Relationship Between Coronary Plaque Morphology on Coronary CT Angiography and Invasive Functional Assessment in Stable Coronary Artery Disease

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Abstract

Background: Stable coronary artery disease (SCAD) remains a major contributor to cardiovascular morbidity and mortality worldwide despite substantial advances in diagnostic imaging and preventive cardiology. Accurate identification of hemodynamically significant coronary lesions is essential for guiding revascularization decisions and optimizing patient outcomes. Although invasive physiological assessment using fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) remains the reference standard for determining lesion-specific ischemia, coronary computed tomography angiography (CCTA) has rapidly evolved from a purely anatomical imaging modality into a comprehensive noninvasive tool capable of evaluating plaque morphology, atherosclerotic burden, and ischemia-related plaque characteristics. Contemporary evidence suggests that specific plaque features identified on CCTA may correlate strongly with invasive functional lesion significance beyond conventional assessment of luminal stenosis severity alone.

High-risk plaque characteristics including low-attenuation plaque, positive remodeling, spotty calcification, napkin-ring sign, and increased total plaque burden have been associated with impaired coronary flow dynamics and physiologically significant ischemia. These imaging biomarkers reflect underlying plaque vulnerability, inflammatory activity, necrotic core expansion, and adverse vascular remodeling that contribute to functional coronary obstruction. In addition, advances in quantitative plaque analysis, computational flow modeling, and computed tomography-derived fractional flow reserve (FFR-CT) have enhanced the ability of CCTA to predict lesion-specific ischemia noninvasively and improve risk stratification in patients with stable coronary artery disease.

Recent studies have demonstrated significant correlations between adverse plaque morphology on CCTA and abnormal invasive physiological indices, supporting the growing role of multimodality imaging in precision cardiovascular medicine. The integration of anatomical plaque characterization with functional assessment may improve patient selection for invasive angiography, reduce unnecessary coronary interventions, and facilitate individualized management strategies. Furthermore, emerging technologies including artificial intelligence-assisted plaque analysis and machine learning algorithms may further refine ischemia prediction and prognostic assessment in stable coronary artery disease.

This review discusses the relationship between coronary plaque morphology assessed by coronary CT angiography and invasive functional lesion assessment in stable coronary artery disease. Particular emphasis is placed on high-risk plaque features, physiological significance, invasive coronary physiology, CT-derived functional assessment, prognostic implications, and future directions in precision coronary imaging and personalized cardiovascular care.

Keywords: Plaque Criteria, Multi-Slice Computed Tomography, Stable Coronary Artery Diseases

Introduction

Stable coronary artery disease (SCAD) remains one of the leading causes of cardiovascular morbidity and mortality worldwide despite major advances in preventive cardiology, pharmacotherapy, and coronary revascularization strategies. Accurate identification of functionally significant coronary artery stenoses is essential for guiding appropriate therapeutic decisions and improving long-term cardiovascular outcomes. Traditionally, coronary angiography has served as the standard anatomical modality for evaluating coronary artery disease; however, luminal stenosis severity alone frequently fails to correlate with the true physiological impact of coronary lesions. Consequently, increasing emphasis has been placed on integrating anatomical plaque characterization with functional lesion assessment to improve diagnostic accuracy and optimize individualized patient management [1,2].

Invasive coronary physiological assessment using fractional flow reserve (FFR) and, more recently, instantaneous wave-free ratio (iFR) has become the reference standard for determining lesion-specific ischemia. Multiple clinical trials demonstrated that physiology-guided coronary intervention improves cardiovascular outcomes while reducing unnecessary revascularization procedures compared with angiography-guided strategies alone. Nevertheless, invasive physiological assessment requires coronary catheterization, pressure-wire manipulation, procedural expertise, and additional costs, limiting its universal application in all patients with stable coronary artery disease [3,4].

Coronary computed tomography angiography (CCTA) has evolved substantially over the past two decades from a purely anatomical imaging modality into a comprehensive noninvasive tool capable of evaluating coronary stenosis severity, plaque burden, plaque composition, vascular remodeling, and high-risk plaque features. Technological improvements in scanner resolution, image acquisition speed, radiation reduction protocols, and post-processing software have significantly enhanced the diagnostic and prognostic capabilities of CCTA. Contemporary studies increasingly demonstrate that plaque morphology assessed by CCTA may correlate more closely with lesion-specific ischemia than stenosis severity alone [5].

Atherosclerotic plaque characteristics play a fundamental role in determining coronary flow limitation and ischemic potential. High-risk plaque features such as low-attenuation plaque, positive remodeling, spotty calcification, napkin-ring sign, and large noncalcified plaque burden are associated with increased inflammatory activity, necrotic core expansion, endothelial dysfunction, and adverse hemodynamic alterations. These morphological characteristics may impair coronary flow reserve and contribute to ischemia even in lesions with only moderate angiographic stenosis. Conversely, some heavily calcified lesions may appear severe anatomically while producing limited physiological significance [6,7].

Recent advances in quantitative plaque analysis and computational imaging have further strengthened the role of CCTA in functional coronary assessment. Quantitative evaluation of total plaque burden, fibrofatty plaque volume, low-density noncalcified plaque, and perivascular fat attenuation now provides valuable information regarding plaque vulnerability and ischemic potential. In addition, computed tomography-derived fractional flow reserve (FFR-CT) has emerged as a noninvasive modality capable of integrating anatomical and physiological assessment within a single imaging platform. FFR-CT uses computational fluid dynamics to estimate lesion-specific pressure gradients and has demonstrated good correlation with invasive FFR measurements [8].

Several contemporary studies have shown strong associations between adverse plaque morphology on CCTA and abnormal invasive physiological indices. Lesions demonstrating positive remodeling, low-attenuation plaque, extensive noncalcified plaque burden, and high-risk plaque patterns are more likely to exhibit physiologically significant ischemia during invasive assessment. These findings suggest that coronary plaque composition and biological activity may contribute substantially to lesion-specific hemodynamic impairment beyond simple luminal narrowing [9].

The growing integration of anatomical plaque characterization and invasive functional assessment reflects the broader transition toward precision cardiovascular medicine. Rather than relying solely on stenosis severity, modern coronary evaluation increasingly incorporates plaque morphology, physiological significance, inflammatory activity, and patient-specific clinical risk into individualized

diagnostic and therapeutic decision-making. Emerging technologies including artificial intelligence-assisted plaque analysis, machine learning algorithms, and advanced computational imaging are expected to further refine ischemia prediction and cardiovascular risk stratification in stable coronary artery disease [10].

Despite significant progress, important challenges remain regarding the optimal integration of plaque imaging and invasive physiology in clinical practice. The relative prognostic importance of individual plaque features, standardization of quantitative plaque assessment, and the incremental value of plaque morphology beyond FFR and iFR continue to evolve. Accordingly, this review aims to discuss the relationship between coronary plaque morphology assessed by coronary CT angiography and invasive functional lesion assessment in stable coronary artery disease, with particular emphasis on high-risk plaque features, physiological significance, CT-derived functional assessment, and emerging concepts in precision coronary imaging.

Pathophysiological Basis of Coronary Plaque Morphology and Functional Ischemia

Coronary atherosclerosis is a dynamic inflammatory disease characterized by lipid accumulation, endothelial dysfunction, vascular remodeling, inflammatory cell infiltration, and progressive plaque evolution within the coronary arterial wall. Although luminal stenosis severity has traditionally been used to estimate the likelihood of myocardial ischemia, contemporary evidence demonstrates that plaque morphology and composition substantially influence coronary flow limitation and lesion-specific physiological significance. Consequently, the relationship between coronary plaque characteristics and ischemia extends beyond simple anatomical narrowing and reflects complex interactions between plaque burden, vascular remodeling, endothelial function, and coronary hemodynamics [11,12].

The development of coronary atherosclerosis begins with endothelial injury and dysfunction triggered by hypertension, dyslipidemia, diabetes mellitus, smoking, oxidative stress, and systemic inflammation. Endothelial dysfunction increases vascular permeability and promotes subendothelial accumulation of low-density lipoprotein cholesterol, inflammatory cell recruitment, and foam-cell formation. Progressive inflammatory activation contributes to necrotic core expansion, fibrous cap thinning, smooth muscle cell migration, and extracellular matrix remodeling, ultimately leading to formation of vulnerable atherosclerotic plaques [13].

Coronary plaque morphology significantly affects coronary flow dynamics and myocardial perfusion. Lesions with large plaque burden and extensive noncalcified components may impair coronary flow reserve despite only moderate luminal stenosis on angiography. Conversely, some heavily calcified lesions may appear anatomically severe while producing limited physiological ischemia because of preserved vessel remodeling and stable plaque architecture. This discrepancy highlights the limitations of relying exclusively on luminal stenosis severity for determining lesion significance [14].

Positive remodeling represents one of the most important plaque characteristics associated with functional ischemia and adverse cardiovascular outcomes. In positively remodeled lesions, outward expansion of the vessel wall initially preserves luminal diameter despite progressive plaque accumulation. Although angiographic stenosis may therefore appear only moderate, these lesions frequently contain large lipid-rich necrotic cores, extensive inflammatory activity, and impaired endothelial function capable of producing substantial physiological flow limitation. Multiple studies demonstrated strong associations between positive remodeling and abnormal invasive FFR measurements [15].

Low-attenuation plaque is another critical high-risk plaque feature strongly associated with ischemia-producing lesions. Low-attenuation plaques typically reflect lipid-rich necrotic cores with high inflammatory burden and increased plaque vulnerability. These plaques may impair coronary vasomotor function, reduce coronary flow reserve, and promote endothelial dysfunction, thereby contributing to lesion-specific ischemia even before severe luminal obstruction develops. CCTA studies consistently demonstrated that low-attenuation plaque volume correlates independently with invasive physiological significance [16].

Spotty calcification and the napkin-ring sign are additional markers of vulnerable plaque morphology

associated with adverse hemodynamic and clinical consequences. Spotty calcification reflects active microcalcification and ongoing inflammatory activity within unstable plaques, whereas the napkin-ring sign represents a ring-like peripheral high-attenuation area surrounding a low-attenuation necrotic core. These imaging characteristics are frequently observed in plaques associated with physiological ischemia and future acute coronary syndromes [17].

Plaque burden itself may play a more important role in determining ischemia than stenosis severity alone. Quantitative plaque analysis studies demonstrated that total atherosclerotic burden, noncalcified plaque volume, fibrofatty plaque content, and low-density plaque volume correlate strongly with abnormal invasive FFR values. Lesions with extensive diffuse plaque accumulation may impair coronary flow reserve through cumulative resistance along the vessel length even in the absence of severe focal stenosis [18].

Coronary flow limitation is also influenced by endothelial dysfunction and microvascular abnormalities associated with vulnerable plaque biology. Inflammatory cytokines, oxidative stress, and endothelial injury impair nitric oxide bioavailability and vasodilatory capacity, resulting in abnormal coronary vasomotor regulation. This dysfunction contributes to impaired hyperemic flow reserve and may exaggerate the physiological significance of anatomically intermediate lesions [19].

The relationship between plaque morphology and physiological significance is particularly important in stable coronary artery disease because many ischemia-producing lesions exhibit only moderate angiographic stenosis. Studies integrating CCTA plaque characterization with invasive physiological assessment demonstrated that high-risk plaque features independently predict lesion-specific ischemia beyond luminal narrowing alone. These findings support the growing concept that coronary plaque biology and morphology are major determinants of functional coronary obstruction [20].

Advances in computational imaging, machine learning, and quantitative plaque analysis continue to improve understanding of the complex relationship between coronary plaque morphology and ischemia. Emerging technologies now enable automated quantification of plaque components, prediction of hemodynamic significance, and integration of anatomical and physiological data within precision cardiovascular imaging platforms. As imaging technologies evolve, comprehensive plaque assessment may become increasingly central to individualized risk stratification and therapeutic decision-making in stable coronary artery disease [21].

Coronary CT Angiography Plaque Characteristics Associated With Hemodynamically Significant Coronary Lesions

Coronary computed tomography angiography has evolved from a modality focused primarily on luminal stenosis assessment into an advanced imaging platform capable of detailed plaque characterization and risk stratification. Contemporary evidence increasingly demonstrates that specific plaque characteristics identified on CCTA correlate strongly with invasive physiological significance assessed by fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR). These plaque features reflect underlying biological plaque activity, vascular remodeling, and hemodynamic disturbance that contribute to myocardial ischemia independently of stenosis severity alone [22,23].

Among the most extensively studied plaque features, low-attenuation plaque has consistently shown a strong association with lesion-specific ischemia. Low-attenuation plaques generally represent lipid-rich necrotic cores with increased inflammatory activity and plaque vulnerability. These lesions are associated with impaired endothelial function, abnormal vasomotor regulation, and reduced coronary flow reserve. Multiple studies demonstrated that lesions containing low-attenuation plaque are significantly more likely to exhibit abnormal invasive FFR values compared with plaques lacking these characteristics [24].

Positive remodeling is another major plaque characteristic associated with physiologically significant coronary lesions. Positive remodeling refers to outward expansion of the vessel wall in response to progressive plaque accumulation, often preserving luminal diameter during the early stages of disease progression. Although angiographic stenosis severity may therefore appear only moderate, positively remodeled plaques frequently contain large lipid cores, high inflammatory burden, and substantial total

plaque volume capable of impairing coronary hemodynamics. Studies integrating CCTA and invasive physiology consistently demonstrated strong correlations between positive remodeling and ischemia-producing lesions [25].

The napkin-ring sign has emerged as one of the most important imaging markers of vulnerable plaque morphology. This sign is characterized by a peripheral ring-like high-attenuation area surrounding a central low-attenuation necrotic core on CCTA. Histopathological studies suggest that the napkin-ring sign reflects advanced fibroatheroma with thin fibrous cap architecture and high inflammatory activity. Lesions demonstrating this feature are frequently associated with abnormal invasive physiological measurements and increased risk of future acute coronary events [26].

Spotty calcification also represents an important marker of adverse plaque biology and functional significance. Unlike extensive stable calcification, spotty calcification reflects active microcalcification and ongoing inflammatory activity within unstable plaques. Spotty calcifications are commonly identified in plaques associated with endothelial dysfunction, positive remodeling, and impaired coronary flow reserve. Their presence on CCTA independently predicts lesion-specific ischemia and adverse cardiovascular outcomes [27].

Total plaque burden and noncalcified plaque volume may provide even greater prognostic and physiological information than isolated plaque features alone. Quantitative plaque analysis studies demonstrated that lesions with extensive total plaque burden, increased fibrofatty plaque content, and large volumes of low-density noncalcified plaque are more likely to exhibit abnormal FFR values. Importantly, diffuse plaque accumulation may impair coronary flow through cumulative resistance along the vessel length despite the absence of severe focal stenosis [28].

Several studies have shown that plaque morphology may outperform luminal stenosis severity in predicting functional ischemia. Intermediate stenoses between 40% and 70% frequently demonstrate variable physiological significance depending on plaque composition, remodeling pattern, and overall plaque burden. Consequently, reliance solely on anatomical stenosis severity may lead to inaccurate estimation of lesion-specific ischemia and inappropriate clinical decision-making [29].

Coronary artery calcium scoring also contributes to ischemia prediction and cardiovascular risk stratification. Although heavily calcified plaques may not always produce flow-limiting ischemia, increasing calcium burden generally reflects advanced atherosclerotic disease and greater total plaque burden. High coronary calcium scores are associated with increased likelihood of multivessel disease, impaired coronary flow reserve, and adverse cardiovascular outcomes. However, calcified plaque alone may correlate less strongly with functional significance than noncalcified or mixed plaque components [30].

Recent advances in quantitative plaque analysis software have enabled automated measurement of plaque composition, plaque burden, remodeling index, and high-risk plaque characteristics. These technologies improve reproducibility and facilitate integration of plaque analysis into clinical practice. Artificial intelligence-assisted plaque quantification may further refine prediction of lesion-specific ischemia and support individualized patient management in stable coronary artery disease [31].

The growing recognition that plaque morphology contributes substantially to functional ischemia has important clinical implications. Integrating CCTA plaque characterization with invasive physiological assessment may improve patient selection for invasive angiography and coronary intervention, reduce unnecessary procedures, and enhance precision cardiovascular care. As imaging technologies continue to evolve, comprehensive plaque assessment is expected to become increasingly central to noninvasive ischemia prediction and personalized coronary artery disease management [32].

Invasive Functional Assessment of Coronary Lesion Significance

Invasive coronary physiological assessment has become the reference standard for determining the hemodynamic significance of coronary artery stenoses in patients with stable coronary artery disease. While coronary angiography provides anatomical visualization of luminal narrowing, it frequently fails to identify whether a lesion produces clinically relevant myocardial ischemia. Consequently, invasive physiological indices such as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) have

emerged as essential tools for lesion-specific ischemia assessment and revascularization decision-making [33,34].

Fractional flow reserve is the most extensively validated invasive physiological index used in contemporary interventional cardiology. FFR is defined as the ratio of distal coronary pressure to proximal aortic pressure during maximal hyperemia, typically induced by adenosine administration. An FFR value ≤0.80 is generally considered indicative of physiologically significant coronary obstruction requiring revascularization. Multiple landmark studies demonstrated that FFR-guided coronary intervention improves clinical outcomes, reduces unnecessary PCI procedures, lowers healthcare costs, and decreases major adverse cardiovascular events compared with angiography-guided strategies alone [35].

The physiological basis of FFR lies in its ability to evaluate the impact of coronary stenosis on maximal achievable myocardial blood flow. During pharmacologically induced hyperemia, microvascular resistance becomes minimized and relatively constant, allowing pressure gradients across coronary lesions to accurately reflect flow limitation. Lesions producing substantial pressure drops during hyperemia are considered functionally significant because they impair coronary perfusion reserve and may induce myocardial ischemia during stress conditions [36].

Despite its proven clinical utility, FFR has several practical limitations. Adenosine administration may cause chest discomfort, dyspnea, flushing, atrioventricular block, hypotension, and increased procedural duration. In addition, FFR measurements may be influenced by microvascular dysfunction, diffuse coronary disease, serial stenoses, left ventricular hypertrophy, and acute coronary syndromes. These limitations contributed to the development of nonhyperemic pressure-derived indices such as iFR [37].

Instantaneous wave-free ratio is an adenosine-independent physiological index measured during a specific diastolic wave-free period in which coronary microvascular resistance is naturally minimized and stable. Because hyperemic agents are not required, iFR improves patient comfort, reduces procedural complexity, shortens procedure duration, and lowers costs while maintaining excellent diagnostic performance. An iFR value ≤0.89 is generally considered physiologically significant [38].

Large randomized trials including DEFINE-FLAIR and iFR SWEDEHEART demonstrated the noninferiority of iFR compared with FFR regarding major adverse cardiovascular events, including death, myocardial infarction, and unplanned revascularization. Long-term follow-up analyses confirmed sustained clinical safety and efficacy of iFR-guided revascularization strategies. These findings established iFR as an important alternative physiological modality in contemporary coronary intervention [39,40].

The relationship between invasive physiological assessment and plaque morphology has become an area of major research interest. Several studies demonstrated that lesions exhibiting adverse plaque characteristics on CCTA—including low-attenuation plaque, positive remodeling, spotty calcification, and large noncalcified plaque burden—are significantly more likely to produce abnormal invasive FFR or iFR values. These observations suggest that plaque biology and composition contribute importantly to lesion-specific ischemia beyond luminal stenosis severity alone [41].

Invasive physiological assessment is particularly valuable in intermediate coronary stenoses where angiographic interpretation is often uncertain. Lesions with 40%–70% diameter stenosis frequently demonstrate discordance between anatomical appearance and physiological significance. Some moderate lesions produce substantial ischemia because of extensive plaque burden or adverse remodeling, whereas other severe-appearing lesions may exhibit preserved coronary flow reserve. Physiological assessment therefore provides critical information for individualized treatment decisions [42].

Pressure-wire pullback assessment represents another important advancement in invasive coronary physiology. Pullback analysis allows identification of focal versus diffuse pressure gradients along the coronary artery and may help distinguish lesions most responsible for ischemia. This technique is particularly useful in diffuse atherosclerosis and serial lesions, where cumulative plaque burden may contribute significantly to coronary flow limitation. Integration of pullback physiology with plaque

imaging may further enhance precision revascularization strategies [43].

The growing integration of invasive physiology with coronary CT plaque characterization reflects the evolving concept of precision cardiovascular medicine. Combining anatomical plaque analysis with physiological assessment improves understanding of lesion-specific ischemia, optimizes patient selection for coronary intervention, and reduces unnecessary invasive procedures. As imaging and physiological technologies continue to evolve, multimodality integration is expected to play an increasingly important role in personalized management of stable coronary artery disease [44].

Integration of Coronary CT Plaque Morphology With Invasive Physiological Assessment

The integration of coronary plaque morphology assessed by coronary CT angiography (CCTA) with invasive physiological assessment has emerged as a central concept in modern precision cardiovascular medicine. Traditionally, coronary artery disease evaluation relied heavily on visual estimation of luminal stenosis severity; however, growing evidence demonstrates that plaque composition, plaque burden, vascular remodeling, and inflammatory activity contribute substantially to lesion-specific ischemia and cardiovascular risk. Consequently, combining anatomical plaque characterization with invasive physiological indices such as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) provides a more comprehensive understanding of coronary lesion significance [45,46].

Several studies have demonstrated that lesions with similar degrees of angiographic stenosis may exhibit markedly different physiological behavior depending on plaque morphology. Intermediate stenoses frequently represent the greatest diagnostic challenge because visual assessment alone poorly predicts ischemic significance. Lesions containing extensive low-attenuation plaque, positive remodeling, and large noncalcified plaque burden are significantly more likely to demonstrate abnormal FFR values despite only moderate luminal narrowing. Conversely, heavily calcified lesions may appear severe anatomically while producing limited functional ischemia [47].

One of the most important findings in contemporary coronary imaging research is the independent association between high-risk plaque features and lesion-specific ischemia. Studies integrating CCTA with invasive FFR consistently demonstrated that positive remodeling, low-density noncalcified plaque, napkin-ring sign, and spotty calcification independently predict abnormal physiological measurements. These observations suggest that adverse plaque biology contributes to impaired coronary hemodynamics through mechanisms extending beyond simple luminal obstruction [48].

The relationship between plaque burden and ischemia has also gained increasing attention. Quantitative plaque analysis revealed that total plaque volume and noncalcified plaque burden correlate strongly with invasive physiological significance. Diffuse atherosclerotic disease may impair coronary flow reserve through cumulative resistance across long arterial segments, even in the absence of severe focal stenosis. This concept highlights the limitations of conventional diameter stenosis assessment and supports the importance of comprehensive plaque quantification in ischemia prediction [49].

Computed tomography-derived fractional flow reserve (FFR-CT) represents one of the most important technological advances integrating anatomical and functional coronary assessment. FFR-CT uses computational fluid dynamics applied to standard CCTA datasets to estimate lesion-specific pressure gradients noninvasively. Multiple studies demonstrated good agreement between FFR-CT and invasive FFR measurements, with significantly improved diagnostic accuracy compared with anatomical stenosis assessment alone. This technology allows simultaneous evaluation of plaque morphology and functional significance within a single imaging examination [50].

The PLATFORM and ADVANCE trials demonstrated the clinical utility of FFR-CT in patients with suspected stable coronary artery disease. Use of FFR-CT reduced unnecessary invasive coronary angiography, improved patient selection for revascularization, and enhanced diagnostic efficiency without compromising clinical outcomes. These findings support the growing role of integrated anatomical-functional imaging in personalized coronary artery disease management [51,52].

Integration of plaque morphology and physiology also provides important prognostic information. Lesions demonstrating both adverse plaque characteristics and abnormal physiological significance are associated with substantially higher risks of future adverse cardiovascular events compared with lesions

exhibiting either abnormality alone. Combined anatomical and physiological assessment therefore improves cardiovascular risk stratification and may facilitate more individualized preventive and therapeutic strategies [53].

Artificial intelligence and machine learning technologies are increasingly being incorporated into multimodality coronary assessment. AI-assisted algorithms now enable automated plaque quantification, high-risk plaque detection, prediction of lesion-specific ischemia, and integration of imaging and physiological data. These technologies may improve diagnostic reproducibility, reduce interobserver variability, and facilitate precision-based clinical decision-making in stable coronary artery disease [54].

Despite significant progress, challenges remain regarding standardization of plaque analysis, optimal thresholds for high-risk plaque characterization, and integration of multimodality imaging into routine clinical workflows. Variability in imaging acquisition protocols, plaque quantification software, and physiological interpretation may influence diagnostic consistency. Additional large-scale prospective studies are needed to clarify the incremental prognostic value of combined plaque and physiological assessment beyond traditional risk stratification models [55].

The future of coronary artery disease evaluation will likely depend increasingly on comprehensive multimodality integration combining anatomical imaging, plaque characterization, invasive and noninvasive physiology, computational flow modeling, and artificial intelligence-assisted analysis. Such precision-based approaches may improve ischemia prediction, optimize patient selection for invasive intervention, reduce unnecessary procedures, and enhance long-term cardiovascular outcomes in patients with stable coronary artery disease [56].

Clinical and Prognostic Implications in Stable Coronary Artery Disease

The relationship between coronary plaque morphology and invasive functional lesion significance has important clinical implications for diagnosis, risk stratification, and therapeutic decision-making in stable coronary artery disease. Traditionally, treatment decisions were guided mainly by stenosis severity; however, contemporary evidence shows that adverse plaque characteristics and physiological significance together provide a more accurate estimate of future cardiovascular risk. Lesions demonstrating both high-risk plaque morphology on CCTA and abnormal FFR or iFR are more likely to represent clinically important disease requiring intensified medical therapy, closer surveillance, and possible revascularization when appropriate [57,58].

CCTA plaque characterization may help refine patient selection for invasive coronary angiography. Patients with intermediate stenosis but without adverse plaque features may often be managed conservatively with guideline-directed medical therapy, whereas those with low-attenuation plaque, positive remodeling, napkin-ring sign, or extensive noncalcified plaque burden may require further functional evaluation. This strategy can reduce unnecessary invasive procedures while ensuring that patients with biologically active and potentially ischemia-producing lesions are not underestimated [59].

The integration of plaque morphology and invasive physiology may also improve revascularization decisions. Physiologically significant lesions with adverse plaque features may derive greater benefit from revascularization than lesions with abnormal stenosis appearance alone. Conversely, anatomically severe but physiologically insignificant lesions may be safely deferred in selected patients under optimal medical therapy. This approach supports a more personalized model of stable CAD management, balancing ischemic risk, plaque vulnerability, symptom burden, and procedural risk [60].

High-risk plaque morphology also has implications for preventive pharmacotherapy. Identification of vulnerable plaque features on CCTA may justify intensification of lipid-lowering therapy, antiplatelet strategies when appropriate, strict blood pressure control, glycemic optimization, smoking cessation, and lifestyle modification. Importantly, plaque regression and stabilization have become therapeutic goals beyond simple symptom relief, emphasizing the role of CCTA as both a diagnostic and risk-monitoring tool in stable CAD [61].

From a prognostic perspective, total plaque burden and noncalcified plaque volume are powerful

predictors of adverse cardiovascular events. Patients with diffuse atherosclerosis and high-risk plaque features may remain at elevated risk even when individual lesions are not severely stenotic. Therefore, CCTA provides valuable information that complements invasive physiology, which primarily identifies lesion-specific ischemia but may not fully capture global plaque vulnerability or future plaque rupture risk [62].

Ultimately, combining CCTA plaque analysis with invasive functional assessment enables a more comprehensive evaluation of stable coronary artery disease. This multimodality strategy distinguishes anatomical disease burden, biological plaque vulnerability, and hemodynamic significance, allowing clinicians to tailor management more precisely. As artificial intelligence, quantitative plaque software, and CT-derived physiology continue to mature, this integrated approach is expected to become increasingly central to precision cardiovascular care [63].

The field of coronary CT angiography continues to evolve rapidly with the integration of advanced imaging technologies, computational physiology, artificial intelligence, and quantitative plaque analysis. These developments are transforming CCTA from a predominantly anatomical imaging modality into a comprehensive platform for precision cardiovascular medicine capable of evaluating plaque biology, ischemic potential, vascular inflammation, and individualized cardiovascular risk. Emerging technologies are expected to further improve diagnostic accuracy, optimize patient selection for invasive intervention, and refine personalized management strategies in stable coronary artery disease [64,65].

Artificial intelligence (AI) and machine learning have become major areas of innovation in cardiovascular imaging. AI-assisted algorithms now enable automated coronary plaque segmentation, plaque composition analysis, stenosis quantification, and high-risk plaque detection with improved reproducibility and reduced observer variability. Machine learning models integrating clinical variables, plaque morphology, coronary calcium burden, and physiological data may improve prediction of future cardiovascular events and lesion-specific ischemia beyond conventional risk assessment models [66].

Quantitative plaque analysis represents another important advancement in modern CCTA. Contemporary software platforms can automatically quantify total plaque burden, noncalcified plaque volume, fibrofatty components, calcified plaque, remodeling index, and low-attenuation plaque characteristics. These quantitative biomarkers may facilitate objective monitoring of plaque progression or regression during medical therapy and provide incremental prognostic information beyond visual interpretation alone [67].

Perivascular fat attenuation imaging has emerged as a novel marker of coronary inflammation and vascular biology. Changes in perivascular adipose tissue attenuation on CCTA reflect inflammatory signaling originating from the vascular wall and may identify biologically active coronary plaques before the development of severe stenosis. Elevated perivascular fat attenuation has been associated with increased cardiovascular mortality, plaque vulnerability, and adverse coronary events, highlighting its potential role in future cardiovascular risk stratification [68].

Computed tomography-derived fractional flow reserve (FFR-CT) continues to expand as a noninvasive alternative to invasive physiological assessment. Ongoing technological refinements and faster computational processing have improved diagnostic performance and clinical applicability of FFR-CT in routine practice. Future integration of plaque morphology, FFR-CT, and AI-assisted computational modeling may enable fully noninvasive characterization of lesion-specific ischemia and plaque vulnerability within a single imaging examination [69].

Photon-counting computed tomography represents one of the most promising next-generation CT technologies. This imaging platform provides improved spatial resolution, enhanced tissue characterization, lower image noise, and reduced radiation exposure compared with conventional CT systems. Photon-counting CT may improve visualization of coronary plaque microstructure, microcalcification, stent evaluation, and small-vessel imaging, potentially enhancing the assessment of plaque vulnerability and lesion significance [70].

Radiomics and deep-learning image analysis are also expected to influence future coronary imaging.

Radiomics involves extraction of large amounts of quantitative imaging features beyond human visual interpretation, potentially allowing identification of subtle plaque characteristics associated with ischemia and future cardiovascular events. Combined with machine learning, radiomics may improve prediction of invasive physiological significance and support precision-based treatment decisions in stable CAD [71].

Future clinical management strategies will likely emphasize multimodality integration combining anatomical plaque characterization, computational physiology, vascular inflammation imaging, and patient-specific risk profiling. This approach reflects the broader transition toward personalized cardiovascular medicine in which diagnostic and therapeutic decisions are increasingly individualized according to plaque biology, ischemic burden, and overall cardiovascular risk rather than stenosis severity alone [72].

Despite these advances, several challenges remain before widespread implementation of precision coronary imaging becomes routine clinical practice. Standardization of quantitative plaque analysis, validation of AI-assisted algorithms, reduction of computational costs, and integration into clinical workflows remain important priorities. Additional large-scale prospective studies are needed to clarify the long-term prognostic value of emerging imaging biomarkers and determine how these technologies influence clinical outcomes and therapeutic decision-making [73].

As coronary imaging technologies continue to advance, future evaluation of stable coronary artery disease will increasingly rely on comprehensive integration of anatomical, physiological, and biological plaque assessment. This evolving paradigm may improve early detection of high-risk disease, refine revascularization strategies, optimize preventive therapies, and ultimately enhance long-term cardiovascular outcomes through more precise and individualized patient care [74].

Conclusion

Coronary plaque morphology assessed by coronary CT angiography has emerged as a critical determinant of lesion-specific ischemia and cardiovascular risk in patients with stable coronary artery disease. Contemporary evidence demonstrates that adverse plaque characteristics—including low-attenuation plaque, positive remodeling, spotty calcification, napkin-ring sign, and increased noncalcified plaque burden—correlate strongly with invasive physiological significance assessed by fractional flow reserve and instantaneous wave-free ratio beyond conventional stenosis severity alone. The integration of anatomical plaque characterization with invasive and noninvasive functional assessment represents an important advancement in precision cardiovascular medicine, enabling more accurate risk stratification, improved selection for invasive angiography and revascularization, and more individualized therapeutic decision-making. Emerging technologies including CT-derived fractional flow reserve, quantitative plaque analysis, artificial intelligence, and radiomics are expected to further refine ischemia prediction and personalized management strategies. As multimodality coronary imaging continues to evolve, combining plaque biology with functional assessment may substantially improve diagnostic accuracy, optimize clinical outcomes, and enhance long-term cardiovascular care in stable coronary artery disease.

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