Paulo, Brazil. Feb 17, 2020.
25. OCT, fundamentals of interpretation and clinical indications. CALA Kickoff Meeting. Abbott Vascular. 2020. Sao Paulo, Brazil. Feb 18, 2020.
26. OCT, How to perform, interpret and correlate intravascular imaging. 12th International Cardiology Meeting. CADECI. 2020. Guagalajara, Mexico. Feb 22, 2020.
27. Coronary Physiology. Resting indexes. (RFR-iFR). OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.
28. Coronary physiology. Fractional Flow Reserve (FFR) vs. Resting Indexes (RFR- IFR). OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.
29. Optical Coherence Tomography (OCT) vs. Intravascular Ultrasound (IVUS) OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.
30. Optical Coherence Tomography (OCT) in left main. OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.

31. Optical coherence tomography and coronary physiology: clinical use in special clinical situations. XV Colombian Interventional Cardiology Congress. 2019. Cartagena, Colombia.
32. Discussion Panel: Coronary Anatomy and Physiology in special situations. XV Colombian Interventional Cardiology Congress. 2019. Cartagena, Colombia.
33. Novel intravascular imaging hybrid catheter, IVUS and OCT. TCT Innovation I: Global Perspectives in MedTech and Emerging Technological Trends. Transcatheter Cardiovascular Therapeutics 2019. San Francisco, California, United States.
34. Case Presentations From Former CRF Intravascular Fellows- Part 1. Intravascular Imaging Stent Guidance: Part 1- The Basics. Transcatheter Cardiovascular Therapeutics 2019. San Francisco, California, United States.
35. OCT: Now that I see It, I know how to treat It: A hands-on OCT skills Lab. Training Pavilion. Transcatheter Cardiovascular Therapeutics 2019. San Francisco, California, United States.
36. Image interpretation and clinical indications. Canadian Interventional Cardiology Fellows Course. 2019. Toronto, Ontario, Canada.
37. OCT. PCI Optimization. Canadian Interventional Cardiology Fellows Course. 2019. Toronto, Ontario, Canada.
38. How OCT changed my clinical practice. WebEx Quebec and Ottawa. Abbott Vascular. 2019. Hamilton, Ontario, Canada.
39. Case Presentation: A Patient With STEMI and Multivessel Disease. American College of Cardiology. ACC 2019. New Orleans, Louisiana, United States.
40. IVUS-OCT Novel Hybrid Imaging catheter. Canadian Coronary Physiology and Invasive Imaging Symposium. CPI 2019. Montreal, Quebec, Canada.

41. The orange is the new black. CALA Kickoff Meeting. Abbott Vascular. 2019. Orlando, Florida, United States.
42. OCT: Coherent though on Coherent optics. Excellence in Interventional Cardiology. EIC 2018. Whistler, British Columbia, Canada.
43. Functional Vs. Anatomical Approach to Coronary Artery Disease. Cardiology Niagara 22nd Annual Cardiac Meeting. 2018. St. Catharines, Ontario, Canada.
44. OCT Interpretation and Clinical Indications. OCT Symposium. SOLACI- SOCIME Congress 2018. Mexico City, Mexico.
45. OCT Image Acquisition and Image Review. OCT Training Course. Fundación Clinica Shaio. Bogota, Colombia. Jun 27, 2018.
46. Technical Aspects and Decision Making in STEMI. Combined Interventional Cardiology and Stroke Journal Club. Ancaster, Ontario, Canada. Nov 8, 2017.
47. Antiplatelet Therapy in Patients with Acute Coronary Syndrome. Essentials II Cardiologia. 2017. San Jose de Costa Rica, Costa Rica.
48. Coronary Percutaneous Interventions. Essentials II Cardiologia. 2017. San José de Costa Rica, Costa Rica.
49. Case Presentation: Multivessel Disease in a Patient with Large Inferior STEMI with RCA Culprit and Proximal LAD Non-culprit Lesion. Transcatheter Cardiovascular Therapeutics. TCT 2016. Washington DC, Washington, United States.
50. COMPLETE Trial. NACSIC Cardiovascular Science investigators Congress. 2015. Orlando, Florida, United States.
51. Angiographic Core Lab for COMPLETE Trial. Investigator Meeting at American Heart Association Congress. AHA 2015. Orlando, Florida, United States.
52. Angiographic Core Lab for COMPLETE Trial. Canadian Investigators Meeting at Canadian Cardiovascular Congress. 2015. Toronto, Ontario, Canada.

10.2 WORKSHOPS

1. Tips and Tricks to facilitate interventions with intracoronary imaging - Workshop. CITIC 2021. Mexico. Sep 23, 2021.
2. OCT Advanced Sizing Workshop. Canadian OCT Symposium. 2019. Montreal, Quebec, Canada.
3. OCT Workshop. Tremblant Interventional Cardiology. TIC 2019. Tremblant, Quebec, Canada.
4. OCT Sizing Workshop. Canadian OCT Symposium. 2018. Mississauga, Ontario, Canada.
5. OCT Workshop. Round table with 6 cases. Canadian Interventional Cardiology Fellows Course. 2018. Toronto, Ontario, Canada.

10.3 FACULTY DEVELOPMENT COURSES

1. Fundamentals OCT Course. McMaster University. Canada
2. Canadian Fellowship OCT rounds. McMaster University. Canada
3. Latin-American Fellowship OCT rounds. McMaster University. Canada
4. Hamilton Intravascular Imaging Rounds. McMaster University. Canada
5. OCT Skills Lab. Abbott Vascular. USA

10.4 LIVE CASES

1. Live Case 1. Assessing coronary physiology on borderline coronary artery disease. OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.
2. Live case 2. Coronary Physiology and OCT in stent failure. OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.
3. Live Case 3. Coronary Physiology and OCT in left main disease. OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.
4. Live Case 4. OCT in stent restenosis. OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.
5. Live Case 5. OCT in borderline left main disease. OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.
6. Live Case 6. OCT in ambiguous culprit lesion. OCT and Physiology Workshop. Abbott Vascular. 2019. Medellin, Colombia.

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