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Doctoral Dissertation
Doctoral Program in Bioengineering and
medical and surgical sciences (37th Cycle)

From Flow to Failure: The Interplay Between Haemodynamics and Coronary Plaque Stability

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A handwritten signature in black ink, consisting of a stylized 'A' followed by a long horizontal stroke, positioned above a dotted line.

Alessandro
Candreva

Turin, January 15, 2025

Summary

The identification of coronary lesions at a higher risk of destabilization remains one of the foremost challenges in contemporary cardiovascular research. The intricate interplay between vessel structure and circulating blood has emerged as a critical factor influencing the evolution and destabilization of atherosclerotic plaques. Understanding and quantifying these interactions are essential for advancing diagnostic precision and improving therapeutic strategies.

In this research, we employed cutting-edge computational fluid dynamics (CFD) methodologies to simulate the complex physical phenomena occurring at the blood-endothelium interface. Shear forces, which are central to the pathophysiological processes governing plaque vulnerability, cannot be directly measured *in vivo*. By leveraging CFD, we developed advanced tools to study and quantify these forces, identifying anatomic-functional predictors of plaque destabilization that can be translated into clinical practice.

Three-dimensional coronary models were reconstructed from standard angiographic projections using dedicated software, and CFD simulations were performed, incorporating vessel-specific boundary conditions tailored to patient anatomy. Traditional descriptors, such as time-averaged wall shear stress (TAWSS), were complemented by innovative metrics introduced and tested for the first time in human studies. Among these, the Topological Shear Variation Index (TSVI) quantified the expansion-contraction action of pulsatile shear forces on the endothelium and proved to be superior predictors of future myocardial infarctions (MI) within a five-

year timeframe, outperforming conventional markers like percentage area stenosis and translesional pressure gradients.

These methodologies were further extended to investigate the pathophysiology of spontaneous coronary artery dissection (SCAD), an enigmatic condition. By analysing vessel geometry and local hemodynamic patterns, we identified distinct hemodynamic and structural signatures associated with dissection origins, shedding light on the complex mechanisms behind SCAD.

This comprehensive approach bridges bioengineering and clinical cardiology, offering novel insights into coronary artery disease. By enhancing the predictive capabilities of diagnostic tools and identifying high-risk lesions with greater precision, this research represents a significant step toward pre-emptive clinical interventions, ultimately aiming to improve patient outcomes.

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*To my dearly beloved
and greatly missed godfather
Angelo*

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Chapter 1

Introduction

Acute myocardial infarction (AMI) stands as a principal cause of global cardiac morbidity and mortality, predominantly arising from acute epicardial coronary artery occlusion due to atherosclerotic lesion rupture and subsequent thrombosis. In these cases, urgent vessel reperfusion is performed by the interventional cardiology team, utilizing balloon angioplasty and stent deployment to alleviate obstruction and stabilize the lesion. While large literature exists supporting the immediate implementation of percutaneous coronary intervention (PCI) in the setting of an acute coronary syndrome (ACS) and particularly in the setting of an ST-segment elevation myocardial infarction (STEMI), evidence on how to identify those 'vulnerable' coronary lesions remains sparse, highlighting a significant gap in predictive capabilities and preventive strategies.¹

The vulnerability of coronary plaques can be discerned through invasive coronary angiography, utilising a differentiated approach. This method encompasses an evaluation of lesion geometry, the constitution of the plaque, and translesional haemodynamics.

1.1 Geometrical analysis and lesion vulnerability assessment

Anatomical lesion analysis through coronary angiography provides high-resolution visualisation of atherosclerotic plaques, employing quantitative coronary angiography (QCA) for detailed evaluation of vessel and lesion geometry. This method identifies predictors of lesion progression, such as percentage area stenosis (AS) and minimal lumen area (MLA), which have been linked to cardiovascular events.²

Advancements in QCA allow for volumetric plaque analysis, offering deeper insights into plaque characteristics. Additionally, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) enhance lesion assessment, overcoming some limitations of the angiography-based analysis by providing cross-sectional measurements for accurate reconstruction.

1.2 Plaque composition and lesion vulnerability assessment

Invasive intravascular imaging techniques, such as IVUS and OCT, are key for analysing coronary lesion composition. These modalities enable the classification of plaques based on the reflected wave analysis. At the IVUS, each lesion phenotype, from hypoechoic attenuated plaques to echolucent lesions rich in lipids (Figure 1), presents unique characteristics indicating varying degrees of vulnerability.³

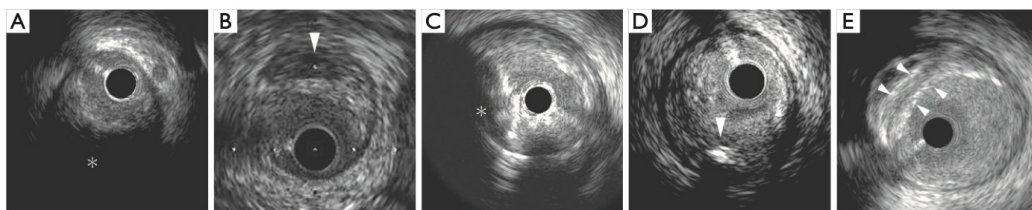


Figure 1. Grayscale IVUS identifies plaque types(A) Attenuated plaque shows reduced echogenicity, indicating softer composition; (B) Echolucent plaque, highlighted by an arrowhead, suggests a lipid-rich area within the plaque; (C) Calcified nodules are seen as protrusions indicating hardened plaque areas; (D) Spotty calcification, marked by an arrow, reveals small calcium deposits; (E) Multiple layer appearance indicates varied plaque layers. This differentiation aids in assessing plaque stability and risk. Reproduced from: Honda S. et al. *Cardiovasc Diagn Ther* 2016;6(4):368-381

Utilizing near-infrared light at 1,300 nm, OCT captures in vivo plaque images with a resolution roughly tenfold higher than IVUS, achieving 10 μm axially and up to 20 μm laterally. This enhancement allows not only for precise plaque phenotype classification (fibrous, lipid, calcific), but also for the identification of critical microstructures, such as thin fibrous caps (defined as $<65 \mu\text{m}$), macrophage infiltration, microchannels, and cholesterol crystals. In this way, the identification of the particularly dangerous thin-cap fibroatheromas (TCFAs) is facilitated (Figure 2).³ While

OCT excels in monitoring sub-endothelial plaque microstructures, its limited penetration depth may restrict visibility of deeper components. Additionally, OCT image quality heavily relies on effective blood clearance during contrast medium infusion, making it somewhat dependent on the operator's proficiency.

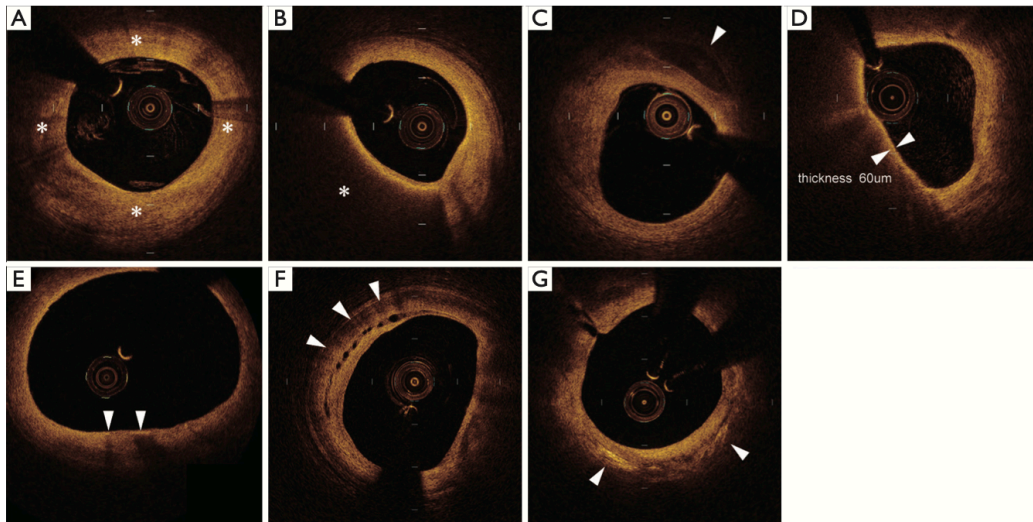


Figure 2. Images of plaque phenotype on optical coherence tomography (OCT). (A) Fibrous plaques; (B) Lipid-rich plaque; (C) Fibrocalcific plaque (arrow: calcification); (D) Thin fibrous cap (double arrow); (E) Macrophages (arrow heads); (F) Microchannel; (G) Cholesterol crystals. Reproduced from: Honda S. et al. *Cardiovasc Diagn Ther* 2016;6(4):368-381

More recently, intravascular near-infrared spectroscopy (NIRS), integrated with an IVUS catheter, allowed the quantitative assessment of atherosclerotic plaques' lipid content. Calculated as a fraction of yellow pixels in the chemogram (from 1 to 1'000), a lipid core burden index (LCBI) over 400 is indicative of a higher risk for future adverse events.⁴

Even though the identification of lesions with vulnerability traits has been enabled by studying their geometry and composition, large trials using intracoronary imaging have shown that lesions with several vulnerability traits (e.g., TCFA, plaque burden $\geq 70\%$, and MLA $\leq 4 \text{ mm}^2$) remain however stable (or *senescent*) in more than 80% of cases after a median follow-up of over three years.⁵

This suggests that more complex mechanisms are involved in the destabilization of a vulnerable coronary lesion.

1.3 Intravascular haemodynamics and lesion vulnerability assessment

The concept that intravascular haemodynamics could play a pivotal role in influencing plaque nucleation, progression, and destabilization – known as the *hemodynamic hypothesis* of atherosclerosis – stems from the observation that atherosclerosis, although a systemic condition, shows a predilection for specific anatomical regions, such as the coronary, carotid, and lower-limb arteries, and particular vascular sites, like inner curvatures and bifurcations. At these specific sites, the unique intracoronary haemodynamics may interact with local vascular elements, potentially affecting plaque stability.⁶

The study of intracoronary haemodynamics traditionally focuses on analysing intracoronary pressure gradients. Fractional flow reserve (FFR), measured during maximal hyperaemic response, is pivotal for evaluating intracoronary perfusion, with values below 0.80 signalling significant flow impairment and predicting adverse outcomes if angioplasty is not performed.⁷ Surrogate non-hyperaemic pressure ratios (NHPR), like the instantaneous wave-free ratio (iFR) and resting full-cycle ratio (RFR), assess pressure gradients in resting condition, considering a gradient of 0.89 as hemodynamically significant.⁸

More recent evidence has shown that lesions where PCI has been deferred due to a non-pathological FFR or NHPR might still be sites of future MI due to overlooked instability. Accordingly, research has shifted towards analysing translesional pressure gradients in lesion progression, rather than just the distal vascular pressure drops. In this context, pullback pressure gradient (PPG) tracings (Figure 3), which identify pressure drops across stenoses, offer deeper insights into coronary lesion assessment, linking focal pressure variations to more severe disease.⁹

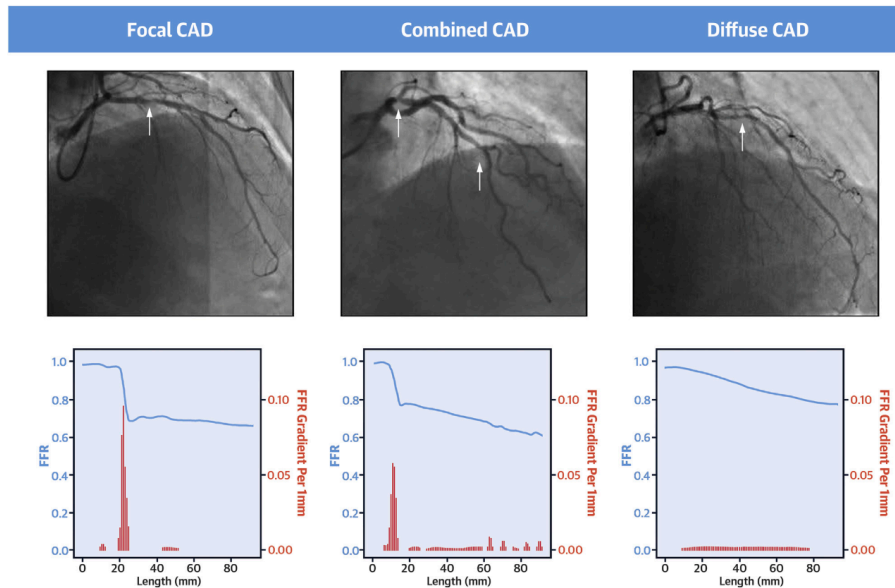


Figure 3. Pullback pressure gradient (PPG) tracing for focal, combined and diffuse coronary artery disease (CAD). In the focal CAD (left), a clear pressure drop (or step-up) in the PPG tracing can be seen, while in the diffuse CAD (right) a progressive pressure loss without focalities can be seen. Reproduced from: Collet C. et al. JACC VOL. 74, NO. 14, 2019

Building on this, the application of computational fluid dynamics (CFD) has been introduced for a more advanced examination of intracoronary haemodynamics. CFD algorithms facilitate the detailed simulation of intracoronary pressure and coronary flow, encompassing both the blood-endothelium interface, referred to as near-wall haemodynamics, and the broader intravascular context.¹⁰ This approach has particularly underscored the significance of near-wall haemodynamics in maintaining endothelial function and its implications for both physiological and pathological states.

Wall shear stress (WSS) maintained within the physiological range of 1-5 Pa is indicative of robust endothelial function and contributes to plaque stability. Conversely, diminished WSS values have been implicated in the advancement and destabilisation of lesions, highlighting their predictive value in assessing cardiovascular risk.¹¹ Lower WSS values were, in fact, associated with plaque progression, while higher WSS values with endothelial dysfunction and augmented risk of plaque destabilization.^{12, 13}

However, coronary lesions displaying low WSS, even when accompanied by traits indicating vulnerability in lesion composition, typically

remain inactive in most cases. This results in a predictive accuracy of less than 50% for the necessity of unplanned coronary interventions during follow-up.¹⁴ Consequently, as of the current writing, no combination of data on plaque anatomy, composition, and functional status has been able to offer adequate predictive evidence to support pre-emptive therapeutic interventions, such as the sealing or mechanical stabilization of vulnerable plaques.

1.4 Thesis objectives and outline

My research focus has been on decoding intracoronary physiology and its implications for plaque vulnerability. Collaborating with a dedicated team of bioengineers specialized in CFD and cardiologists across Belgium, Switzerland, and Italy, we embarked on pioneering studies. These studies not only introduced foundational fluid dynamics principles into the realm of human coronary artery research, but also ensured their clinical application, with a high degree of scientific rigor and compelling evidence.

Accordingly, this thesis is organised into two principal sections. The first section focuses on investigations into the role of intracoronary shear forces in patients with coronary artery disease. The second section presents supplementary studies on intracoronary physiology, encompassing the exploration of novel anatomical and physical descriptors, as well as investigations into alternative pathological models, such as spontaneous coronary artery dissection (SCAD).

Chapter 2

Risk of Myocardial Infarction based on Endothelial Shear Stress Analysis Using Coronary Angiography

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Risk of Myocardial Infarction based on Endothelial Shear Stress Analysis Using Coronary Angiography

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2.1 Introduction

Coronary arteries – and atherosclerotic plaques – experience a variety of mechanical forces linked to plaque progression and destabilization.^{15, 16} Among them, high pressure gradients across epicardial lesions have been recognized as independent predictors of myocardial infarction (MI).⁷

The frictional force of the flowing blood acting on the endothelium, i.e. wall shear stress (WSS), is also a key mechanism translating hemodynamic signals to vascular biological phenomena.^{17, 18} In addition, WSS has been associated with vulnerable transformation of atherosclerotic lesions: low WSS has been linked to atherosclerosis progression, whereas high WSS has been associated with platelet activation and plaque rupture.^{12, 13}

More recently, WSS-based descriptors able to characterize the contraction/expansion action of endothelial shear forces along the cardiac cycle were associated with vascular pathophysiological processes in coronary and extra-coronary territories.¹⁹⁻²¹ In particular, a recent longitudinal study on swine models showed that early atherosclerotic changes in coronary arteries are associated with the endothelium shear stress contraction/expansion variability along the cardiac cycle, captured by the WSS-based quantity topological shear variation index (TSVI).²¹

The present study evaluates the efficacy of an anatomical and hemodynamic assessment based on computational fluid dynamic (CFD) simulations, obtained from conventional coronary angiography for the identification of lesions prone to cause MI within five years.

2.2 Methods

2.2.1 Study design

This is a case-control multicentre study including three European centres (OLV clinic, Aalst, Belgium; University of Lausanne, Switzerland; Fribourg Cantonal Hospital, Switzerland) designed to identify predictors of MI. Study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the Institution's ethics committee.

Written informed consent was obtained from each patient included in the study.

2.2.2 Study population

Patients presenting with acute MI admitted for invasive coronary angiography were screened to identify those who (i) had a previous coronary angiography (here forth referred as baseline angiography) performed between 1 month and 5 years before the index event, (ii) had the visually identifiable mild lesion ($\leq 50\%$ visual diameter stenosis) culprit for the future MI at the baseline angiography, and (iii) had at the baseline angiography at least one additional non-culprit lesion (NCL) in at least one of the other two major epicardial vessels. Therefore, each patient served as its own control. Patient exclusion criteria were post-coronary artery bypass graft (CABG) status, MI as result of in-stent restenosis or thrombosis, MI in absence of angiographically identifiable coronary lesions, ostial lesions or lesions involving a coronary bifurcation with a side branch diameter ≥ 2 mm. In case of multiple coronary angiographies before the acute event, the latest angiography was selected for analysis.

Lesion selection (for both future culprit lesions, FCL, and NCL) was performed blinded to the information of which lesion evolved towards an MI. Subsequently, three-dimensional geometries derived from coronary angiography of both FCL and NCL were generated for blood flow simulations.

2.2.3 Coronary angiography and blood flow simulations

The workflow of the study is presented in Figure 4.

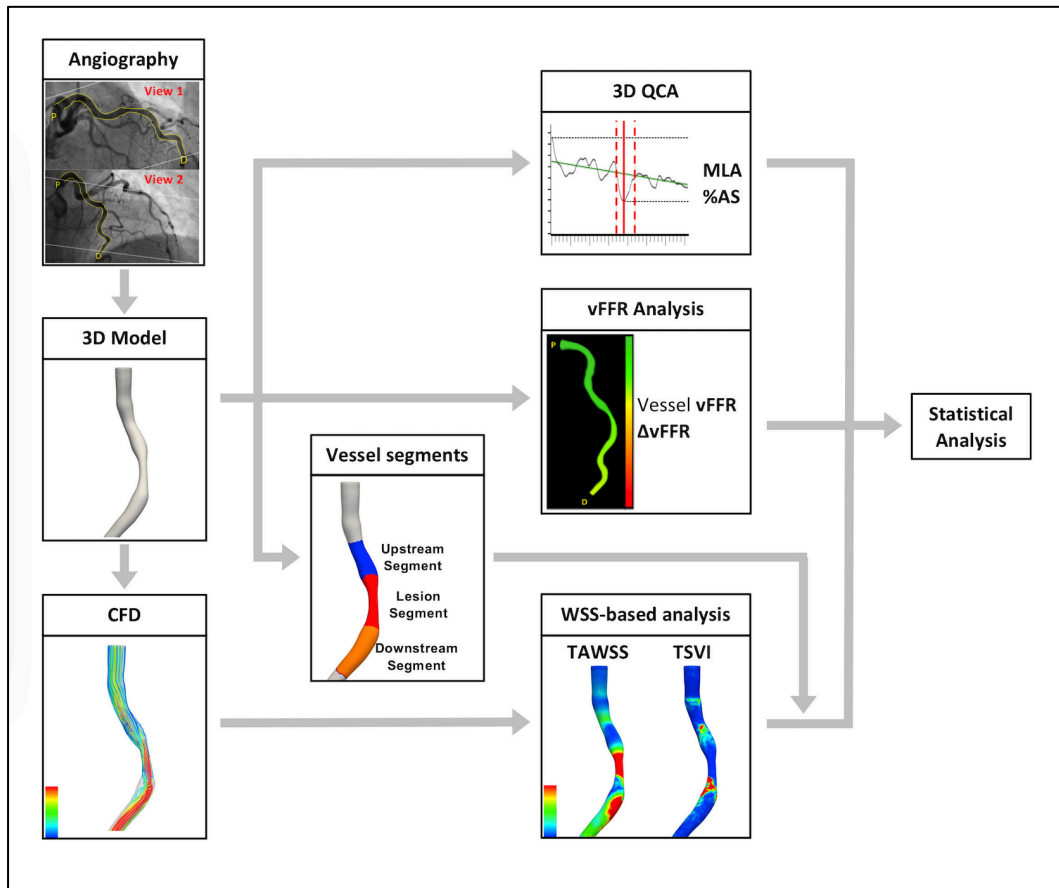


Figure 4. Workflow of the study. The geometrical information of the three-dimensional vessel reconstruction is exploited to compute in parallel quantitative coronary angiography (QCA) analysis as well as virtual fractional flow reserve (vFFR) and computational fluid dynamic (CFD)-derived wall shear stress (WSS) simulations.

Three-dimensional quantitative coronary angiography (3DQCA) reconstructions were performed using two angiographic end-diastolic frames at least 30 degrees apart using the CAAS Workstation WSS software (Pie Medical Imaging, Maastricht, the Netherlands). Automated lumen contour detection was enabled and manually corrected when needed. Three-dimensional coronary reconstruction included at least 20 mm proximally and 20 mm distally from the minimal lumen diameter (MLD). Using the three-dimensional coronary reconstruction, CFD simulations were carried out automatically using a finite element-based code (CAAS Workstation WSS software) to quantify WSS distribution along the cardiac cycle under resting conditions. Details on numerical settings are reported in the on-line Supplemental Methods. Simulations were performed on a

standard computer with processor Intel Xeon W-2123, 3.6GHz, 4 cores, RAM 16Gb.

3DQCA and the angiography-derived virtual fractional flow reserve (vFFR) were obtained using the CAAS Workstation vFFR software (Pie Medical Imaging) on the same angiographic projections selected for three-dimensional vessels reconstruction. Anatomical descriptors included percentage area stenosis (%AS), percentage diameter stenosis, minimal lumen area (MLA) and diameter, reference vessel diameter, lesion length and distance of MLA from the ostium. The distal vFFR, the translesional vFFR difference (Δ vFFR), and the absolute pressure drop in millimetres of mercury (mmHg) at the distal part of the vessel, i.e. distal pressure gradient, were extracted as detailed elsewhere.²²

2.2.4 Wall shear stress-based descriptors

The quantitative characterization of endothelial shear forces included the following WSS-based descriptors (Table 1): time-averaged wall shear stress (TAWSS), obtained by averaging the local values of WSS magnitude along the cardiac cycle;¹¹ oscillatory shear index (OSI);²³ transverse WSS (transWSS);²⁴ TAWSS axial component (TAWSS_{ax}) and secondary component (TAWSS_{sc});²⁵ relative residence time (RRT);²⁶ and topological shear variation index (TSVI).¹⁹⁻²¹ The next paragraph further expands on TSVI.

Endothelial contraction/expansion regions can be mathematically identified analysing the WSS topological skeleton (Figure 5), in particular through negative/positive local values of the divergence of the WSS unit vector field (DIV_{WSS}).²⁷ Technically, the variability of DIV_{WSS} along the cardiac cycle can be measured using the WSS-based quantity TSVI²⁷ (defined as the root mean square deviation of the instantaneous divergence of the unit WSS vector field with respect to its average over the cardiac cycle:

$$\text{TSVI} = \left\{ \frac{1}{T} \int_0^T [\text{DIV}_{\text{WSS}} - \overline{\text{DIV}_{\text{WSS}}}]^2 dt \right\}^{1/2}, \quad (\text{Eq. 1})$$

where T is the duration of the cardiac cycle, and the overbar denotes a cycle-average quantity. Theoretical and technical details on the method of analysis of the WSS topological skeleton here adopted have been exhaustively reported elsewhere.²⁷

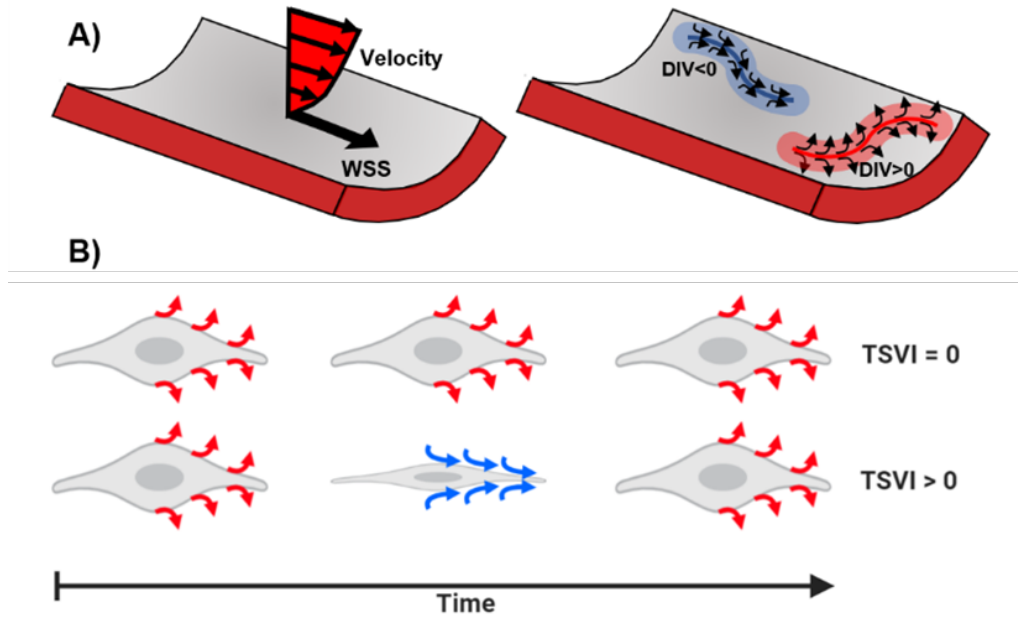


Figure 5. Action of the wall shear stress (WSS) at the blood-endothelium interface. A) Schematic representation of wall shear stress (WSS) at the luminal surface (left) and its push/pull action on the endothelial cells (right), as identified by the divergence of the WSS unit vector field ($DIVWSS$). B) The variability of WSS contraction/expansion action on endothelial cells during the cardiac cycle is captured by the topological shear variation index (TSVI).

The WSS-based descriptors are presented as averaged or maximum and minimum values over three distinct vessel segments: (i) lesion, defined as the segment including the MLA and delimited proximally and distally by the intersection of the QCA diameter function line with the interpolated reference line, (ii) an upstream segment with a length of three times the diameter of the proximal boundary of the lesion, and (iii) a downstream segment with a length of three times the diameter of the distal boundary of the lesion, to ensure a consistent spatial extent across all cases (Figure 6).

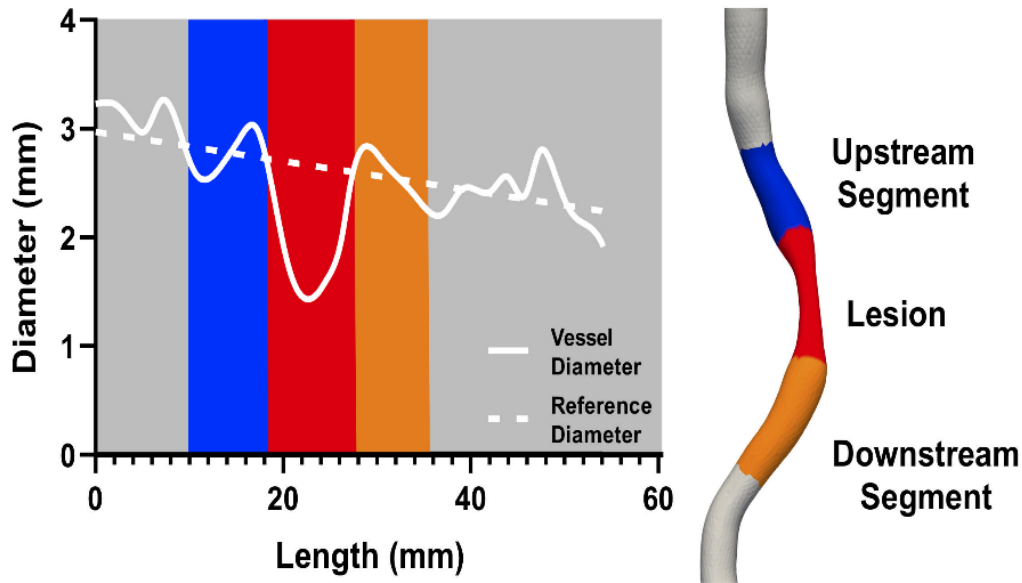


Figure 6. Relative anatomical lesion subdivision. The lesion segment included the minimal lumen area (MLA) and was limited by a proximal and a distal edge. Lesion segment edges were located at the intersection between the measured vessel diameter and the interpolated vessel line upstream and downstream the MLA. The upstream and downstream region extended three times the respective lesion edge diameter upstream and downstream to the lesion segment, to ensure a consistent spatial extent across all cases.

To assess reliability, CFD simulations carried out by physicians (AC) in standard clinical settings (hence denoted as ‘clinical CFD’) using the CAAS Workstation WSS software were tested against state-of-the-art simulations carried out by experts in computational haemodynamics (MLR, VM, DG, CCh, UM) with higher resolution and numerical robustness (‘expert CFD’), as further detailed in the on-line Supplemental Methods. The capability of WSS-based quantities to discriminate FCL vs. NCL groups was tested for both clinical and expert CFD.

To assess the reproducibility of the WSS evaluation process, thirty coronary arteries were randomly selected and WSS simulations were repeated with the same software.

2.2.5 Statistical Methods

All statistical analyses were performed on a per-lesion basis to compare FCL and NCL characteristics. Continuous variables with normal distribution are presented as mean±standard deviation (SD) and non-normally

distributed variables as median (inter-quartile range [IQR]). Categorical variables are presented as percentages. Chi-squared test was used for comparing categorical variables, while Student's tests (or Mann-Whitney tests as appropriate) for continuous ones. To account for the intra-patient correlation, mixed effect model grouping by patient was used to compare FCL and NCL. A p -value <0.05 was considered significant. The relationship between paired, continuous variables was assessed using Spearman correlation coefficients. The predictive capacity of QCA-, vFFR- and WSS-based descriptors was assessed using C-statistics. Receiving operator characteristic (ROC) curve were compared using the DeLong method.²⁸ To determine the net reclassification index (NRI) and relative integrated discrimination improvement (IDI) for each model, continuous variables were dichotomized according to optimal cut-off values from the ROC curves. Three models were defined: the anatomical model (based on %AS) (model 1), the anatomical and pressure model (based on %AS and Δ vFFR) (model 2), and a third model based on %AS, Δ vFFR and a WSS descriptor (model 3). Time-to-event data are presented as Kaplan-Meier estimates. Anatomical and functional variables presenting a univariate relationship with future MI entered the multivariate Cox proportional-hazards regression models. Associated risk for discrete increments was assessed with odds ratio (OR) derived from binary logistic regression. WSS-based quantities reproducibility was assessed with intraclass correlation coefficients (ICC). All analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

2.3 Results

2.3.1 Patient selection

From January 2008 to December 2019, 6885 patients underwent coronary catheterization for acute MI in the three participating centres, 775 (11.3%) patients had a previous angiography, among which 80 (vessel $n=190$; 2.37 ± 0.47 vessel/patient) were included (the sequential screening steps for clinical and analytical exclusion criteria are summarized in Figure 7).

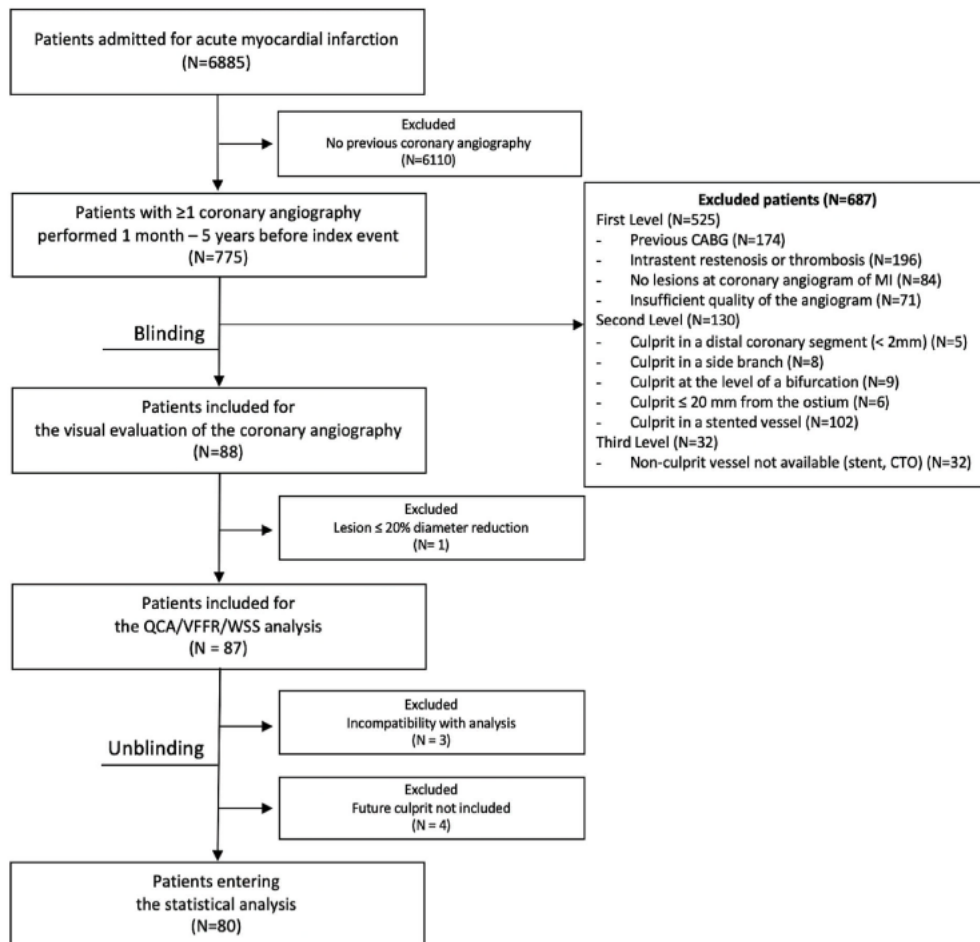


Figure 7. Flowchart of the patients included in the study. Sequential screening steps for clinical and analytical exclusion criteria allowed the selection of ca. 1% of the original queried patients, who met all the study assumptions and whose baseline angiography was successfully postprocessed. From the initial 6885 admitted with MI, only 775 patients had a previous angiography and only 88 met the study inclusion criteria. One case was excluded at the visual evaluation of the baseline coronary angiography for not having identifiable lesions, while three for incompatibility (low pixel number) to run the postprocessing analysis. Finally, after unblinding, four patients were excluded since their FCL were previously excluded. Thus, a total of 80 (1.2%) patients were included in the final analysis.

Clinical characteristics of the selected patients are summarized in Table 2. At the time of the MI, mean age of patients was 70.3 ± 12.7 years, 28.7% were female and 76.3% were on Aspirin and 90.0% on statins. Non-ST elevation myocardial infarction (NSTEMI) and STEMI were reported in 65% and 35% of the studied patients, respectively. Percutaneous coronary intervention was performed in 97.5% (78/80) of cases. The culprit lesion was located in the LAD in 43.8% of cases, in the LCX in 28.7% of cases and

in the RCA in 27.5% of cases. Median time between baseline and index angiography was 25.9 (IQR 21.9-29.8) months. The angiography-based analysis of QCA, vFFR and WSS was equally feasible in 98.9% of vessels (188 vessels, of which FCL n=80, NCL n=108).

2.3.2 Anatomical and functional parameters and risk for subsequent myocardial infarction

Percent AS was significantly higher in the FCL group (63.1 ± 12.4 vs. 55.8 ± 12.5 , $p < 0.001$). Distal vFFR was lower in FCL compared to NCL (0.84 (IQR 0.75-0.90) vs. 0.86 (IQR 0.82-0.92), $p < 0.001$); whereas $\Delta vFFR$ was higher in FCL compared to NCL (0.08 (IQR 0.04-0.13) vs. 0.05 (IQR 0.03-0.08), $p < 0.001$) with a pressure drop across the lesion of 14.5 (IQR 9.0-22.5) mmHg in FCL vs. 12.0 (IQR 8.0-16.0) mmHg in NCL ($p = 0.003$; Table 3). %AS and $\Delta vFFR$ emerged as moderate independent predictors for MI (%AS AUC 0.65, 95%CI 0.57-0.73, $p < 0.001$ and $\Delta vFFR$ AUC 0.63, 95%CI 0.55-0.71, $p < 0.001$), with best cut-off values derived from ROC curves analysis equal to 55.5% for %AS and 0.05 for $\Delta vFFR$ (Table 4).

2.3.3 Wall shear stress descriptors and risk for future myocardial infarction

On average, the computational time per clinical CFD-based WSS analysis was 10.8 ± 1.41 min. Differences in the distribution of WSS-based quantities between the FCL and NCL groups at the lesion level are reported in Figure 8. OSI average values were a scale factor of ten lower than the OSI upper bound value (by construction, $0 \leq OSI \leq 0.50$), and on average approximated zero. For this reason, OSI was not considered in the further analyses. Results of the univariate analysis are reported in Table 4.

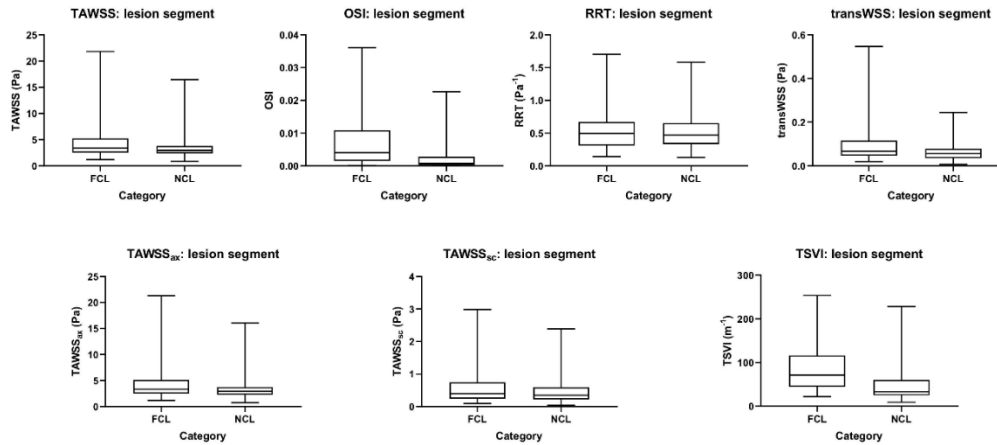


Figure 8. Box plots of WSS-based descriptors in FCL and NCL. Box plots of WSS-based descriptors averaged over the lesion segment in FCL and NCL. The median, the interquartile range, and the extreme values of the distribution (minimum and maximum) are represented. Time-averaged wall shear stress (TAWSS); oscillatory shear index (OSI); relative residence time (RRT); transverse WSS (transWSS); time-averaged axial component of WSS (TAWSS_{ax}); time-averaged secondary direction of WSS (TAWSS_{sc}); topological shear variation index (TSVI).

Both TAWSS and TSVI values were significantly higher in the FCL group at the level of the lesion segment (4.58 Pa in FCL vs. 3.38 Pa in NCL, $p=0.007$ and 89.00 m⁻¹ in FCL vs 49.10 m⁻¹ in NCL, $p<0.001$, respectively), Table 5.

The ROC curves analysis of TAWSS and TSVI, evaluated at the lesion level, showed moderate and high predictive capacity for MI (TAWSS AUC 0.61, 95%CI 0.53-0.69, $p=0.003$; TSVI AUC 0.77, 95%CI 0.71-0.84, $p<0.001$), respectively. The best cut-off values were to 5.01 Pa and 40.50 m⁻¹ for TAWSS and TSVI, respectively. The capacity of TSVI to predict the clinical outcome MI was markedly higher than TAWSS (Figure 9). This was also confirmed when evaluating predictive capacity separately for NSTEMI (TAWSS AUC 0.63, 95%CI 0.53-0.73, $p=0.007$; TSVI AUC 0.74, 95%CI 0.66-0.83, $p<0.001$) and STEMI (TAWSS AUC 0.58, 95%CI 0.44-0.72, $p=0.131$; TSVI AUC 0.83, 95%CI 0.73-0.93, $p<0.001$).

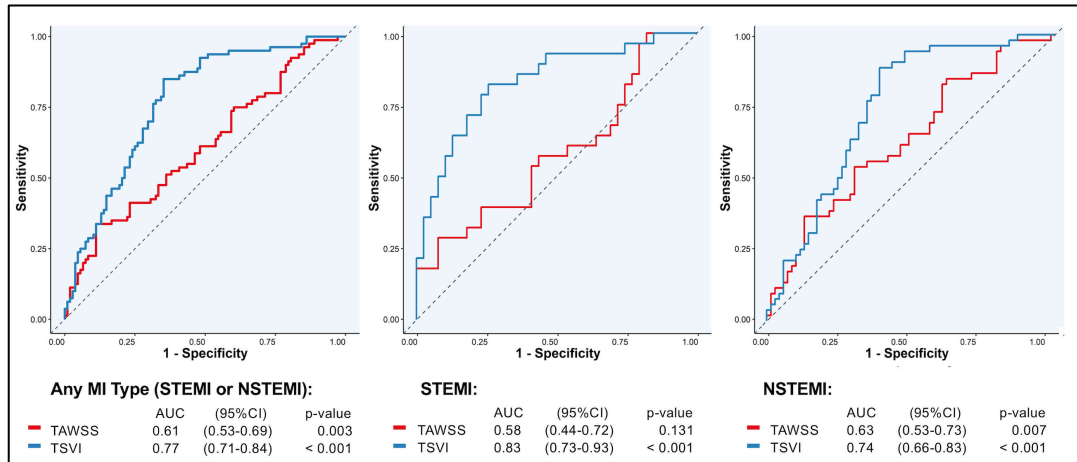


Figure 9. Receiver operating characteristic (ROC) curves of the adopted wall shear stress descriptors. Topological shear variation index (TSVI) resulted in a good predictive capacity for any type of myocardial infarction (MI), which was significantly superior to the time-averaged wall shear stress (TAWSS). The best performance of TSVI was found in ST segment elevation myocardial infarction (STEMI).

The comparison of the heat maps of WSS-based quantities as obtained from the two CFD approaches are presented in Figure 10, from which emerges that the clinical CFD is adequately robust to replicate the results obtained using expert CFD in terms of capability of the WSS-based quantities to discriminate with statistical significance between the FCL and NCL groups. Correlation between clinical and expert CFD-derived WSS descriptors was high (Spearman coefficients >0.75) and highly significant ($p < 0.001$) in all cases.

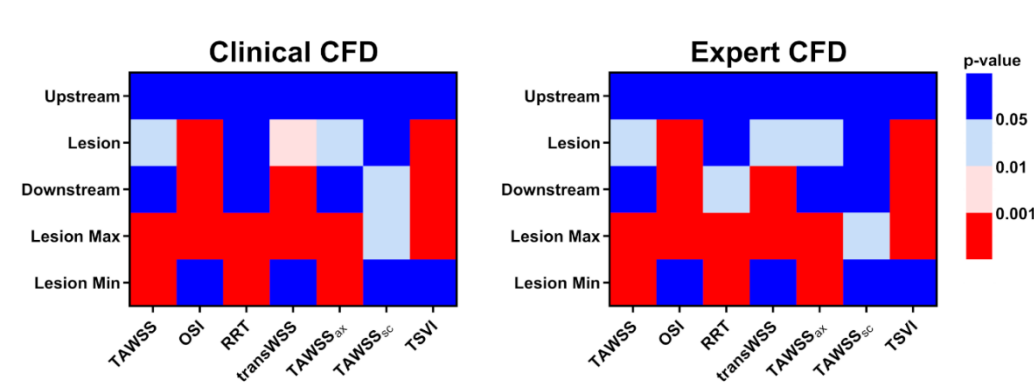


Figure 10. Heat maps for clinical vs. expert CFD simulations. Statistically significant differences between FCL and NCL assessed with Mann-Whitney test for WSS-based descriptors: time-averaged wall shear stress (TAWSS), oscillatory shear index (OSI), relative residence time (RRT), transverse WSS (transWSS), time-averaged axial component of WSS (TAWSSax), time-averaged secondary direction of WSS (TAWSSsc), and topological shear

variation index (TSVI) obtained with clinical and expert CFD. The colour bar ranges from blue (not significant differences, $p>0.05$) to red ($p<0.001$).

The reproducibility of the CFD-based WSS analyses quantities was excellent (TAWSS ICC 0.98, 95%CI 0.95-0.99 and TSVI ICC 0.96, 95%CI 0.91-0.98).

2.3.4 Multivariable predictive models for myocardial infarction

Compared with the anatomical model with %AS (model 1), the inclusion of $\Delta vFFR$ (model 2), while not adding predictive capacity (model 1: AUC 0.65, 95%CI 0.57-0.73; model 2: AUC 0.66, 95%CI 0.58-0.74; $p=0.460$), led to a significant improvement in the reclassification and in the discrimination capacity (NRI 0.53, 95%CI 0.25-0.80, $p<0.001$; relative IDI 0.03, 95%CI 0.001-0.05, $p=0.020$) for the identification of lesions culprit of subsequent MI. Similarly, the addition of TAWSS (model 3 based on TAWSS) led to a non-significant increase in the predictive capacity of the model for detecting FCL (model 2: AUC 0.66, 95%CI 0.58-0.74; model 3 based on TAWSS: AUC 0.69, 95%CI 0.61-0.76; $p=0.099$) with a significant improvement in the reclassification capacity and discriminatory gain (NRI 0.45, 95%CI 0.21-0.69, $p<0.001$; relative IDI 0.04, 95%CI 0.01-0.07, $p=0.008$). On the contrary, the addition of TSVI to the anatomical and pressure model, led to a significant increase in predictive capacity for MI (model 2: AUC 0.66, 95%CI 0.58-0.74; model 3 based on TSVI: AUC 0.77, 95%CI 0.70-0.84; $p<0.001$; Figure 11) with incremental reclassification and discriminatory capacity (NRI 1.04, 95%CI 0.81-1.27, $p<0.001$; relative IDI 0.22, 95%CI 0.16-0.27, $p<0.001$). Up to 22.4% of vessels were reclassified as FCL when adding $\Delta vFFR$ and lesion TSVI to %AS.

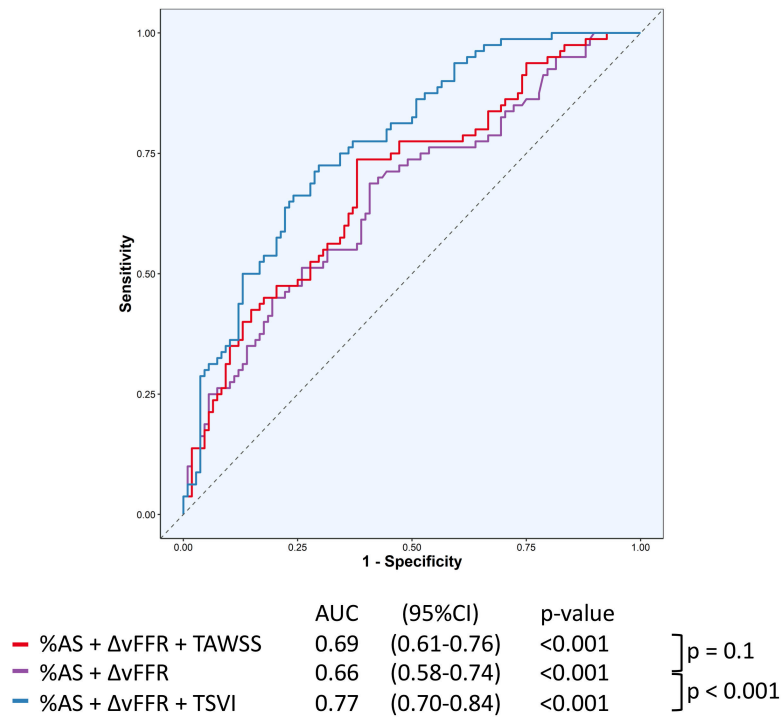


Figure 11. Receiver operating characteristic (ROC) curves of the multivariate models. A non-significant incremental predictive capacity was obtained by adding time-averaged wall shear stress (TAWSS) to a prediction model with percentage area stenosis (%AS) and translesional difference in virtual fractional flow reserve ($\Delta vFFR$) ($\Delta AUC +0.03$, $p=0.1$). On the contrary, adding topological shear variation index (TSVI) to the model with %AS and $\Delta vFFR$ added significant gain in predictive capacity ($\Delta AUC +0.11$, $p<0.001$).

2.3.5 Time-to-event analysis

Event-free probabilities were investigated for %AS, $\Delta vFFR$, TAWSS and TSVI (Figure 12). The single strongest predictor of MI at the lesion level was TSVI (adjusted HR 6.21, 95%CI 3.13-12.3, $p<0.001$). An increment of TSVI of 100 m^{-1} was associated with six-fold increased odds for a future MI (adjusted OR 6.29, 95%CI 3.07-14.3).

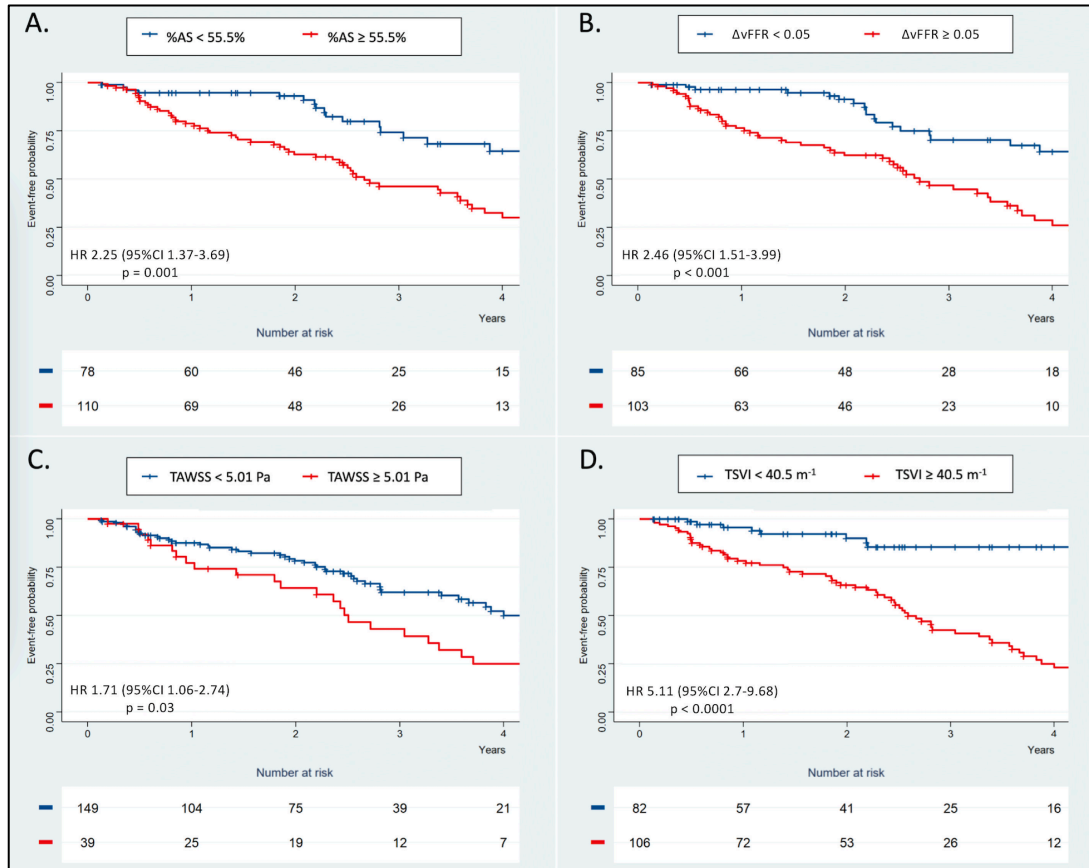


Figure 12. Time-to-event curves. Significantly divergent Kaplan-Meier curves for future myocardial infarction are represented at 4-year follow-up for percentage area stenosis (%AS, panel A), translesional difference in virtual fractional flow reserve ($\Delta vFFR$, panel B), lesion time-averaged wall shear stress (TAWSS, panel C) and lesion topological shear variation index (TSVI, panel D). Red and blue curves refer to values above or below the threshold values obtained from the ROC analysis, respectively. Hazard ratio (HR) refers to the whole follow-up time interval (i.e. 5 years).

2.4 Discussion

The present study proved that a comprehensive approach based on a novel 3DQCA software is able to identify lesions culprit of future MI. The main findings of the study can be summarized as follows: (i) a 3DQCA-based software was able to provide in few minutes reliable WSS-based quantities from CFD simulations from standard angiographic images; ii) FCL had higher area stenoses, higher pressure gradients, and higher TAWSS and TSVI values than the control lesions; (iii) a model integrating anatomical, pressure and WSS descriptors showed improved discriminatory and reclassification capacity in identifying lesions culprit of future MI

compared with a model based on anatomy and pressure gradients alone; (iv) a recently introduced WSS-based descriptor measuring the variability of the contraction/expansion action exerted by the WSS on the endothelium along the cardiac cycle, TSVI,²⁹ exhibited strong predictive capacity for future MI; and (v) the first in human application of a WSS estimation made in a standard clinical setting, this approach resulted in enhanced prediction of clinical outcomes. The study design reduced the influence of external confounding factors (e.g. differential demographics, therapeutic regimes, etc.) on the presented results, since for any given culprit vessel at least one non-culprit vessel from the same patient served as control.

Studies based on intravascular imaging led to the identification of several markers of plaque vulnerability.^{5, 30} Nevertheless, the vast majority of these 'high-risk plaques' become quiescent over time, thus challenging the vulnerable plaque concept.⁵ On the other hand, since mild lesions outnumber severe stenoses, a sizable proportion of MI occurs at the site of mild lesions.²⁹ Using coronary computed tomography angiography (CCTA) the EMERALD study demonstrated the added value of the integration of hemodynamic features with plaque characteristic to identify lesions prone to rupture.³¹ Pursuing a similar aim, the present study combined angiographic information with translesional pressure and WSS-based quantities. Lesions were classified as culprit and non-culprit according to an overt clinical event, and NCL served as internal control, thus accounting for the intrinsic biological variability. In contrast to previous studies, the culprit criterion referred to a clinically relevant endpoint (i.e. MI), thus minimizing biases related to softer endpoints, such as anatomical plaque progression or target vessel revascularization.^{32, 33}

The temporal aspect of MI risk assessment is crucial when interpreting the prognostic value of ESS. While previous studies have demonstrated that low ESS correlates with plaque progression in short-term follow-ups (e.g., 6–12 months),¹³ our study extends this understanding by demonstrating its predictive capability over a longer follow-up period (5 years). The distinction between short- and long-term risk stratification is particularly relevant since plaque evolution is not uniform, and the interplay between hemodynamic forces and plaque remodeling may vary over time.

2.4.1 Applicability and reliability of CFD simulations based on conventional angiography

Based on recent studies confirming the reliability of angiographically-derived WSS,³⁴ the present work nurtured from the combination of conventional coronary angiography and CFD algorithms, allowing for a multidimensional lesion evaluation. Despite this complexity, a remarkable clinical implication of the present study is that all analyses were obtained by a clinician in 10.8 ± 1.41 minutes from conventional angiography using a standard computer. Hence, the methodological approach offered in the present study brings WSS and derived quantities closer to the clinical environment, where otherwise CFD simulations require substantial computational efforts, and in most cases mandate the support of experts.

To further legitimate the clinical application of the investigated clinical CFD approach, the reliability for WSS calculation was tested against simulations with higher resolution and numerical robustness carried out by experts in computational haemodynamics. The reliability of the clinical CFD approach was tested in terms of correlation and statistical significance. The comparison of the heat maps of WSS-based quantities as obtained from the two CFD approaches highlighted that the clinical CFD is adequately robust to replicate the results obtained using expert CFD, in terms of MI predictivity. The clinical CFD allowed for a WSS calculation in shorter time without substantial loss in accuracy and WSS predictive strength of MI. This served as clinical validation for the investigated WSS methodology, which was implemented here for the first time in humans for clinical outcome prediction.

2.4.2 Inclusion of computational haemodynamics for MI prediction

Anatomical lesion severity and translesional vFFR had a significant albeit modest capacity of detecting lesions culprit of future MI. For this reason, this study also investigated the action of shear forces at the blood-endothelium interface. Previous studies have shown that low TAWSS (<1.50 Pa) was associated with endothelial dysfunction and plaque progression,¹² while high TAWSS (>4.71 Pa) in the proximal segments of

the atherosclerotic plaque was predictive of plaque disruption and MI.¹³ More recently, a maximal TAWSS above 4.95 Pa over 3 mm vascular segment independently predicted adverse cardiovascular events requiring revascularization.³⁴ A significant association between TAWSS and the occurrence of MI was confirmed also in the present study ($p=0.011$), and in line with previous findings TAWSS significantly predicted MI, albeit weakly (TAWSS AUC 0.61, 95%CI 0.53-0.69, $p=0.003$). Moreover, the TAWSS cutoff (i.e. 5.01 Pa) supports previous reports.¹³ However, in contrast with the EMERALD study and the FAME 2 WSS sub-analysis,^{13, 31} the present study cohort had a lower functional lesion severity as depicted by the proportion of hemodynamically significant lesions (19.7% vs. 49.0% vs. 100.0% in the current study, EMERALD and FAME 2, respectively). More recently, vessels with borderline FFR values (0.81-0.85) and lesions with %AS <58% and maximum TAWSS <7.69 Pa had a long-term prevalence of lesion-oriented events below 6%.³⁵ Our study confirmed similar predictive cutoffs for both %AS (55.5%) and maximum TAWSS (7.30 Pa).

These findings highlight the potential usefulness of the current approach in stratifying mild lesions, hence tailoring preventive therapeutic strategies in patients without hemodynamically significant lesions.

2.4.3 Emerging role of TSVI

WSS topological skeleton features identify blood flow stagnation, recirculation and separation regions,³⁶ previously identified as flow disturbances promoting atherosclerosis (Figure 13).¹¹

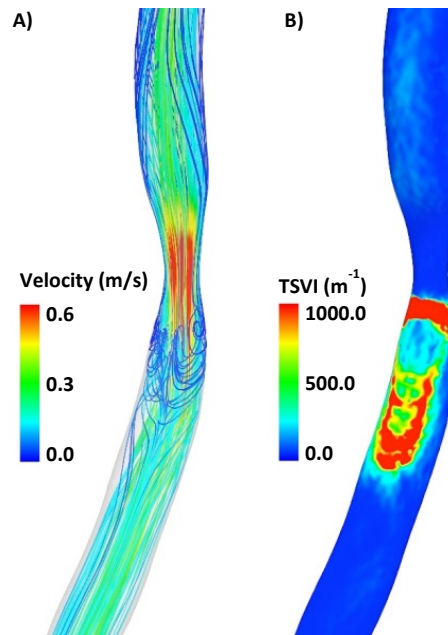


Figure 13. Explanatory case of flow patterns and TSVI. A) Streamlines of time averaged velocity vector field; B) TSVI luminal distribution.

Among WSS topological skeleton features, TSVI was initially associated with development of long-term re-stenosis after carotid endarterectomy in humans¹⁹. Recently, TSVI has been linked with early atherosclerotic changes in coronary arteries in preclinical swine models.²¹ Of note, high TSVI not only co-localized with higher wall thickness, but also predicted wall thickening longitudinally.²¹

Based on these recent findings, this is the first study investigating the link between TSVI and MI. More specifically, TSVI quantifies the variability in the contraction/expansion action exerted by the WSS on the endothelium along the cardiac cycle.^{19, 27} Translating this into mechanistic implications, high WSS contraction/expansion variability, inducing endothelial intra- and intercell tension variability, might promote shrinking/widening of cellular gaps,³⁶ fibrous cap fragility, accelerated disease progression, up to plaque rupture with impact on clinical outcomes.¹⁷ This hypothesis, although warranting further investigation, is grounded on the predictive capacity for MI of TSVI at the lesion level and downstream of the lesion in the present

study. Moreover, among lesions with %AS, $\Delta vFFR$ and TSVI above the threshold values, 75.0% evolved into a MI, while only 8.0% remained free from adverse events at 5 years. This enhanced discrimination for plaques vulnerable to rupture or, conversely, prone to senescence may provide the foundations for future clinical studies addressing different therapeutics strategies in this subgroup of patients. Of note, the best predictive performance was achieved by TSVI in predicting STEMI at 5 years (AUC 0.83, 95%CI 0.73-0.93, $p<0.001$).

Taken together with the previous evidence, current results support the role of the WSS contraction/expansion action along the cardiac cycle in promoting biological events, including plaque formation, progression^{19, 27} and, ultimately, destabilization. However, TSVI-associated changes in plaque characteristic remains to be elucidated.

2.4.4 Limitations

This study has several limitations. First, the small number of patients included in the final analysis. While explained by selection criteria of the retrospective screening, selection biases cannot be excluded. Second, the retrospective study design limited our ability of controlling for potential confounding factors, e.g. administration of intracoronary nitroglycerin before image acquisition. A validation of the present results in an independent prospective cohort is warranted. Third, no information on plaque burden or composition was available. Hence, the influence of positive plaque remodelling on the risk of an event could not be assessed. Fourth, the uncertainty and the level of idealization inherent in the 3D reconstruction and the CFD modelling might have influenced the considered WSS-based descriptors. In particular, the lack of personalized flow measurements and the assumptions made to manage the inflow boundary conditions could have affected the WSS estimation. However, the use of generic Doppler velocity curves scaled to fit patient-specific inlet cross-section diameter was previously validated in vessels presenting luminal cross sectional area reduction $< 50\%$.³⁷ Moreover, in ongoing analyses on diseased coronary arteries with available Doppler and frame count data, TSVI resulted only modestly affected by the adoption of the boundary conditions applied in the

present study. Analytically, a possible explanation for this can be found in the use of the normalized WSS vector in TSVI (see Eq.1).

2.5 Conclusions

The present study demonstrated (i) the value of CFD derived from conventional coronary angiography and performed by clinicians and (ii) the capability of WSS-based quantities to detect lesions culprit for future MI.

Although angiography-derived anatomical lesion severity and pressure drop along the vessel showed capacity in identifying coronary lesions leading to MI, the extension of the functional evaluation to include angiographic derived endothelial shear stress features – TAWSS and TSVI – improved the predictive capacity for MI. TAWSS, the most common WSS-based descriptor, was able to identify culprit lesions of a future MI, but with a modest predictive capacity. In contrast, high TSVI showed to portray a five-fold increase in the risk prediction for MI. Further clinical trials are required to translate these concepts into clinical practice.

2.6 Tables

Table 1 – WSS-based hemodynamic descriptors	
Time Averaged Wall Shear Stress (TAWSS)	$\text{TAWSS} = \frac{1}{T} \int_0^T \text{WSS} \, dt$
Oscillatory Shear Index (OSI)	$\text{OSI} = 0.5 \left[1 - \frac{\left \int_0^T \text{WSS} \, dt \right }{\int_0^T \text{WSS} \, dt} \right]$
Relative Residence Time (RRT)	$\text{RRT} = \frac{1}{\text{TAWSS} \cdot (1 - 2 \cdot \text{OSI})} = \frac{1}{\frac{1}{T} \left \int_0^T \text{WSS} \, dt \right }$
Transverse WSS (transWSS)	$\text{transWSS} = \frac{1}{T} \int_0^T \left \text{WSS} \cdot \left(n \times \frac{\int_0^T \text{WSS} \, dt}{\left \int_0^T \text{WSS} \, dt \right } \right) \right \, dt$
Time-Averaged WSS _{ax} (TAWSS _{ax})	$\text{TAWSS}_{\text{ax}} = \frac{1}{T} \int_0^T \text{WSS}_{\text{ax}} \, dt$
Time-Averaged WSS _{sc} (TAWSS _{sc})	$\text{TAWSS}_{\text{sc}} = \frac{1}{T} \int_0^T \text{WSS}_{\text{sc}} \, dt$

Table 1. WSS is the time-varying wall shear stress vector; T is the cardiac cycle duration; n is the unit vector normal to the arterial surface at each element; WSS_{ax} is the WSS projection along the direction of the tangent to the vessel centreline; WSS_{sc} is the WSS projection along the direction perpendicular to the tangent of the vessel centreline.

Table 2 – Clinical characteristics (N= 80)	
Age	70.3 ±12.7 years
Female	23 28.75%)
Type of MI: NSTEMI	52 (65.00%)
STEMI	28 35.00%)
Treatment: PCI	78 (97.50%)
CABG	1 (1.25%)
Medical therapy	1 (1.25%)
Time from baseline ICA (months)	25.9 ± 17.7
1 ICA before MI, n (%)	67 (83.70%)
≥ 2 ICA before MI, n (%)	13 (16.30%)
Hypertension, n (%)	61 (76.25%)
Hyperlipidaemia, n (%)	63 (78.75%)
Diabetes mellitus, n (%)	20 (25.00%)
Smoking, n (%)	21(26.25%)
LVEF < 55%, n (%)	18 (22.50%)
Reduced kidney function*, n (%)	18 (22.50%)
Prior PCI, n (%)	37 (46.25%)
Aspirin, n (%)	61 (76.25%)
Statin, n (%)	72 (90.00%)

Table 2. Clinical characteristics of the studied population at the time of the acute myocardial infarction (index event). Coronary artery bypass graft (CABG); Invasive coronary angiography (ICA); Left ventricle ejection fraction (LVEF); Myocardial infarction (MI); non-ST segment elevation myocardial infarction (NSTEMI); Percutaneous coronary intervention (PCI); Peripheral vascular disease (PVD); ST segment elevation myocardial infarction (STEMI). * eGFR < 60 ml/min/1.73 m².

Table 3 – Results of QCA and vFFR analysis (Vessel N = 188)			
	FCL (Vessel N = 80)	NCL (Vessel N = 108)	p-value
Vessel category, n (%)			
- RCA	22 (27.5%)	30 (27.8%)	0.928
- LAD	35 (43.8%)	35 (32.4%)	0.184
- LCX	23 (28.7%)	43 (39.8%)	0.207
Area stenosis, %	63.1±12.4	55.8±12.5	< 0.001
Diameter stenosis, %	40.2±10.6	34.3±9.66	< 0.001
Diameter stenosis, n (%)			
- <30%	15 (18.8%)	31 (28.7%)	0.118
- ≥30% and ≤50%	48 (60.0%)	72 (66.7%)	0.350
- >50%	17 (21.2%)	5 (4.6%)	< 0.001
Minimal lumen area (MLA), mm ²	2.31±1.24	2.64±1.23	0.064
Minimal lumen diameter (MLD), mm	1.65±0.46	1.78±0.43	0.045
Reference vessel diameter, mm	2.78±0.63	2.74±0.62	0.668
Lesion length, mm	17.1 (IQR 11.8-26.0)	15.6 (IQR 10.3-28.3)	0.526
Distance MLA from ostium, mm	38.1 (IQR 25.2-54.3)	36.8 (IQR 23.7-55.7)	0.643
Distal pressure drop, mmHg	14.5 (IQR 9.0-22.5)	12.0 (IQR 8.0-16.0)	0.012
Distal vFFR	0.84 (IQR 0.75-0.90)	0.86 (IQR 0.82-0.92)	0.009
Distal vFFR ≤ 0.80, n (%)	27 (33.8%)	10 (9.3%)	<0.001
ΔvFFR	0.08 (IQR 0.04-0.13)	0.05 (IQR 0.03-0.08)	0.002
Contour correction, %	9.5 (IQR 5.5-14.75)	10.2 (IQR 6.0-14.75)	0.486

Table 3. Output of the quantitative coronary angiography (QCA) and virtual fractional flow reserve (vFFR) according to the a priori known clinical classifier (culprit or non-culprit). Interquartile range (IQR). ΔvFFR, translesional vFFR difference.

Table 4 – Results of the univariate prediction models (C-stat) for continuous variables (Vessel N = 188)						
Descriptor	Segment	AUC (95%CI)	Threshold	Specificity	Sensitivity	p-value
%AS	Lesion	0.65 (0.57-0.73)	55.5%	0.52	0.72	<0.001
$\Delta vFFR$	Lesion	0.63 (0.55-0.71)	0.05	0.56	0.70	<0.001
TAWSS	Lesion	0.61 (0.53-0.69)	5.01 Pa	0.89	0.34	0.003
	Upstream	0.53 (0.44-0.61)	1.27 Pa	0.64	0.51	0.745
	Downstream	0.51 (0.42-0.6)	2.49 Pa	0.67	0.44	0.413
	Maximum	0.69 (0.61-0.76)	7.30 Pa	0.58	0.73	<0.001
	Minimum	0.67 (0.59-0.75)	0.49 Pa	0.55	0.77	0.999
TSVI	Lesion	0.77 (0.71-0.84)	40.52 m ⁻¹	0.66	0.86	<0.001
	Upstream	0.58 (0.50-0.66)	38.03 m ⁻¹	0.60	0.55	0.036
	Downstream	0.72 (0.65-0.79)	105.2 m ⁻¹	0.79	0.58	<0.001
	Maximum	0.78 (0.72-0.85)	1266.5 m ⁻¹	0.67	0.79	<0.001
	Minimum	0.54 (0.46- 0.63)	1.40 m ⁻¹	0.34	0.77	0.85

Table 4. Results of the univariate prediction models for FCL with time-averaged wall shear stress (TAWSS) and topological shear variation index (TSVI). TAWSS and TSVI were analysed according to the adopted vessel subdivision: lesion, upstream (US), and downstream (DS) segments. Maximum and minimum nodal values are also reported. Area under the curve (AUC); confidence interval (CI).

Table 5 – Results of the wall shear stress-based descriptors analysis (Vessel N = 188)												
Descriptor	Segment	Future culprit lesion (Vessel N = 80)					Nonculprit lesion (Vessel N = 108)					Adjusted <i>p</i> -value
		Avg	Min	Max	SD	SE	Avg	Min	Max	SD	SE	
TAWSS (Pa)	Lesion	4.58	1.23	21.83	3.50	0.39	3.38	0.84	16.46	2.09	0.2	0.007
	Upstream	1.69	0.56	7.56	1.22	0.14	1.56	0.32	9.25	0.97	0.09	0.409
	Downstream	2.80	0.37	16.36	2.30	0.26	2.64	0.46	12.45	2.06	0.2	0.621
TSVI (m ⁻¹)	Lesion	89.0	21.85	253.5	58.4	6.49	49.1	8.76	228.4	41.6	41.5	<0.001
	Upstream	51.8	6.06	212.1	44.9	5.0	44.2	6.1	238.4	43.8	43.9	0.216
	Downstream	135.2	16.47	485.9	96.1	10.7	74.9	12.5	407.5	66.0	65.6	<0.001

Table 5. Wall shear stress (WSS)-based descriptors distribution stratified for the clinical classifier (future culprit lesion, FCL, or nonculprit lesion, NCL) and the adopted vessel subdivision (lesion, upstream and downstream). Time-averaged wall shear stress (TAWSS); Topological shear variation index (TSVI). Standard deviation (SD); standard error (SE)

Chapter 3

Influence of intracoronary hemodynamic forces on atherosclerotic plaque phenotypes

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Influence of intracoronary hemodynamic forces on atherosclerotic plaque phenotypes

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3.1 Introduction

An elevated translesional pressure gradient is considered the main biomechanical hallmark of atherosclerotic disease,¹⁰ and clinically has been associated with plaque destabilization and adverse clinical events.³⁸ The recent introduction of pullback pressure gradient (PPG) allowed to quantify the distribution of intracoronary pressure decay^{39, 40} promising standardization in the diagnosis of focal vs. diffuse coronary artery disease (CAD) and favouring the identification of vulnerable coronary lesions.⁴¹

Besides pressure gradients, the shear action exerted at the blood-endothelium interface, quantifiable in terms of wall shear stress (WSS), is associated with coronary plaque nucleation, progression and destabilization.¹⁷ WSS characterization based on computational fluid dynamics (CFD) simulations applied to three-dimensional (3D) coronary vessel models identifies vascular segments with dysfunctional endothelial function¹² or vulnerable plaques.^{13, 35, 42-44} Furthermore, WSS calculation predictive of plaque rupture can now be made based on conventional coronary angiography, potentially facilitating its use in clinical practice.⁴⁵

In the present investigation longitudinal invasive pressure assessment, WSS profiles obtained from angiography-derived CFD simulations, and atherosclerotic plaque phenotype identification based on intracoronary optical coherence tomography (OCT) were combined to explore possible links between focal vs. diffuse intracoronary pressure gradients, WSS and atherosclerotic plaque features.

3.2 Methods

The workflow of the study is graphically illustrated in Figure 14.

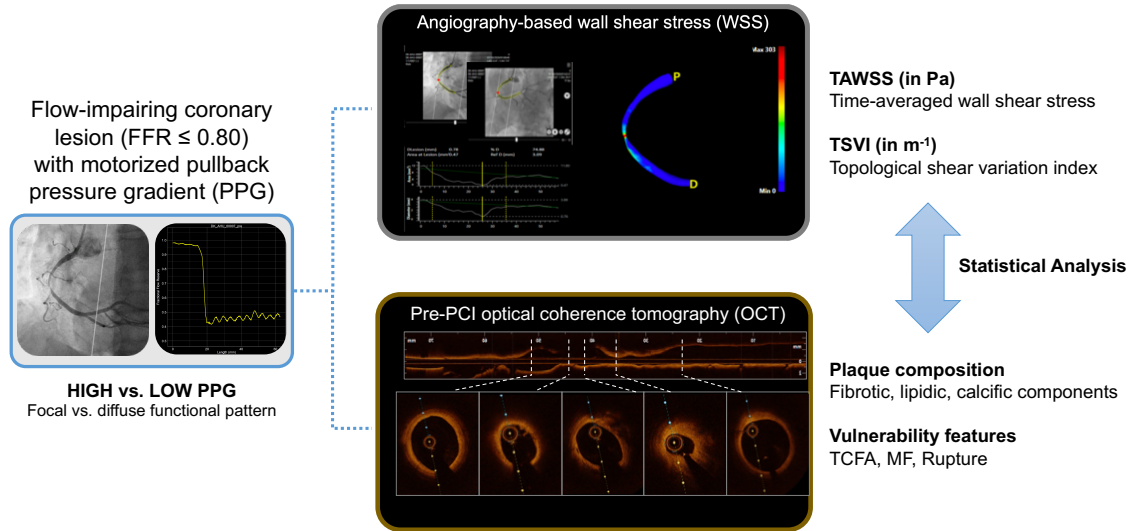


Figure 14. Study workflow. The present sub-analysis of the Precise PCI Plan (P3) study investigated coronary lesions with a pathological fractional flow reserve ($\text{FFR} \leq 0.80$) with motorized pullback pressure gradient (PPG). From the PPG, lesions were classified as presenting a focal functional pattern (PPG above the median value) or as presenting a diffuse functional pattern (PPG below the median value). Next, angiography-based three-dimensional vessel reconstructions were obtained from two angiographic projections and used to run computational fluid dynamics (CFD) simulations with the measurement of time-averaged wall shear stress (TAWSS) and topological shear variation index (TSVI) at the level of the throat of the lesion. In parallel, pre-PCI optical coherence tomography (OCT) acquisitions of each lesion were independently assessed for the adjudication of plaque composition and vulnerability features. Finally, association between functional parameters (derived from the PPG and WSS analyses) and anatomical parameters (derived from the quantitative angiography and the OCT analyses) was statistically investigated. TCFA = thin-cap fibrous atheroma; MF = macrophage infiltration.

3.2.1 Study design

The P3 study was an investigator-initiated, multicentre, prospective, single-arm study of patients electively referred to invasive coronary angiography (ICA). The study aimed to validate the accuracy of coronary computed tomography angiography-derived fractional flow reserve (FFR_{CT}) planner for post-percutaneous coronary intervention (PCI) invasive FFR prediction. Patients were included in the P3 study if invasive distal FFR demonstrated a significant flow impairment ($\text{FFR} \leq 0.80$). The design and results of the P3 Study are presented extensively elsewhere.^{46, 47} Patients undergoing motorized FFR pullbacks, angiography-derived WSS and OCT were included.

The registered study protocol (NCT03782688) was approved by the investigational review board or ethics committee at each participating centre, and all enrolled patients provided written informed consent before study procedures. The P3 study was sponsored by the Cardiac Research Institute Aalst (Aalst, Belgium), with unrestricted grants from HeartFlow (Redwood City, CA, USA) and CardioPath (University of Naples, Naples, Italy).

3.2.2 Pullback Pressure Gradient

Motorized FFR pressure pullback tracings were acquired using a pullback device (Volcano R100, Volcano Corporation, San Diego, USA) at a speed of 1 mm per second and were used for quantitative invasive translesional pressure gradients before and after PCI. Technically, from the FFR pullback pressure curves the PPG (a non-dimensional pullback FFR-based quantity ranging from 0 “diffuse disease” to 1 “focal disease”) ³⁹ was calculated with commercial software (CoroFlow v3.5, Corovantis Research, Uppsala, Sweden). Functional descriptors based on hyperaemic pressure pullbacks included PPG, maximal pressure gradient over 20 mm (MaxPPG_{20mm}), and length of functional disease, and are detailed in the elsewhere.³⁹

3.2.3 Quantitative coronary angiography

Individual coronary vessel geometries were reconstructed based on 3D quantitative coronary angiography (3D-QCA) using two angiographic end-diastolic frames at least 30 degrees apart (CAAS Workstation WSS software, Pie Medical Imaging, Maastricht, The Netherlands). Automatic lumen contour detection was enabled and manually corrected only if needed. 3D vascular models were reconstructed from vessel ostium to pressure sensor position. Vessels presenting ostial lesions identified in terms of minimal lumen area (MLA) located at ≤ 20 mm distance from the ostium or presenting side branches with diameter ≥ 2.0 mm were excluded from the analysis.

The *lesion* was quantified as percentage area stenosis (%AS) and defined as the coronary segment including the MLA, delimited proximally

and distally by the intersection of the 3D-QCA diameter function line with the interpolated reference line.² The mid lesion segment included the MLA section and its length was proximally and distally delimited on the 3D-QCA reference diameter function line using a threshold value set at 60% of the hydraulic diameter of the MLA section relative severity value. The rationale for the choice of this threshold lies on the supposition of a Gaussian stenosis distribution profile, wherein the relative severity is maximal and equal to 100% at the MLA, while the proximal and distal cross-sections at a relative severity of 60% subdivide the lesion segment into three sub-segments of equal length.

3.2.4 Blood flow simulations and wall shear stress

Realistic CFD simulations of coronary haemodynamics were carried out on the reconstructed 3D vascular geometries using a finite element-based code (CAAS Workstation WSS software, Pie Medical Imaging, Maastricht, The Netherlands). Using CFD data, the WSS distribution on the luminal surface was quantified along the cardiac cycle. In details, two WSS-based quantities, namely the time-averaged wall shear stress (TAWSS) and the recently proposed topological shear variation index (TSVI, a measure of the variability of the WSS contraction/expansion action exerted on the endothelium along the cardiac cycle), were computed as extensively reported in previous studies.^{27, 45, 48, 49} TAWSS and TSVI data reported in the following text refer uniquely to their values averaged over the mid segment of the lesion.

3.2.5 Optical coherence tomography

OCT pullbacks of 75 mm length were acquired using Dragonfly OPTIS Imaging Catheter (Abbott Vascular, St. Paul, MN, USA). OCT acquisitions performed after lesion pre-dilatation were excluded from the present analysis. OCT-based plaque composition analysis was performed at the lesion level as extensively detailed elsewhere.⁵⁰

3.2.6 Statistical analysis

The statistical analysis was performed on a per-vessel basis. The median PPG value was used to define groups with focal or diffuse disease. Median TAWSS and TSVI values were adopted to define “high or low TAWSS” and “high or low TSVI” sub-groups.

Normality of distribution was assessed with the Shapiro–Wilk test. Continuous variables with normal distribution are presented as mean $\pm$ standard deviation (SD) and non-normally distributed variables as median and inter-quartile range [IQR]. Categorical variables are presented as percentage. The Chi-squared test was used for comparing categorical variables, the Student’s t test (or Mann-Whitney test as appropriate) for continuous ones. Linear relationship between continuous variables was assessed using correlation coefficients. Uni- and multivariate generalized linear models were used to perform regression analyses on continuous OCT variables and PPG- or WSS-based quantities. The logistic generalized linear model was used in case of categorical OCT variables. Odd ratios (OR) per unit increase in the independent variable and their 95% confidence interval (95% CI) were obtained from the exponential of the standardized correlation coefficients. A p-value < 0.050 was considered significant. The discriminatory capacity for high-risk plaque features of %AS, PPG, TAWSS and TSVI were assessed using C-statistics. Receiving operator characteristic (ROC) curves were compared in terms of area under the curve (AUC) and using the DeLong method.²⁸

All analyses were performed using R (Version 1.2.5033, R Foundation for Statistical Computing, Vienna, Austria) and MATLAB (Version R2022, MathWorks, Natick, MA, USA).

3.3 Results

Of 120 vessels (117 patients) with PPG tracings, 105 (87.5%) underwent 3D vessel reconstruction and WSS analysis. Of those, 51 (42.5%) had OCT pullbacks performed before any intracoronary intervention, Figure 15.

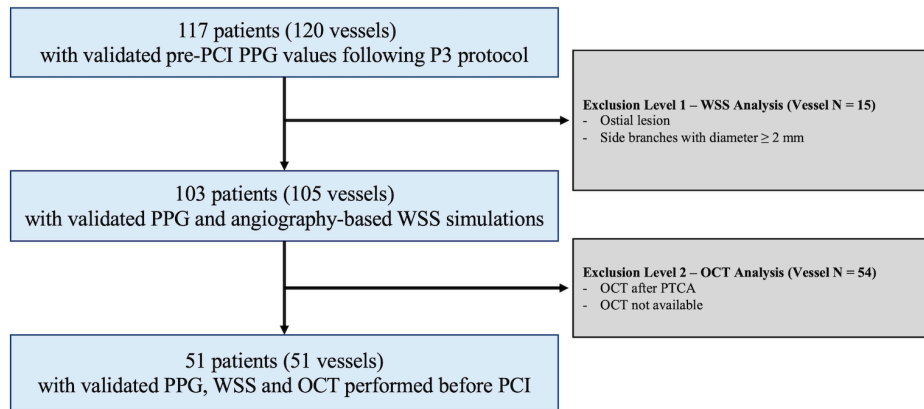


Figure 15. Study Population. The present sub-analysis of the *Precise PCI Plan (P3)* study was performed on 105 vessels from 103 patients with pressure pullback gradient (PPG) tracings and angiography-based wall shear stress (WSS) simulations. In a subset of 51 vessels studied with optical coherence tomography (OCT) before PCI, plaque composition was associated with WSS-based descriptors, FFR = fractional flow reserve; FFRCT = CT-derived FFR.

3.3.1 Baseline characteristics

Baseline patient characteristics and results from the analysis of WSS and PPG data are reported in Table 6. Median FFR and mean PPG were 0.70 [IQR 0.56-0.77] and 0.66 ± 0.13 , respectively. Vessels in the high PPG group exhibited significantly higher %AS, and significantly lower FFR. The haemodynamics in vessels presenting with high PPG (focal CAD) was characterized by a two-fold increase in the TAWSS and TSVI values.

3.3.2 Association of CAD patterns and wall shear stress profiles

There was an association between WSS profiles and CAD patterns, Figure 16. After adjustment for other lesion features such as %AS and lesion length, the independent association with PPG was retained only for TSVI. Results from the uni- and multivariate analysis for the association between CAD patterns and WSS profiles are presented in Table 7.

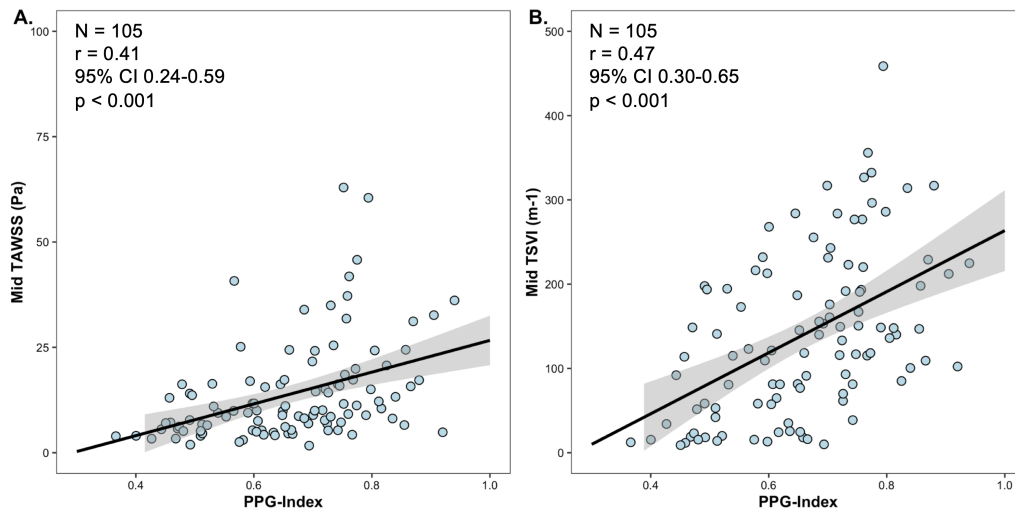


Figure 16. Linear correlation between intracoronary pressure gradients and translesional shear forces. X-axis “PPG-Index” = pullback pressure gradient index. Panel A) Y-axis “Mid TAWSS” = time-averaged wall shear stress measured at the mid lesion segment (throat). Panel B) Y-axis “Mid TSVI” = topological shear variation index measured at the mid lesion segment (throat).

3.3.4 Association of coronary plaque features with wall shear stress

A summary of the investigated pre-PCI OCT-based plaque characteristics are displayed in Table 8. The relationship between pressure gradients and WSS with plaque phenotype is summarized in Figure 17. Fibrocalcific plaque was the most common observed plaque phenotype (60.8%). Thin cap fibroatheroma (TCFA) and plaque rupture were more prevalent among high PPG than among low PPG vessels. TAWSS was associated with macrophage plaque infiltration. TSVI was associated with plaque rupture and cholesterol crystals. Other associations between WSS and OCT plaque features are presented in Table 9.

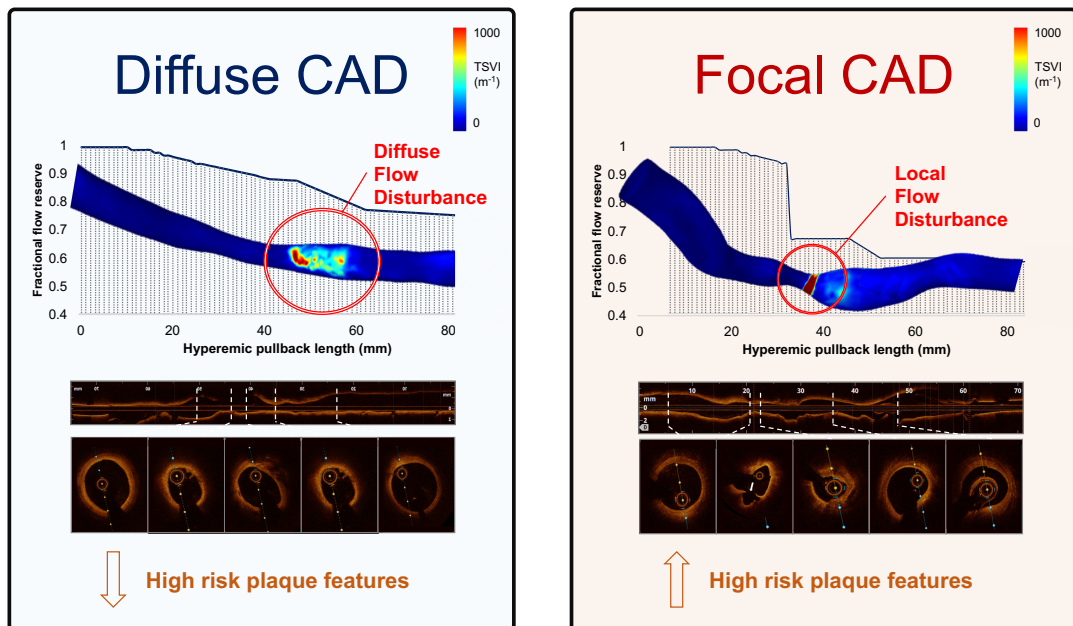


Figure 17. Interplay between intracoronary haemodynamics and plaque composition. Lesions with a diffuse pressure drop (left panel “diffuse CAD”) presented milder local flow disturbances and less frequently high-risk plaque phenotypes. Conversely, lesions presenting a focal pressure drop (right panel “focal CAD”) had increased local flow disturbances and were associated with the presence of macrophage infiltration, plaque rupture (white arrow) and cholesterol crystals at the pre-PCI optical coherence tomography assessment. PPG = pullback pressure gradient.

The predicted capacity for identification of high-risk plaque features by %AS, WSS and PPG are shown in Figure 18.

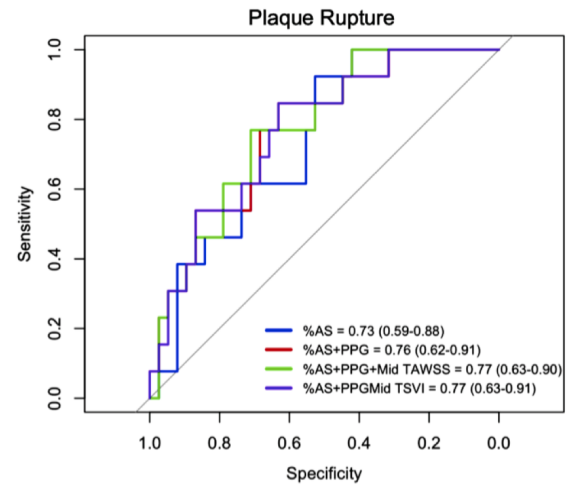
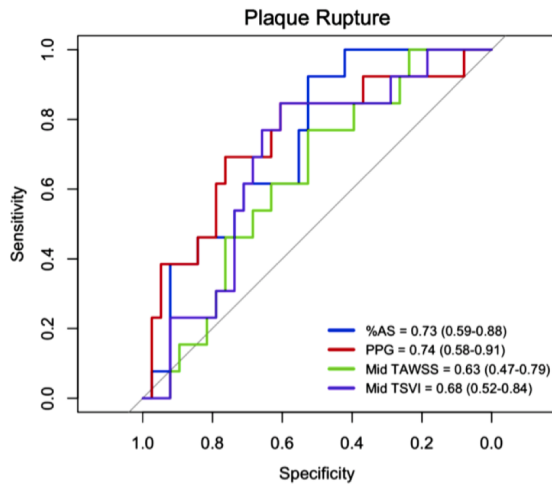
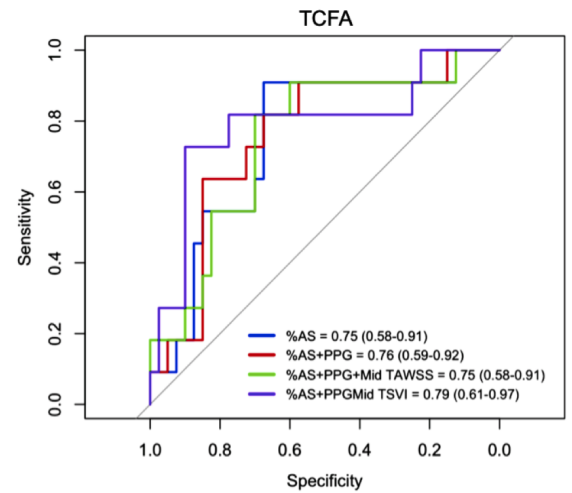
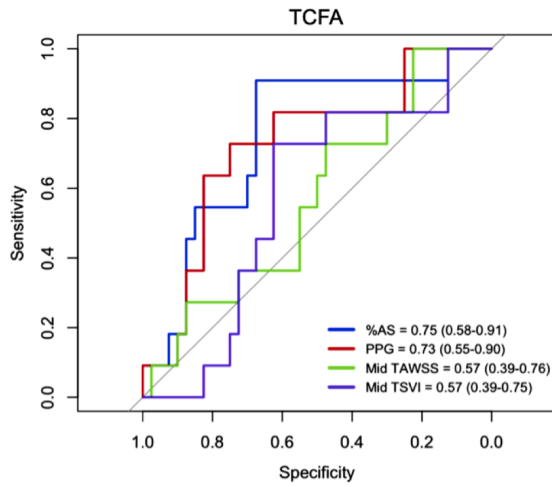


Figure 18. Receiver operating characteristic curves for thin-cap fibrous atheroma (TCFA) and plaque rupture. C-statistics is provided for percentage area stenosis (%AS), pullback pressure gradient (PPG), time-averaged wall shear stress measured at the mid lesion segment (mid TAWSS) and topological shear variation index measured at the mid lesion segment (mid TSVI) as univariate models for association with TCFA (Panel A) or plaque rupture (Panel C) and as multivariate models for association with TCFA (Panel B) or plaque rupture (Panel D). Pairwise area under the curve (AUC) comparison not significant in all cases, with exception of AUC%AS vs AUCTAWSS for TCFA (DeLong p-value = 0.048), AUC%AS vs AUCTSVI for TCFA (DeLong p-value = 0.045).

3.3.5 Association of coronary plaque features with intracoronary pressure gradients

PPG was associated with the extension of the lipid circumferential infiltration, thin cap fibroatheroma and plaque rupture, and inversely associated to the fibrous cap thickness. Other associations between PPG and OCT plaque features are presented in Table 9. PPG was associated with fibrous cap thickness independently from TAWSS and TSVI (Table 10 and 11).

When combining CAD and WSS patterns, vessels presenting high PPG presented thinner fibrous caps, higher prevalence of TCFA and plaque rupture in both low and high TAWSS and TSVI conditions (Table 12 and 13).

3.4 Discussion

In this study, we addressed the inter-relationship between intravascular hemodynamic forces exerted by the blood and plaque composition. The main findings of the study are: (i) higher values of TAWSS (depicting the WSS magnitude averaged along the cardiac cycle) and TSVI (a measure of the contraction/expansion variability exerted by the shear forces on the endothelium along the cardiac cycle) were found in vessels presenting a focal rather than diffuse disease; (ii) focal disease and elevated shear forces were associated with high-risk plaque phenotypes at the OCT evaluation; (iii) vessels with a diffuse pattern of disease based on coronary physiology showed milder local flow disturbances and less frequently presented plaque vulnerability features.

3.4.1 Wall shear stress and pressure gradients

High pressure gradients across epicardial lesions have been recognized as independent predictors of cardiovascular events.⁷ In simple cases, as per Hagen-Poiseuille theory, pressure gradients and WSS are in direct linear relationship in cylindric conduits.⁵¹ Still, the nature of such a relationship becomes more intricate in coronary arteries, mainly because of

anatomical complexity and flow pulsatility. However, because of their effect on coronary flow rate, pressure gradients reflect on the shear forces acting at the level of the blood-endothelium interface.⁵² The existence of such a link was confirmed by a sub-analysis from the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II (FAME II) trial, where Kumar et al. suggested that in flow-impairing lesions high TAWSS values were predictive of lesion destabilization and clinically overt MI.¹³ Moreover, high TAWSS and mostly high TSVI identified lesions with negative FFR leading to future adverse events,³⁵ and showed incremental power for MI prediction on top of lesion anatomical severity and translesional pressure gradients.⁴⁵

In the present analysis, in addition to time-averaged magnitude of WSS (TAWSS), also the time-dependent variability in the contraction-expansion action exerted by the shear forces on the endothelium was quantified by TSVI. Focal lesions (high PPG) were anatomically more severe than in vessels with diffuse disease (low PPG) (percentage AS = 83.73% vs 72.86%, $p < 0.001$). This more pronounced anatomical severity reflected not only on a more pronounced flow impairment in the focal pressure drop group with lower FFR values (0.57 vs. 0.75, $p < 0.001$), but also in deranged WSS profiles at the lesion level. In fact, vessels with a focal disease presented elevated TAWSS and TSVI (14.78 Pa and 163.93 m^{-1}) values, exceedingly above the known values associated with adverse coronary events (5-7 Pa for TAWSS and 40.5 m^{-1} for TSVI).^{11, 45} On the other hand, lesions with diffuse pressure losses presented with lower TAWSS and TSVI values (7.03 Pa and 76.82 m^{-1}), and in half of cases with TAWSS values within the physiological range (i.e., 1-7 Pa).¹¹ These findings suggested a more stable endothelial shear stress profile in lesions with diffuse disease defined by longitudinal intracoronary pressure assessment.

3.4.2 Wall shear stress and plaque composition

Links between adverse endothelial shear stress patterns and plaque progression have been described *post-mortem* and *in vivo*.^{12, 49, 53} Less well characterized is the relationship between WSS patterns and plaque composition. Extensive preclinical experience related WSS with the

development of lipid-rich, inflamed or thin-capped (vulnerable) plaques.^{54, 55} In humans, lower WSS areas have been associated with larger plaque burden, predicting adverse clinical events.¹⁴ Notably, as plaques grow sufficiently to encroach into the lumen, translesional pressure gradients increase and low WSS areas at the throat of the stenoses turn into high WSS areas, altering the hemodynamic microenvironment and increasing the risk of plaque destabilization and rupture.^{13, 56} Focal intracoronary pressure gradients were previously associated with higher plaque burden and increased lipidic plaque components, while a diffuse intravascular pressure decay was associated with an increased calcific plaque component.⁴¹ In a prospective study based on virtual histology intravascular ultrasound (VH-IVUS), WSS patterns were associated with adverse alterations in plaque composition (rather than plaque size), pointing towards the need for a wider intracoronary flow patterns description to capture the complexity of plaque evolution.¹⁵ In the present study, OCT-defined plaque rupture was associated with TSVI. TSVI has also been linked to the development of long-term restenosis after carotid endarterectomy,⁴⁸ to the longitudinal coronary vessel wall thickening,⁴⁹ and the longitudinal risk of MI.⁴⁵ These studies demonstrated that TSVI represents a different hemodynamic signal to the endothelium with respect to TAWSS and relates to high-risk features previously link with adverse events.^{27, 48}

This is consistent with the findings of the present study, where TSVI (rather than TAWSS) showed an association with OCT plaque characteristics. In fact, TAWSS associated significantly with macrophage infiltration, while TSVI with plaque rupture, cholesterol crystals and inversely with the thickness of the calcium component of the plaque. Finally, focal disease presented with larger lipid components and thinner fibrotic caps, often (subclinically) ruptured. These findings confirm that coronary lesions with a focal pressure gradient pattern present also adverse WSS features, which might synergically interplay favouring plaque destabilization and rupture. On the contrary, diffusely diseased vessels exhibited lower TAWSS and TSVI and a more favourable plaque phenotype, with lower TCFA or plaque rupture prevalence.

3.4.3 Making sense of the ‘*alphabet soup*’ of hemodynamic quantities in focal and diffuse flow-limiting lesions

The observed results suggest a differential interplay between translesional pressure gradients, WSS and plaque composition. Lesions generating an abrupt local increase in epicardial resistance (high PPG, i.e. high focal pressure gradients) elicit more marked flow disturbances, captured by high TAWSS values, and alter the physiological topology of the WSS field, as documented by high TSVI values. Conceptually, while an interaction of pressure gradients with TAWSS was expected (see e.g. the above-mentioned simple fluid mechanics paradigm of Hagen-Poiseuille theory), an interaction with TSVI is not a foregone conclusion: the obtained results cannot be easily justifiable on the basis of very simple fluid mechanics examples, as they come up from the hemodynamic richness within coronary vessels presenting with severe lesions and in general in the presence of marked flow disturbances in arteries.

Nonetheless, the clustering of hemodynamic factors (focal pressure gradients and adverse WSS profiles) may result in a worsening of the endothelial function, unphysiological intra- and intercellular tensions, and the widening in the intercellular gaps.³⁶ This Favours further plaque infiltration while the shearing of the fibrotic cap increases, and with it the risk of plaque destabilization and plaque rupture when humoral forces exceed the plaque strength.^{17, 57} For this reason, the presence of high translesional focal pressure gradients combined with adverse plaque features may permit a refined plaque risk stratification, where pre-emptive strategies with sealing effect on those vulnerable plaques might be tested.⁵⁸ On the other hand, flow-impairing lesions with a diffuse pressure drop pattern might accommodate better local blood flow disturbances, resulting in a less vulnerable plaque phenotype.

3.4.4 Limitations

Some limitations merit consideration. First, the uncertainty inherent in the reconstruction of vascular geometries from angiographic images as well as the idealizations introduced in modelling coronary flows with CFD might

have influenced the calculation of the considered WSS-based quantities. However, previous sensitivity studies ^{11, 59} suggest that the generalization of the results can be affected only modestly. Second, given the relatively small sample size, a larger population is required to confirm the presented findings. In the OCT sub-analysis, only patients with native OCT lesion crossings were considered, excluding any crossings after lesion manipulation. This selection ensured a genuine evaluation of native lesions. Nonetheless, the here investigated dataset is the first cohort combining motorized pressure recordings along the epicardial vessel and high-resolution OCT imaging acquisitions. Third, the report is restricted to the description of the association between CAD patterns and WSS profiles, the clinical implications of these findings require further investigation.

3.5 Conclusions

The present investigation related intracoronary pressure gradients with angiography-based WSS analysis from CFD simulations and plaque composition in vessels presenting flow-impairing lesions in the elective setting of a chronic coronary syndrome. The findings of this study support the hypotheses that: (i) the hemodynamic profile identified by pressure gradient and the WSS-based quantities TAWSS and TSVI is different in patients presenting with focal and diffuse CAD; (ii) the different hemodynamic profiles characterizing focal and diffuse CAD are associated with different atherosclerotic plaque phenotype. Taken together, these findings point towards a central role of adverse WSS features in the destabilization mechanisms of coronary lesions presenting a focal pressure drop pattern.

3.6 Tables

Table 6 – Clinical and anatomo-functional baseline characteristics.				
	Overall (Patient n = 103)	Low PPG (Patient n = 52)	High PPG (Patient n = 51)	<i>p-value</i> (two-sided)
Age, years (mean ± SD)	63.85 ± 9.17	64.92 ± 8.64	62.72 ± 9.65	0.226
Male, n (%)	85 (82.5)	44 (84.6)	41 (80.4)	0.613
BMI, kg/m2 (mean ± SD)	26.8 ± 3.23	26.67 ± 3.44	26.67 ± 3.04	0.681
Dyslipidaemia, n (%)	78 (75.7)	39 (75.0)	39 (76.5)	1.000
Hypertension, n (%)	57 (55.3)	27 (51.9)	30 (58.8)	0.554
Diabetes mellitus, n (%)	22 (21.4)	12 (23.1)	10 (19.6)	0.811
- under insulin, n (%)	4 (3.9)	4 (7.7)	0 (0.0)	0.118
Current smoker, n (%)	20 (19.4)	11 (21.2)	9 (17.6)	0.804
Coronary artery disease, n (%)	4 (3.9)	2 (3.8)	2 (3.9)	1.000
Clinical Presentation				
Silent ischemia, n (%)	24 (23.3)	16 (30.8)	8 (15.7)	0.091
Stable angina CCS I, n (%)	33 (32.0)	19 (36.5)	14 (27.5)	
Stable angina CCS II, n (%)	36 (35.0)	14 (26.9)	22 (43.1)	
Stable angina CCS III, n (%)	7 (6.8)	2 (3.8)	5 (9.8)	
Stable angina CCS IV, n (%)	1 (1.0)	1 (1.9)	0 (0.0)	
Unstable angina, n (%)	2 (1.9)	0 (0.0)	2 (3.9)	

Creatinine Clearance, mL/min (mean $\pm$ SD)	78.94 $\pm$ 22.65	74.80 $\pm$ 18.12	83.16 $\pm$ 25.99	0.061
LVEF, % (mean $\pm$ SD)	60.14 $\pm$ 6.11	60.16 $\pm$ 7.09	60.12 $\pm$ 4.98	0.978
Anatomical and functional characteristics				
	Overall (Vessel N = 105)	Low PPG (Vessel N = 53)	High PPG (Vessel N = 52)	p-value (two-sided)
LAD, n (%)	76 (72.4)	51 (96.2)	25 (48.1)	< 0.001
LCX, n (%)	12 (11.4)	1 (1.9)	11 (21.1)	
RCA, n (%)	17 (16.2)	1 (1.9)	16 (30.8)	
%AS (mean $\pm$ SD)	78.24 $\pm$ 11.64	72.86 $\pm$ 10.53	83.73 $\pm$ 10.12	<0.001
Anatomical lesion length, mm (mean $\pm$ SD)	19.48 $\pm$ 10.57	20.45 $\pm$ 10.46	18.49 $\pm$ 10.70	0.345
FFR (median [IQR])	0.70 [0.56-0.77]	0.75 [0.68-0.78]	0.57 [0.45-0.70]	<0.001
PPG (mean $\pm$ SD)	0.66 $\pm$ 0.13	0.55 $\pm$ 0.08	0.77 $\pm$ 0.06	<0.001
TAWSS, Pa (median [IQR])	9.93 [5.75-16.35]	7.03 [4.80-11.67]	14.78 [8.62-24.34]	<0.001
TSVI, m ⁻¹ (median [IQR])	123.13 [58.39-198.03]	76.82 [23.10-140.95]	163.9 [117.6-249.2]	<0.001

Table 6. Results for categorical variables are presented as count and percentage. Results for continuous variables are presented as mean $\pm$ standard deviation (SD) or as median and interquartile range (IQR). %AS = percentage area stenosis; BMI=body mass index; CCS=Canadian cardiovascular society; FFR = fractional flow reserve; LVEF=left ventricle ejection fraction; MaxPPG20mm= maximum pressure gradients over 20 mm; PPG=pullback pressure gradient; TAWSS = time-averaged wall shear stress measured at the mid lesion segment (throat); TSVI = topological shear variation index measured at the mid lesion segment (throat).

Table 7 – Uni- and multivariate analyses for the association with the PPG (Vessel N = 105).						
	Univariate models		Multivariate model With TAWSS		Multivariate model With TSVI	
	OR (95% LCI to UCI)	<i>p-value</i>	OR (95% LCI to UCI)	<i>p-value</i>	OR (95% LCI to UCI)	<i>p-value</i>
- Lesion length	0.9997 (0.9973 to 1.0021)	0.797	0.9983 (0.9963 to 1.0002)	0.082	0.9984 (0.9965 to 1.0004)	0.118
- %AS	1.0063 (1.0045 to 1.0081)	<0.0001	1.0056 (1.0035 to 1.0077)	<0.0001	1.0052 (1.0030 to 1.0074)	<0.0001
- TAWSS	1.0046 (1.0026 to 1.0065)	<0.0001	1.0020 (0.9999 to 1.0040)	0.059	-	-
- TSVI	1.0006 (1.0004 to 1.0008)	<0.0001	-	-	1.0003 (1.0000 to 1.0005)	0.030

Table 7. The PPG is assumed as continuous quantitative variable. Univariate models: PPG vs. anatomical lesion length, PPG vs. percentage area stenosis (%AS); PPG vs. TAWSS or TSVI. Multivariate models: PPG vs. anatomical lesion length + %AS + TAWSS or TSVI. OR = odds ratio of the univariate or multivariate analysis; 95% LCI to UCI = 95% lower and upper confidence intervals. %AS = percentage area stenosis; TAWSS = time-averaged wall shear stress measured at the mid lesion segment (throat); TSVI = topological shear variation index measured at the mid lesion segment (throat).

Table 8 – Optical coherence tomography (OCT) plaque analysis before PCI (Vessel N = 51).				
	Total (Vessel N = 51)	Low PPG (Vessel N = 38)	High PPG (Vessel N = 13)	<i>p-value</i> (two-sided)
Lipid-rich plaque, n (%)	29 (56.9)	20 (52.6)	9 (69.2)	0.297
Lipid-rich plaque $\geq 180^\circ$, n (%)	21 (41.2)	14 (36.8)	7 (53.8)	0.282
Lipidic arc, degree ($^\circ$)	205 [143 – 237]	203 [126 – 235]	267 [182 – 360]	0.107
Calcific plaque, n (%)	42 (82.4)	31 (81.6)	11 (84.6)	0.804
Calcium thickness, mm	0.89 [0.73 – 1.16]	0.89 [0.73 – 1.20]	0.90 (0.68 – 1.16]	0.933
Calcium arc, degree ($^\circ$)	140 [86 – 308]	139 [80 – 308]	206 [94 – 360]	0.107
Fibrocalcific plaque, n (%)	31 (60.8)	25 (65.8)	6 (46.2)	0.211
Fibrous cap thickness, μm	77.0 (61.0 – 99.0)	91.0 (66.5 – 105.5)	61.0 (54.0 – 71.0)	0.005
TCFA, n (%)	11 (21.6)	5 (13.2)	6 (46.2)	0.013
Plaque rupture, n (%)	13 (25.5)	7 (18.4)	6 (46.2)	0.048
Macrophage, n (%)	14 (27.5)	10 (26.3)	4 (30.8)	0.756
Cholesterol crystals, n (%)	21 (41.2)	14 (36.8)	7 (53.8)	0.282

Table 8. Frequencies of coronary plaque features independently adjudicated from optical coherence tomography (OCT) acquisition before any percutaneous coronary intervention (PCI). Results for categorical variables are presented as count and percentage. Results for continuous variables are presented as median and interquartile range (IQR). TCFA = Thin-cap fibrous atheroma.

Table 9 – Association between TAWSS, TSVI or PPG and OCT plaque phenotypes (Vessel N = 51).						
OCT-based plaque feature	TAWSS Mid		TSVI Mid		PPG	
	OR (95% LCI to UCI)	<i>p-value</i>	OR (95% LCI to UCI)	<i>p-value</i>	OR (95% LCI to UCI)	<i>p-value</i>
Lipid-rich plaque $\geq 180^\circ$	0.935 (0.846 to 1.033)	0.176	1.002 (0.994 to 1.010)	0.702	3.171 (1.021 to 9.845)	0.046
Lipidic arc	0.153 (0.004 to 5.677)	0.296	1.195 (0.830 to 1.720)	0.327	7.776 (6.186 to 9.773)	0.003
Calcific plaque	1.111 (0.925 to 1.334)	0.251	1.004 (0.995 to 1.014)	0.373	1.052 (0.422 to 2.625)	0.911
Calcium thickness	0.988 (0.973 to 1.002)	0.094	0.998 (0.997 to 0.999)	0.032	0.548 (0.195 to 1.541)	0.247
Calcium arc	0.990 (0.962 to 1.019)	0.611	1.000 (0.998 to 1.002)	0.756	2.021 (0.378 to 10.796)	0.401
Fibrocalcific plaque	0.967 (0.865 to 1.081)	0.540	0.994 (0.986 to 1.002)	0.135	0.309 (0.094 to 1.009)	0.052
Fibrous cap thickness	1.000 (0.999 to 1.001)	0.964	1.000 (0.999 to 1.000)	0.562	0.898 (0.845 to 0.954)	0.001
TCFA	0.999 (0.873 to 1.146)	0.999	1.000 (0.993 to 1.008)	0.907	2.847 (1.112 to 7.825)	0.029
Plaque rupture	1.043 (0.913 to 1.192)	0.523	1.012 (1.001 to 1.024)	0.024	4.943 (1.815 to 13.465)	0.002
Macrophage	1.154 (1.021 to 1.304)	0.018	1.010 (0.999 to 1.020)	0.061	1.008 (0.339 to 2.995)	0.988
Cholesterol crystals	1.131 (0.980 to 1.304)	0.084	1.008 (1.000 to 1.015)	0.041	1.293 (0.378 to 4.430)	0.676

Table 9. Association between TAWSS, TSVI or PPG and OCT plaque phenotypes (Vessel N = 51). OR = Odds ratio of the univariate analysis; 95% LCI to UCI = 95% lower and upper confidence intervals. PPG = pullback pressure gradients; TAWSS = time-averaged wall shear stress measured at the mid lesion segment (throat); TCFA Thin-cap fibrous atheroma; TSVI = topological shear variation index measured at the mid lesion segment (throat).

Table 10 – Multivariate analyses for the association of TAWSS and OCT plaque phenotype with the PPG (Vessel N = 51).		
Models:	OR (95% LCI to UCI)	<i>p-value</i>
Lipid-rich plaque TAWSS	1.161 (0.355 to 3.794) 1.027 (0.930 to 1.134)	0.800 0.586
Lipid-rich plaque $\geq 180^\circ$ TAWSS	1.420 (0.426 to 4.730) 1.033 (0.936 to 1.140)	0.558 0.503
Lipidic arc TAWSS	1.001 (1.000 to 1.001) 1.006 (1.001 to 1.011)	0.001 0.021
Calcific plaque TAWSS	0.857 (0.168 to 4.370) 1.033 (0.933 to 1.143)	0.849 0.521
Calcium thickness TAWSS	0.974 (0.865 to 1.098) 1.006 (1.001 to 1.012)	0.663 0.020
Calcium arc TAWSS	1.000 (1.000 to 1.000) 1.007 (1.002 to 1.012)	0.219 0.010
Fibrocalcific plaque TAWSS	0.782 (0.233 to 2.625) 1.029 (0.933 to 1.134)	0.683 0.560
Fibrous cap thickness TAWSS	0.055 (0.009 to 0.318) 1.004 (0.999 to 1.009)	0.002 0.149
TCFA TAWSS	1.384 (0.321 to 5.973) 1.026 (0.929 to 1.134)	0.655 0.603

Plaque rupture TAWSS	1.496 (0.377 to 5.935) 1.026 (0.930 to 1.131)	0.557 0.601
Macrophage TAWSS	0.949 (0.232 to 3.877) 1.030 (0.929 to 1.142)	0.940 0.561
Cholesterol crystals TAWSS	1.095 (0.330 to 3.628) 1.028 (0.932 to 1.135)	0.879 0.567

Table 10. Multivariate analyses for the association of TAWSS and OCT plaque phenotype with the PPG (Vessel N = 51). PPG = pullback pressure gradients; TAWSS = time-averaged wall shear stress measured at the mid lesion segment (throat); TCFA = Thin-cap fibrous atheroma.

Table 11 – Multivariate analyses for the association of TSVI and OCT plaque phenotype with the PPG (Vessel N = 51).		
Models:	OR (95% LCI to UCI)	<i>p-value</i>
Lipid-rich plaque TSVI	1.157 (0.353 to 3.787) 1.003 (0.996 to 1.010)	0.805 0.388
Lipid-rich plaque ≥ 180° TSVI	1.290 (0.390 to 4.270) 1.003 (0.996 to 1.010)	0.669 0.386
Lipidic arc TSVI	1.001 (1.000 to 1.001) 1.000 (1.000 to 1.001)	0.004 0.139
Calcific plaque TSVI	1.067 (0.217 to 5.256) 1.003 (0.996 to 1.010)	0.934 0.401
Calcium thickness TSVI	1.019 (0.907 to 1.144) 1.001 (1.000 to 1.001)	0.748 0.001
Calcium arc TSVI	1.000 (1.000 to 1.000) 1.001 (1.000 to 1.001)	0.509 0.001
Fibrocalcific plaque TSVI	0.822 (0.242 to 2.792) 1.003 (0.996 to 1.010)	0.747 0.392
Fibrous cap thickness TSVI	0.074 (0.014 to 0.389) 1.000 (1.000 to 1.001)	0.004 0.083
TCFA TSVI	1.530 (0.327 to 7.166) 1.003 (0.995 to 1.010)	0.579 0.504

Plaque rupture	1.339 (0.320 to 5.592)	0.681
TSVI	1.003 (0.995 to 1.010)	0.456
Macrophage	1.004 (0.259 to 3.883)	0.996
TAWSS	1.003 (0.996 to 1.011)	0.377
Cholesterol crystals	1.004 (0.295 to 3.419)	0.995
TSVI	1.003 (0.996 to 1.011)	0.382

Table 11. Multivariate analyses for the association of TSVI and OCT plaque phenotype with the PPG (Vessel N = 51). PPG = pullback pressure gradients; TSVI = topological shear variation index measured at the mid lesion segment (throat); TCFA = Thin-cap fibrous atheroma.

Table 12 – OCT variables according to low and high PPG/TAWSS (Vessel N = 51).					
	Low PPG low TAWSS (Vessel N = 29)	Low PPG high TAWSS (Vessel N = 9)	High PPG low TAWSS (Vessel N = 6)	High PPG high TAWSS (Vessel N = 7)	p-value (two-sided)
Lipid-rich plaque, n (%)	15 51.72%	5 55.56%	5 83.33%	4 57.14%	0.566
Lipid-rich plaque $\geq 180^\circ$, n (%)	12 41.38%	2 22.22%	5 83.33%	2 28.57%	0.102
Lipidic arc, degree ($^\circ$)	203 143 - 234	126 108 - 248	332 267 - 360	182 167 - 279	0.141
Calcific plaque, n (%)	23 79.31%	8 88.89%	4 66.67%	7 100.00%	0.397
Calcium thickness, mm	0.950 0.730 - 1.330	0.820 0.745 - 0.925	0.717 0.677 - 0.955	0.960 0.850 - 1.260	0.477
Calcium arc, degree ($^\circ$)	139 70 - 302	171 98 - 334	203 150 - 283	217 80 - 360	0.702
Fibrocalcific plaque, n (%)	20 68.97%	5 55.56%	2 33.33%	4 57.14%	0.415
Fibrous cap thickness, mm	0.089 0.069 - 0.106	0.097 0.061 - 0.105	0.054 0.054 - 0.070	0.066 0.060 - 0.075	0.046

TCFA, n (%)	3 10.34%	2 22.22%	4 66.67%	2 28.57%	0.023
Plaque rupture, n (%)	3 10.34%	4 44.44%	4 66.67%	2 28.57%	0.014
Macrophage, n (%)	7 24.14%	3 33.33%	1 16.67%	3 42.86%	0.682
Cholesterol crystals, n (%)	9 31.03%	5 55.56%	3 50.00%	4 57.14%	0.403

Table 12. OCT variables according to low and high PPG/TAWSS (Vessel N = 51). Frequencies of optical coherence tomography (OCT)-based coronary plaque features according to high and low PPG and TAWSS sub-groups. PPG = pullback pressure gradients; TAWSS = time-averaged wall shear stress measured at the mid lesion segment (throat); TCFA = Thin-cap fibrous atheroma.

Table 13 – OCT variables according to low and high PPG/ TSVI (Vessel N = 51).					
	Low PPG low TSVI (Vessel N = 19)	Low PPG high TSVI (Vessel N = 19)	High PPG low TSVI (Vessel N = 6)	High PPG high TSVI (Vessel N = 7)	p-value (two- sided)
Lipid-rich plaque, n (%)	11 57.89%	9 47.37%	4 66.67%	5 71.43%	0.671
Lipid-rich plaque $\geq 180^\circ$, n (%)	7 36.84%	7 36.84%	4 66.67%	3 42.86%	0.591
Lipidic arc, degree ($^\circ$)	203 108 - 234	207 189 - 248	332 250 - 360	199 167 - 295	0.168
Calcific plaque, n (%)	16 84.21%	15 78.95%	5 83.33%	6 85.71%	0.968
Calcium thickness, mm	0.925 0.775 - 1.115	0.870 0.650 - 1.360	0.683 0.670 - 0.850	1.060 0.900 - 1.260	0.306
Calcium arc, degree ($^\circ$)	179 106 - 331	97 70 - 308	206 101 - 300	208 93.6 - 360	0.562
Fibrocalcific plaque, n (%)	13 68.42%	12 63.16%	2 33.33%	4 57.14%	0.485
Fibrous cap thickness, mm	0.097 0.072 - 0.105	0.087 0.061 - 0.106	0.066 0.057 - 0.074	0.059 0.054 - 0.071	0.045

TCFA, n (%)	1 5.26%	4 21.05%	3 50.00%	3 42.86%	0.048
Plaque rupture, n (%)	2 10.53%	4 21.05%	3 50.00%	4 57.12%	0.049
Macrophage, n (%)	5 26.32%	5 26.32%	2 33.33%	2 28.57%	0.988
Cholesterol crystals, n (%)	6 31.58%	8 42.11%	5 83.33%	2 28.57%	0.133

Table 13. OCT variables according to low and high PPG/ TSVI (Vessel N = 51). Frequencies of optical coherence tomography (OCT)-based coronary plaque features according to high and low PPG and TSVI sub-groups. PPG = pullback pressure gradients; TCFA = Thin-cap fibrous atheroma; TSVI = topological shear variation index measured at the mid lesion segment (throat).

Chapter 4

Is spontaneous coronary artery dissection (SCAD) related to local anatomy and haemodynamics? An exploratory study

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Is spontaneous coronary artery dissection (SCAD) related to local anatomy and haemodynamics? An exploratory study

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4.1 Introduction

Spontaneous coronary artery dissection (SCAD) is an emergently recognised clinical condition, leading to acute myocardial infarction (MI), cardiac arrest, and cardiac death in a mostly younger patient population with a higher female prevalence.^{60, 61} Being angiographically recognized as a luminal narrowing with or without the presence of a radiolucent flap or a false lumen retaining contrast medium,⁶² pathophysiological mechanics of SCAD still remain unclear. In fact, whereas a spontaneous intimal tear and intramural hematoma are the two recognised main pathophysiological mechanisms of the intimo-medial flap and false lumen generation,⁶³ the underlying biological events triggering these phenomena remain to be elucidated. Among others, hormonal conditions, systemic inflammatory diseases, and arteriopathies were identified as predisposing conditions for SCAD development.⁶² Moreover, it was reported that a tortuous coronary anatomy is highly prevalent in SCAD, pointing towards a role of adverse anatomical features in the mechanisms for arterial dissection.⁶⁴ In this regard, as anatomy shapes blood flow,⁶ the association between SCAD and vascular anatomical features suggests an involvement of local hemodynamic forces in SCAD.

Personalized computational fluid dynamics (CFD) simulations have recently gained scientific momentum as valuable investigational tool of the intracoronary hemodynamics,^{11, 52} allowing the calculation of the wall shear stress (WSS) acting at the level of the endothelium-blood interface. WSS profiles were related to adverse coronary events,¹³ even in vessels presenting non-flow-limiting lesions.⁶⁵ WSS-based quantities have demonstrated to be capable to reflect near-wall flow disturbances, e.g. identifying coronary lesions prone to cause a MI.⁴⁵

In the present study, morphometric analysis and personalized CFD simulations were used to investigate local anatomy and haemodynamics at sites of healed SCAD lesions.

4.2 Methods

4.2.1 Study population

Consecutive patients with healed SCAD without intracoronary intervention were included in the study. Healed SCADs were defined angiographically as a complete healing of the dissection (*'restitutio ad integrum'*) at a planned angiographic control ('second look') following the first coronary angiogram – when the diagnosis of SCAD was made ('index procedure'). All included patients provided informed consent and were enrolled retro- or prospectively in the InterSCAD Registry at the University Hospital of Zurich (Zurich, Switzerland).

4.2.2 SCAD classification and localization

Coronary angiographies were visually assessed by trained personnel (MW, TG and CT). The type of SCAD was adjudicated on the index angiography as per current international consensus.⁶² Next, the SCAD proximal initiation point was visually identified at the baseline angiography and localized on the healed vessel segment at the angiographic second look.

4.2.3 Three-dimensional vessel reconstruction and morphometry assessment

Three-dimensional (3D) quantitative coronary angiography (QCA) reconstructions including bifurcations with side branch diameter larger than 1 mm were performed using two angiographic end-diastolic frames at least 25° apart, combining the QAngio XA Bifurcation RE software (Medis medical imaging systems, Leiden, The Netherlands) and a custom-made algorithm.⁵⁹ The vessel centreline, which represents the main geometric attribute of the vessel, was reconstructed using the vascular modelling toolkit (VMTK, Orobix, Bergamo, Italy). Then a centreline-based morphometric analysis of coronary arteries was performed, with local vessel curvature and torsion values ⁶⁶ obtained from the reconstructed 3D vessels centrelines according to previous studies.⁶⁷⁻⁶⁹ Briefly, considering a point on

a curve in a 3D space (in our case, the vessel centreline), curvature measures how quickly the vessel curves, while torsion measures how quick the vessel twists.

More in details, local curvature is defined as the reciprocal of the radius of the circle lying on the osculating plane (identified by the normal and tangent vectors to the curve at that point) to measure the rate of change in the tangent vector orientation along the curve.⁶⁶ Local torsion measures the deviation of curve C from the osculating plane. Technically, the curvature (κ) and the torsion (τ) of a curve C along the curvilinear abscissa s are defined as:

$$\kappa(s) = \frac{|C'(s) \times C''(s)|}{|C'(s)|^3}$$

$$\tau(s) = \frac{[C'(s) \times C''(s)] \cdot C'''(s)}{|C'(s) \times C''(s)|^2}$$

where C' , C'' , and C''' are respectively the first, second, and third derivatives of the curve C.

4.2.4 Angiography-based blood flow simulations

On the same 3D vessels reconstructions transient CFD simulations were performed adopting the finite volume-based code Fluent (Ansys Inc., Canonsburg, PA, USA). From simulated data, the luminal surface distribution of the time-averaged WSS (TAWSS) and of the topological shear variation index (TSVI) were calculated as in previous studies.^{11, 48} Briefly, TAWSS represents the value of the WSS magnitude applied to the luminal surface averaged along the cardiac cycle. TSVI quantifies the variability of the contraction/expansion action exerted by the WSS on the endothelium along the cardiac cycle.^{27, 48}

Time average wall shear stress (TAWSS) is defined averaging wall shear stress (WSS) magnitude instantaneous values along the cardiac cycle according to the formula:

$$TAWSS = \frac{1}{T} \int_0^T |WSS| dt$$

where T is the duration of the cardiac cycle.

WSS contraction/expansion action acting on endothelium can be identified by negative/positive values of the divergence of normalized WSS vector field (DIV_{WSS}).²⁷ Then, the amount of variation of contraction/expansion action along the cardiac cycle can be quantified in terms of topological shear variation index (TSVI),⁴⁸(defined as the root mean square deviation of instantaneous DIV_{WSS} with respect to its average over the cardiac cycle:

$$TSVI = \left\{ \frac{1}{T} \int_0^T [DIV_{WSS} - \overline{DIV_{WSS}}]^2 dt \right\}^{1/2}$$

where the overbar denotes a cycle-average quantity.

4.2.5 Anatomical and hemodynamic hot spots assessment and co-localization scoring

Hot spots of curvature and torsion were identified as those local peak values along the centreline belonging to the 90th and 98th percentile, respectively, of the corresponding vessel-specific quantity distribution (Figure 19). A higher percentile (98th) was assumed for torsion given its typical peaked distribution along arterial centrelines. Hot spots of TAWSS and TSVI were identified in terms of luminal surface areas exposed to values belonging to the 90th percentile of the corresponding vessel-specific quantity distribution. Vessel segments and luminal areas exposed to peak values were visually mapped on the reconstructed 3D vessels geometries as red areas.

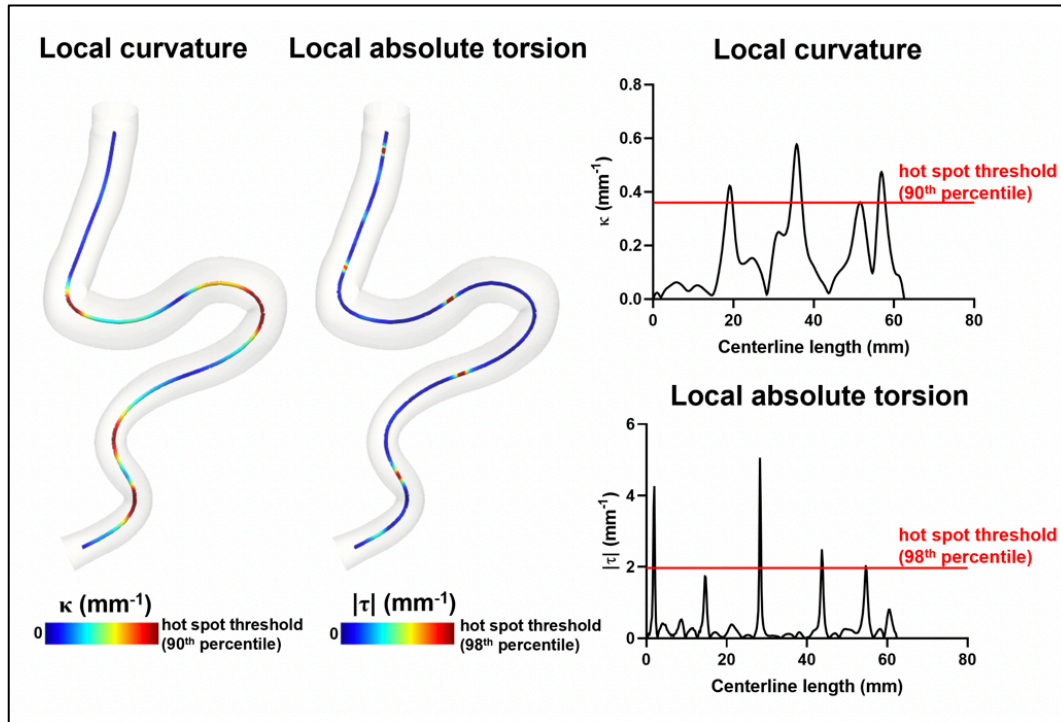


Figure 19. Case example with distribution of curvature and tortuosity along vessel centreline. In the explanatory vessel reconstruction on the left-hand side, local curvature values (vessel reconstruction on the left) and local tortuosity absolute values (vessel reconstruction on the right) are colour coded on the vessel centreline (low variable values in blue, high in red). In the two plots on the right-hand side, variable distributions along vessel centreline are presented (x-axis = length of vessel centreline in mm; y-axis = local curvature values or torsion absolute values in mm^{-1}). Hot spot threshold (red line) was set at the 90th percentile for local curvature, and at the 98th percentile for local torsion (given its typical peaked distribution along vessel centreline).

The region of interest (ROI) spanned not beyond 3 mm upstream and downstream from the SCAD proximal initiation point localized on the reconstructed vessel luminal surface: in case a morphometric- or WSS-based quantity hot spot fell within such segments as per visual assessment by three independent researchers (AC, MLR and UM), positive co-localization of the given quantity hot spot with the proximal SCAD region was adjudicated with a tick mark ('V'), see Figure 20. Conversely, a missing co-localization of a given quantity peak with the ROI was marked with an 'X'. A co-localization scoring system was implemented and based on the sum of positive co-localization 'V' marks, hence ranging from 0 (i.e., absence of hot spots in the ROI) to 4 (i.e., co-localization of all hot spots, of curvature, torsion, TAWSS and TSVI, with the identified segment around SCAD initiation).

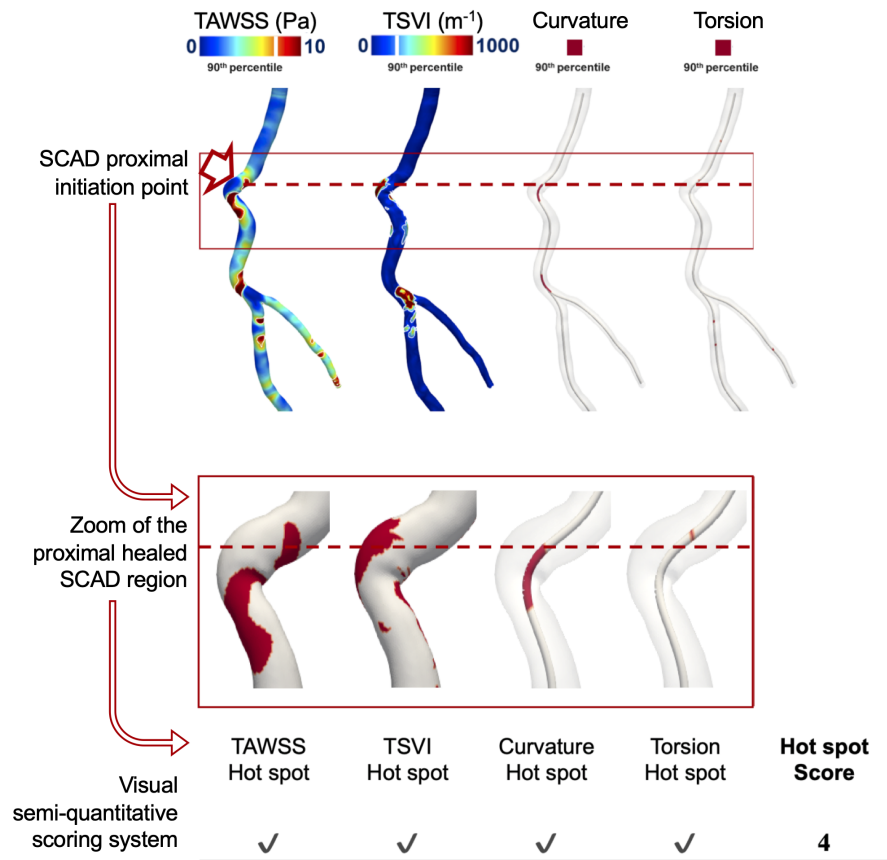


Figure 20. Case example of co-localization of the hot spots of the four tested variables. Upper panel: The coronary artery with spontaneously healed dissection is reconstructed from the projections from the angiographic second look and the localization of the proximal SCAD initiation point (arrow and dashed line) is obtained from the index angiography. Time-averaged wall shear stress (TAWSS) and topological shear variation index (TSVI) distribution are represented on the vessel luminal reconstruction in a color-coded fashion, while peak values of the curvature and torsion indices are represented in red on the vessel centrelines. Lower panel: Zoom of the proximal region of the healed coronary dissection. TAWSS and TSVI peaks are presented as red stains on the reconstructed vessel luminal surface. The co-localization of the hot spots of the morphometric and WSS-based quantities under investigation is assessed visually. The amount of hot spots co-localizing in the proximity of the proximal SCAD initiation point is obtained and summed up to give the result of the hot spot score (in this case 4).

4.2.6 Statistical methods

Statistical analyses were performed on a per-patient and -vessel basis. Bifurcation involvement was used for group-wise comparison. Continuous variables with normal distribution are presented as mean $\pm$ standard

deviation (SD) and non-normally distributed variables as median (inter-quartile range [IQR]). Categorical variables are presented as percentages. Chi-squared test was used for comparing categorical variables, while Student's tests or Mann-Whitney tests as appropriate for continuous ones. A p-value <0.05 was considered significant. All analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

4.3 Results

From January 1997 to December 2021, 146 patients with angiographically-confirmed SCAD were screened for study inclusion criteria. A spontaneous and complete healing of the SCAD was angiographically documented in 20 subjects (13.7%). In 13 cases (8.9%), coronary angiography recordings could be retrieved and satisfied the criteria for CFD simulations, Figure 21. The angiographic follow-up was performed at 57 (IQR 45-95) days.

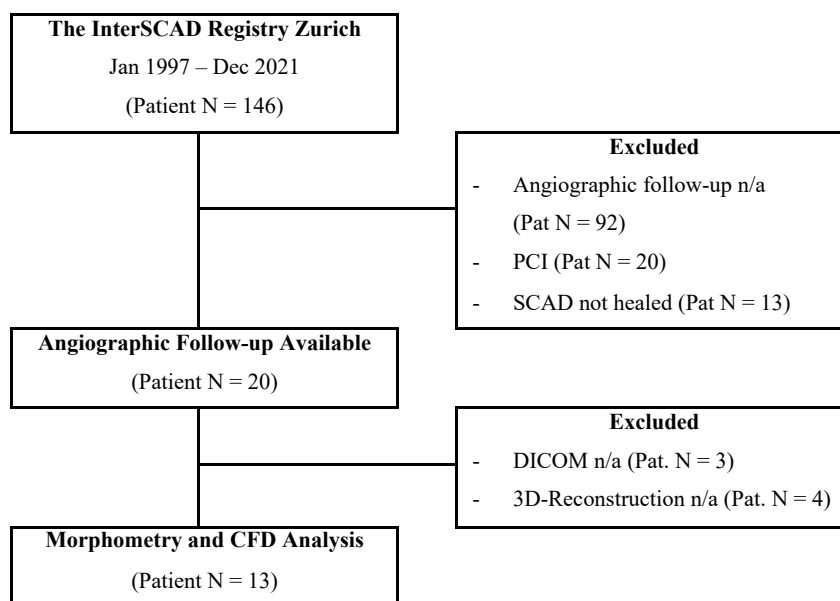


Figure 21. Study flow chart. Patients were consecutive enrolled in one Swiss tertiary centre. Morphometry and computational fluid dynamics (CFD) analysis were performed on those presented presenting a healed spontaneous coronary dissection (SCAD) with available coronary angiography at the follow-up.

4.3.1 Baseline characteristics

Thirteen patients with thirteen SCAD lesions were included in the analysis. In all but one case (92.3%) an acute trigger at the index event could be identified. Mean age was 46 (IQR 42-62) years, and 10 (76.9%) patients were women. SCAD presented in most cases as non-ST segment elevation myocardial infarction (NSTEMI, 61.5%). Angiographically, type 2b was the most prevalent SCAD variant (53.9%). Baseline parameters were well balanced among patients with healed SCAD regions with and without proximity to a coronary bifurcation, Table 14.

4.3.2 Anatomical and hemodynamic hot spots co-localization and scoring system

Hot spot adjudication is presented in Figure 22. From the analysis of the co-localization of the morphometry and WSS hot spots with the SCAD initiation segment emerged that 69.2% of the ROI hosted ≥ 3 hot spots. SCAD ROIs scored on average $2.84 (\pm 0.66)$ hot spots and did not differ between lesions with and without proximity to coronary bifurcations (2.86 ± 0.69 vs. 2.83 ± 0.75 , $p = 0.954$), Table 15.

4.3.3 Morphometry in healed SCAD proximal segments

In 12 (92.3%) vessels, anatomical hot spots co-localized with the SCAD offset region. Curvature peaks were more prevalent in healed SCAD regions (84.6%) than torsion peaks (61.5%). The location of curvature and torsion hot spots was not affected by the proximity to a coronary bifurcation (85.7 vs. 83.3%, $p = 0.91$ for curvature hot spot with and without proximity to a coronary bifurcation, and 71.4 vs. 50.0%, $p = 0.43$ for torsion hot spot in ROI, respectively), Table 15.

ANATOMIC-FUNCTIONAL ANALYSIS OF THE PROXIMAL SCAD REGION					
Patient	TAWSS Hot spot	TSVI Hot spot	Curvature Hot spot	Torsion Hot spot	Hot spot Score
1	✓	✓	✓	✓	4
2	✓	✓	✓	✗	3
3	✓	✗	✓	✓	3
4	✗	✓	✓	✓	3
5	✓	✓	✓	✓	3
6	✗	✓	✓	✗	2
7	✗	✓	✗	✓	2
8	✓	✗	✓	✗	2
9	✓	✓	✓	✗	3
10	✓	✗	✓	✓	3
11	✓	✓	✗	✗	2
12	✓	✓	✓	✓	4
13	✓	✓	✓	✗	3

Figure 22. Co-localization of variable hot spot and region of interest. Results of the visual assessment of the co-localization of variable hot spots and proximal dissection area (region of interest or ROI). A match is marked with a tick mark ('V'), a missing match with an 'X'. The count of matches 'V' gives the resulting hot spot score for the given vessel. TAWSS = Time-averaged wall shear stress; TSVI = Topological shear variation index.

4.3.4 Wall shear stress profiles in healed SCAD proximal segments

In all cases, hot spots of TAWSS and/or TSVI co-localized with the dissection ROI. Both TAWSS and TSVI 90th percentile surface area peak values in the ROI were quantitatively higher in the subgroup where the SCAD was not in proximity to a coronary bifurcation (for TAWSS: 3.81 Pa [IQR

2.53-5.17 Pa] vs. 6.65 Pa [IQR 6.20-13.20 Pa], $p = 0.008$; for TSVI: 92.60 s^{-1} [IQR 74.04-109.1 s^{-1}] vs. 129.0 s^{-1} [IQR 108.4-184.1 s^{-1}], $p = 0.138$). TSVI hot spots site of SCAD were less frequently found in proximity to coronary bifurcations than TAWSS (57.1% vs. 100%, $p = 0.034$), Table 15.

4.4 Discussion

The present exploratory study highlighted that vessel segments in the proximal parts of a healed SCAD region were characterized by (i) the presence of local hot spots of curvature and/or torsion as well as of TAWSS and/or TSVI; (ii) the increased prevalence of curvature rather than torsion peaks; and (iii) the presence of local flow disturbances, quantified by WSS.

4.4.1 Role of coronary anatomy in SCAD pathophysiology

SCAD have traditionally been associated with abnormal vessel geometry, and particularly with tortuosity.⁶² Commonly seen in routine angiographies, especially of elderly female patients with long-lasting arterial hypertension,⁷⁰ coronary tortuosity remains a clinical aetiology of unclear definition and clinical significance. It has been experimentally associated with structural changes within the arterial wall (e.g. elastin degradation or deficiency),⁷¹ kinking, and looping arguably originated by an unbalance between tractional, re-tractional, and intraluminal forces applied to the vessel wall, leading ultimately to an irreversible elongation of the vessel.⁷² Tortuosity was associated with delayed coronary perfusion,⁷³ and myocardial ischemia in absence of a severe atherosclerotic lesion.⁷⁴

Translating long-established notions from the cerebrovascular system to the coronary tree,⁷⁵ Eleid et al. proposed an analysis with semi-quantitative tortuosity metrics in SCAD based on the visual assessment of the coronary angiogram, which confirmed a strong association between coronary tortuosity and the presence or even the recurrence of SCAD.⁶⁴ The same methodology was more recently applied to vessel multiplanar reconstructions from coronary computed tomography angiographies (CCTA), confirming once again an association of coronary tortuosity and SCAD.⁷⁶ Conversely, in the present investigation, a vessel centreline-based

quantitative analysis performed on 3D vascular geometries reconstructed from coronary angiography was performed.⁶⁶ This approach allowed to determine the local curvature and torsion values at any given position along the vessel centreline, identifying in a mathematical manner areas of curvature and/or torsion peaks and consequently allowing to quantify rigorously vessel tortuosity. This made the morphometric analysis automatic, quantitative, and operator independent.

4.4.2 Role of local haemodynamics in SCAD pathophysiology

Investigations on intracoronary blood flow in the context of SCAD are scarce. This is surprising, given the above discussed link between tortuosity and SCAD, and the well-known impact of arterial anatomy in shaping local hemodynamics.¹¹ In fact, the presence of sharp bends and non-planarity produces flow separation and stagnation as well as secondary flows and flow recirculation, which in turn may distil into derailed shear force patterns acting on the vessel wall.⁷³ Among the CFD studies focusing on the haemodynamics in SCAD vessels, Di Donna et al. investigated the role of bifurcations upstream of a dissected coronary segment, identifying that an angle between the left anterior descending coronary artery (LAD) and the first adjacent branch $< 90^\circ$ can be a cause of increased instantaneous WSS (with diastolic peaks > 2.66 Pa) on the downstream vessel wall, especially in the primary location of the dissection.⁷⁶ Here, we found that the cardiac cycle-averaged WSS magnitude (i.e., TAWSS) with median peak > 5.0 Pa co-localized in each analysed vessel with the proximal dissection end. This evidence could suggest a direct mechanical effect of shear forces on the local endothelium, possibly leading to an intimal tear with increased wall permeability, smooth muscle cell stimulation and elastin degradation.³⁶ Notably, the mechanism initiated by high WSS action mechanism reconciliates with both theories on the inception of a SCAD, i.e. originating from an endothelial tearing event ('inside-out') or from a vasa vasorum haemorrhage within a elastin-depleted media layer ('outside-in').⁶²

In this study, coronary haemodynamics was also quantified by TSVI, a topological skeleton feature of the WSS recently associated with early

atherosclerotic changes in coronary arteries and risk of plaque destabilization.^{45, 49} TSVI was found markedly elevated especially in dissected coronary segments not in proximity of a bifurcation, suggesting a relevance of the complex blood-endothelium interaction pattern captured by this quantity. In fact, TSVI quantifies the variability in the contraction/expansion action exerted by the WSS on the endothelium along the cardiac cycle.^{27, 48} Recent studies suggest a role for TSVI in altering intracellular and cell-cell tensions.⁴⁹ The findings of the study also suggest that the two different mechanisms quantified by TAWSS and TSVI might act separately, but that also might concur to determine the dissection.

4.4.3 Interaction between vessel geometry and local haemodynamics

The frequent co-localization of hot spots within the ROI might point towards an involvement of the tested anatomic-functional variables in SCAD pathophysiology. A hint might be found when considering the presence or not of coronary bifurcation at the starting point of the dissection. In fact, in these cases numerically higher values for the four tested variables were reported, suggesting that more extreme geometrical and hemodynamic conditions might be necessary in the event of a SCAD in the absence of a vessel partition. Conversely, in the presence of a bifurcation, milder curvatures, torsions, and even less intense shear forces might suffice to Favor the offset of a coronary dissection.

In conclusion, a practical implication derived from our data suggests that when SCAD is clinically suspected, a quantitative analysis of the anatomy of the vessel and of the WSS profiles could support the identification of sites prone to dissection propagation/rupture or even re-dissection. In this regard, attention should be focused on areas downstream of bifurcations (particularly towards the daughter branch with a larger deviation angle) and on non-partitioning coronary segments exhibiting extreme or sequential curvatures and torsions.

4.4.5 Limitations

This study faces some limitations. First, the number of patients included in the final analysis is relatively small. While explained by selection criteria of the retrospective screening, selection biases cannot be excluded. Second, the underlying study assumptions might not be generalizable. However, evidence exist for a post-SCAD complete healing with *restitutio ad integrum*⁶⁰ and orthograde propagation of the dissection was confirmed in the vast majority of cases.⁷⁷ Third, the uncertainty and the level of idealization inherent in 3D reconstruction and CFD simulations might have influenced the quantitative anatomical analysis as well as the calculation of WSS-based quantities.⁷⁸ Last, no information on vessel thickness and composition (e.g., presence of atherosclerotic process and of vasa vasorum) was available, as intravascular imaging was not routinely performed in these patients. Hence, the influence of these variables on vessel wall tension and the associated the risk of dissection could not be assessed. Further research should address the relationship between vessel diameter, vessel composition, vessel wall tension, and SCAD development

4.5 Conclusion

Complex vascular anatomy and local flow disturbances were analytically described in coronary artery segments site of a SCAD after complete healing. The finding of a clear prevalence of high local values of vessel curvature and/or torsion in regions where the dissection was hypothesized to have originated suggested a pathophysiologic interaction. Bifurcation site of dissection presented a milder co-localization with local curvature/torsion peak values. Non-partitioning tortuous vascular segments site of SCAD showed markedly deranged shear forces, with high-magnitude WSS and high variability in the WSS contraction/expansion action along the cardiac cycle, potentially able to affect endothelium continuity. Hence, these results strongly support the hypothesis of a strong interaction between vessel anatomy and shear forces in the pathophysiology of SCAD.

4.6 Tables

Table 14 – Baseline characteristics of patients with SCAD with and without proximity to a bifurcation.				
	Total SCAD (N = 13)	SCAD w/o Bifurcation (N = 6)	SCAD with Bifurcation (N = 7)	p-value (two-sided)
Age, yrs	46 (42-62)	44 (42-65)	47 (38-62)	0.886
Female gender, n (%)	10 (76.9%)	6 (100.0%)	4 (57.1%)	0.067
BMI, Kg/m ²	27.3 ± 6.73	23.4 ± 4.01	30.7 ± 6.97	0.369
LVEF, %	55.1 ± 6.34	50.8 ± 5.34	58.7 ± 4.82	0.306
Serum creatinine, µmol/L	66.2 ± 13.8	62.7 ± 9.11	69.3 ± 17.0	0.358
Type of ACS:				
NSTEMI, n (%)	8 (61.5%)	3 (50.0%)	5 (71.4%)	0.429
STEMI, n (%)	5 (38.5%)	3 (50.0%)	2 (28.6%)	
Type of SCAD:				
Type 1	1 (7.69%)	0 (0.00%)	1 (14.3%)	0.529

Type 2a	5 (38.5%)	3 (50.0%)	2 (28.6%)	
Type 2b	7 (53.9%)	3 (50.0%)	4 (57.1%)	
Type of Vessel:				
LAD	7 (53.9%)	2 (33.3%)	5 (71.4%)	0.133
LCX	5 (38.5%)	4 (66.7%)	1 (14.3%)	
RCA	1 (7.69%)	0 (0.00%)	1 (14.3%)	
Coronary artery disease, n (%)	0 (0.00%)	-	-	
Dilatative arteriopathy, n (%)	4 (30.8%)	1 (16.7%)	3 (42.9%)	0.308
Fibromuscular dysplasia, n (%)	0 (0.00%)	-	-	
Systemic inflammatory disease, n (%)	1 (7.69%)	1 (16.7%)	0 (0.00%)	0.261
Connective tissue disorder, n (%)	0 (0.00%)	-	-	
Hyperthyroidism, n (%)	1 (7.69%)	1 (16.7%)	0 (0.00%)	0.261
Hypertension, n (%)	5 (38.5%)	1 (16.7%)	4 (57.1%)	0.135
T2DM, n (%)	0 (0.00%)	-	-	

Active smoking, n (%)	4 (30.8%)	1 (16.7%)	3 (42.9%)	0.296
Dyslipidaemia, n (%)	6 (46.1%)	1 (16.7%)	5 (71.4%)	0.048
ACE-Inhibitor, n (%)	2 (15.4%)	1 (16.7%)	1 (14.3%)	0.906
Aspirin, n (%)	2 (15.4%)	0 (0.00%)	2 (28.6%)	0.155
Oral anticoagulation, n (%)	1 (7.69%)	1 (16.7%)	0 (0.00%)	0.261
Statin, n (%)	2 (15.4%)	1 (16.7%)	1 (14.3%)	0.906
Oral Antidiabetics or Insulin, n (%)	0 (0.00%)	-	-	
Hormonal replacement therapy, n (%)	0 (0.00%)	-	-	
Betablocker, n (%)	0 (0.00%)	-	-	
Calcium-Antagonist, n (%)	0 (0.00%)	-	-	

Table 14. Baseline characteristics of patients with SCAD with and without proximity to a bifurcation. BMI = Body mass index; LAD = Left anterior descending coronary artery; LCX = Left circumflex coronary artery; LVEF = Left ventricle ejection fraction; NSTEMI = Non-ST segment myocardial infarction; RCA = Right coronary artery; SCAD = Spontaneous coronary artery dissection; STEMI = ST segment myocardial infarction; T2DM = Type-2 diabetes mellitus.

Table 15 – Morphometry and CFD descriptors of healed SCAD lesions with and without proximity to a bifurcation.

	Total SCAD (Vessel N = 13)	SCAD w/o Bifurcation (Vessel N = 6)	SCAD with Bifurcation (Vessel N = 7)	p-value (two-sided)
Morphometry 'hot spot' in ROI	12 (92.3%)	6 (100.0%)	6 (85.7%)	1.00
- Curvature Peak Value	0.18 0.16 - 0.29	0.23 0.18 - 0.32	0.16 0.14 - 0.29	0.445
- Curvature 'hot spot' in ROI	11 (84.6%)	5 (83.3%)	6 (85.7%)	0.906
- Torsion Peak Value	2.34 1.97 - 2.52	2.46 2.34 - 2.79	2.06 1.49 - 2.39	0.073
- Torsion 'hot spot' in ROI	8 (61.5%)	3 (50.0%)	5 (71.4%)	0.429
CFD 'hot spot' in ROI	13 (100.0%)	6 (100.0%)	7 (100.0%)	1.00
- TAWSS Peak Value	5.17 3.81 - 6.33	6.65 6.20 - 13.20	3.81 2.53 - 5.17	0.008
- TAWSS 'hot spot' in ROI	10 (76.9%)	4 (66.7%)	6 (85.7%)	0.416
- TSVI Peak Value	108.4 74.17 - 137.7	129.0 108.4 - 184.1	92.6 74.0 - 109.1	0.138
- TSVI 'hot spot' in ROI	10 (76.9%)	6 (100.0%)	4 (57.1%)	0.034
'Hot spot'	0	0 (0.0%)	0 (0.0%)	0.937

SCORE	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2	4 (30.8%)	2 (33.3%)	2 (28.6%)	
	3	7 (53.8%)	3 (50.0%)	4 (57.1%)	
	4	2 (15.4%)	1 (16.7%)	1 (14.3%)	
	Average	2.84 ± 0.66	2.83 ± 0.75	2.86 ± 0.69	0.954

Table 15. Morphometry and CFD descriptors of healed SCAD lesions with and without proximity to a bifurcation. The ‘Hot spot’ score represents the sum of the ‘hot spots’ of different morphometry and CFD quantity present within the same ROI. For example, a score of two means that two different ‘hot spots’ (e.g. one of Curvature and one of TSVI) co-localize within the same ROI. CFD = Computational fluid dynamics; ROI = Region of interest; TAWSS = Time-averaged wall shear stress; TSVI = Topological shear variation index.

Chapter 5

Impact of endothelial shear stress on coronary atherosclerotic plaque progression and composition: A meta-analysis and systematic review

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Impact of endothelial shear stress on coronary atherosclerotic plaque progression and composition: A meta-analysis and systematic review

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5.1 Introduction

Coronary plaques are subjected to biomechanical forces due to the complex interplay between pulsatile blood flow and the dynamic geometry of arterial vessels.¹⁰ In particular, intracoronary pressure gradients and translesional flow patterns have been associated with coronary plaque progression and lesion destabilization,^{7, 45} thus representing potential diagnostic tools for detecting lesions at higher cardiovascular event risk.

As a direct *in vivo* measurement of the biomechanical stimuli acting at the blood-endothelium interface is not feasible,⁷⁹ increasingly sophisticated computational fluid dynamics (CFD) models have been developed to accurately simulate cardiovascular flows.⁸⁰ These models have been employed in studying intracoronary hemodynamics,⁸¹ revealing hemodynamic factors that not only influence vascular homeostasis, but also the development of atherosclerotic lesions, thus supporting the "hemodynamic risk hypothesis" of atherosclerosis.^{6, 11} However, the evidence of a detrimental effect exerted by abnormal shear forces on the evolution of coronary atherosclerotic lesions failed to reach a wide consensus.

Consequently, it is clinically relevant to thoroughly appraise the influence of biomechanical forces acting at the circulating blood-endothelium interface, specifically endothelial or wall shear stress (WSS), on the progression and composition of coronary atherosclerotic plaques.

5.2 Methods

5.2.1 Literature search and study selection

PubMed, Ovid Embase, Google Scholar, Ovid MEDLINE, and The Cochrane Library (Wiley) databases were searched from their inception to December 31, 2022, for pertinent articles using keywords such as "coronary shear stress", "wall shear stress", "endothelial shear stress", "shear forces", "wall shear forces", "endothelial shear forces", "shear force", "wall shear force", "endothelial shear force", "biomechanics", "biomechanical", and

"hemodynamic forces". Articles were assessed at the title and/or abstract level, with any discrepancies resolved through consensus among three independent reviewers (AC, ALB, MAM). Relevant studies were then obtained in full text, and their bibliographies were manually searched to identify additional studies that met the inclusion criteria.

Included studies were those conducted in humans who underwent computational fluid dynamics (CFD) assessment for wall shear stress (WSS) calculation at baseline and had a subsequent anatomical evaluation at follow-up. Studies with a follow-up period of at least six months were considered. Any type of coronary artery disease presentation (obstructive or non-obstructive, acute or chronic) was included. Animal studies, case reports, conference presentations, editorials, and expert opinions were excluded from the analysis.

5.2.2 Data extraction and meta-analysis endpoints

Data extraction was independently conducted by two investigators (AB, MAM) using pre-specified electronic forms. Full text, supplementary materials, and online resources were utilized. Baseline patient characteristics, including age, gender, and cardiovascular risk factors, were extracted from the studies. Dichotomization in low and high WSS categories was based on the study-specific methodology and thresholds, which will be noted and reported analytically.

The primary endpoint of the meta-analysis was to determine the relationship between endothelial shear forces and plaque progression. Additionally, the effect of shear forces on coronary plaque features, such as differences in plaque area, plaque burden, lumen area, necrotic core, fibrous area, fibrofatty area, and dense calcium deposits, was evaluated.

5.2.3 Statistical analysis

The meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.⁸² Continuous variables were reported as mean (standard deviation, SD) or

median (interquartile range, IQR). Categorical variables were expressed as n (%). Mean differences of plaque features between evaluation at baseline and at follow up were appraised with subgroup analysis according to low, mid and high values of WSS. The RevMan 5 software (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing, respectively, mild, moderate, and extensive statistical heterogeneity. The analyses were repeated excluding the only randomized controlled trials included,⁸² excluding studies including ACS patients^{15, 83, 84} and the only study evaluating WSS with CCT and not with IVUS/CA.⁸³ To account for potential publication bias and to estimate the number of missing studies that would make the observed effect statistically non-significant, Funnel plots, Egger's and Begg's testes as well as a fail-safe N analysis were conducted. For each study, the risk of bias (low, moderate, or high) for selection, performance, attrition, detection, reporting, and overall bias was evaluated following the Agency for Healthcare Research and Quality recommendations.⁸²

5.3 Results

A total of 26 records were identified from online libraries during the initial search and deemed relevant, Figure 23. Among these, six studies were selected for data extraction and analysis (Table 16): one randomized clinical trial⁸² and five observational prospective studies^{15, 33, 83-85}.

The present investigation encompassed a total of 31'385 arterial segments from 136 patients (32% female). The patients' average age was 55.2 ± 2.7 years, with 58% having hypertension, 28% diabetes, and 15% a previous myocardial infarction (Table 17). Baseline CFD simulations were conducted on three-dimensional vessel models obtained from coronary angiography, intravascular ultrasound (IVUS), and/or coronary computed tomography angiography (CCTA). Lower and higher WSS thresholds were consistent in all but one study and derived from the previous literature (Table 18). Serial coronary lesion assessments (mean patient follow-up = 9.0 ± 3.0 months) were performed using virtual histology IVUS (VH-IVUS)

and/or CCTA. Changes (delta, Δ) in plaque architecture and composition between baseline and follow-up were documented in Table 19.

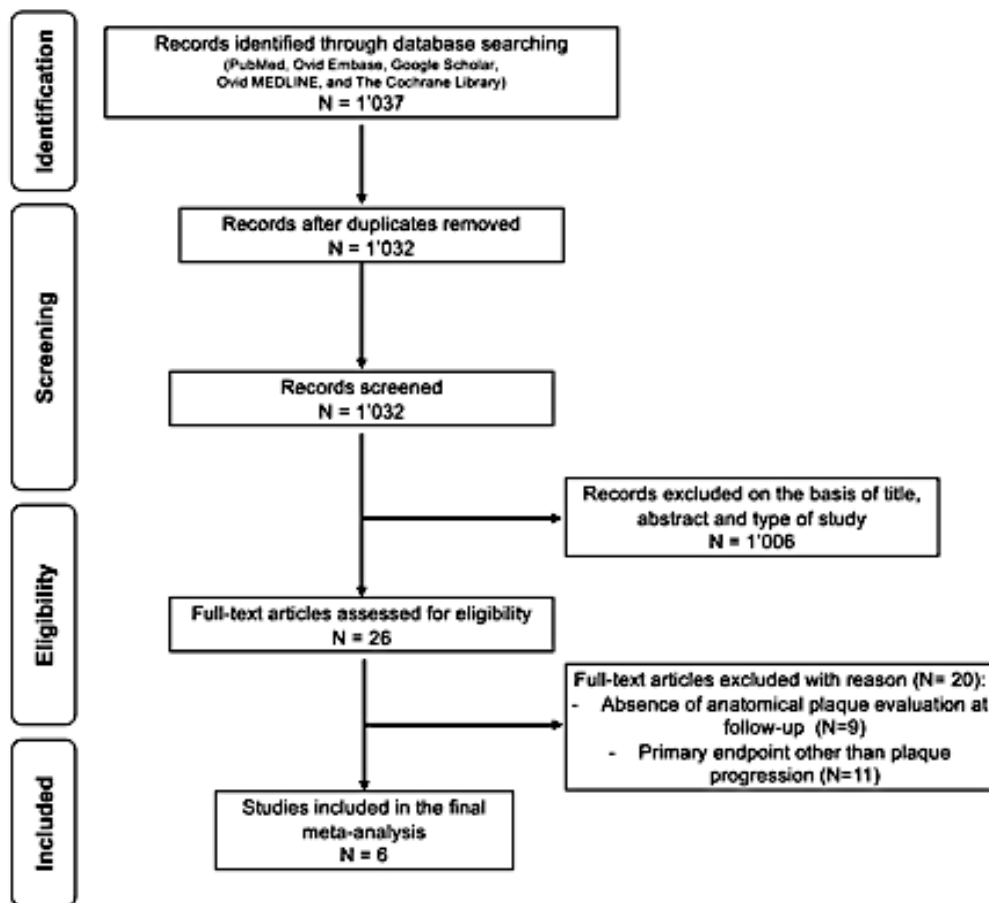
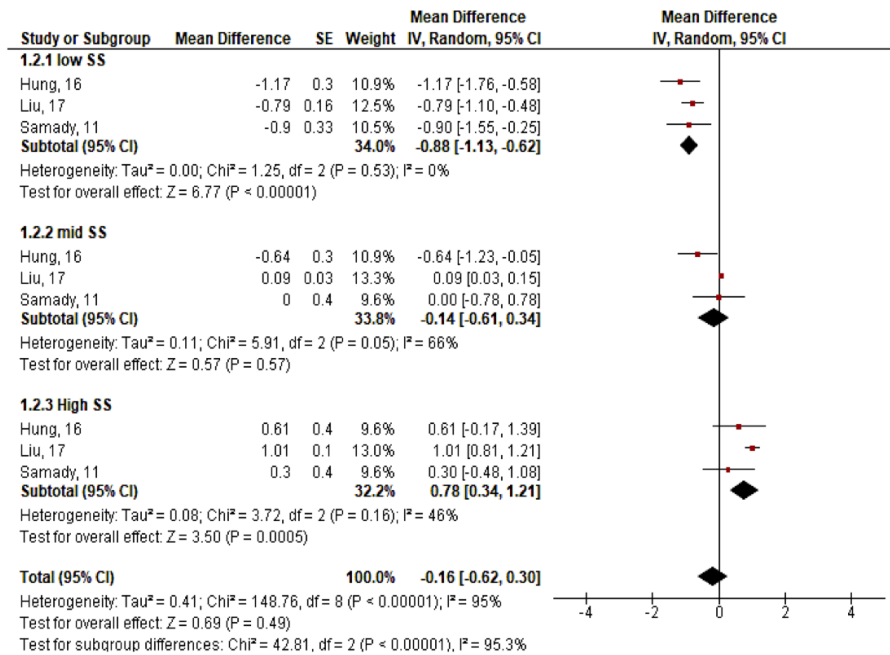


Figure 23. Flowchart for study selection.

Meta-analytically, lower WSS values were significantly associated with a reduction in lumen area at follow-up (mean difference -0.88, 95% CI -1.13 to -0.62), an increase in plaque burden (mean difference 4.32, 95% CI 1.65–6.99), and an increase in necrotic core area (mean difference 0.02, 95% CI 0.02-0.03). Elevated WSS values were associated with an increase in lumen area (mean difference 0.78, 95% CI 0.34-1.21), and a reduction in both fibrofatty (mean difference -0.02, 95% CI -0.03 to -0.01) and fibrous areas (mean difference -0.03, 95% CI -0.03 to -0.03). All results are presented in forest plots shown in Figure 24-26.

Lumen area (mm²)



Plaque burden (%)

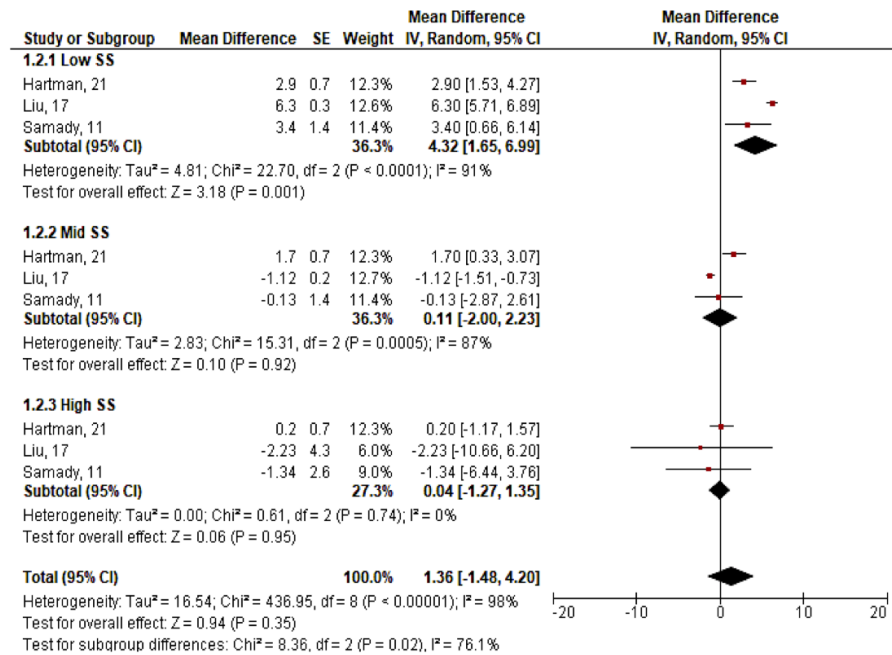
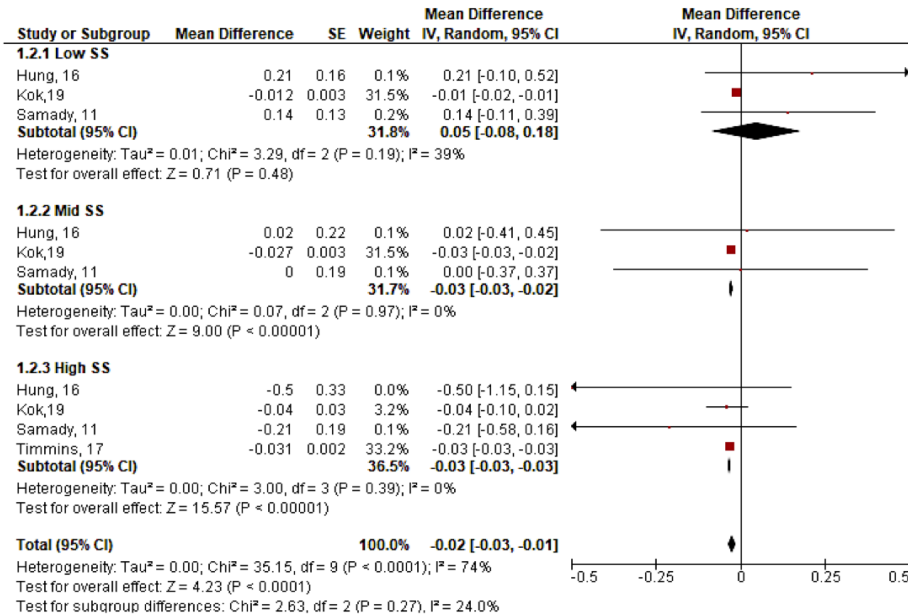


Figure 24. Mean difference in lumen area, and plaque burden in the low, mid, and high shear stress groups. Forest plot analysis is represented for low, mid and high shear stress (SS) groups (from upper to lower row) according to the investigated variable (left Lumen area, in mm²; right Plaque burden, in percentage of vessel area occupied by the atherosclerotic plaque).

Fibrous area (mm²)



Fibrofatty area (mm²)

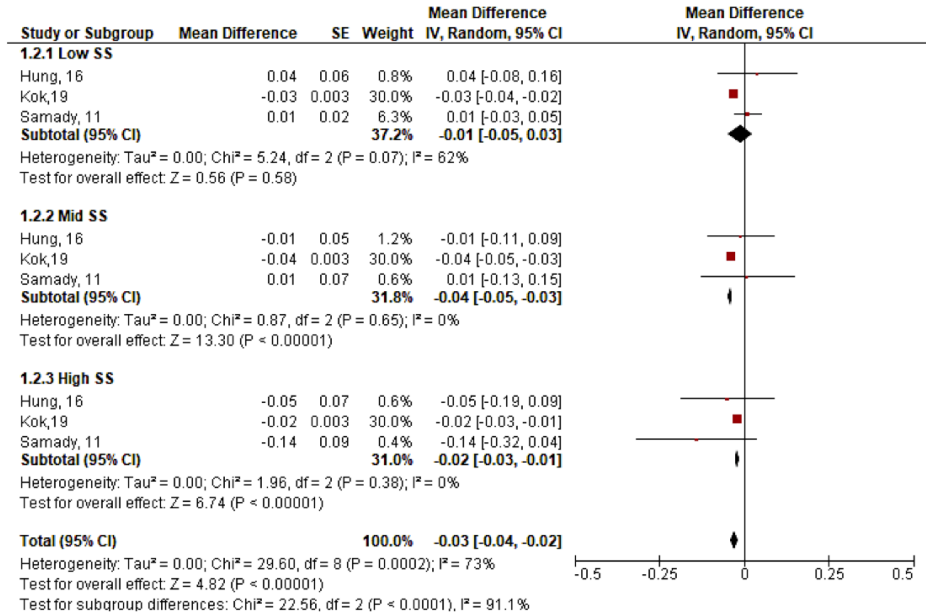
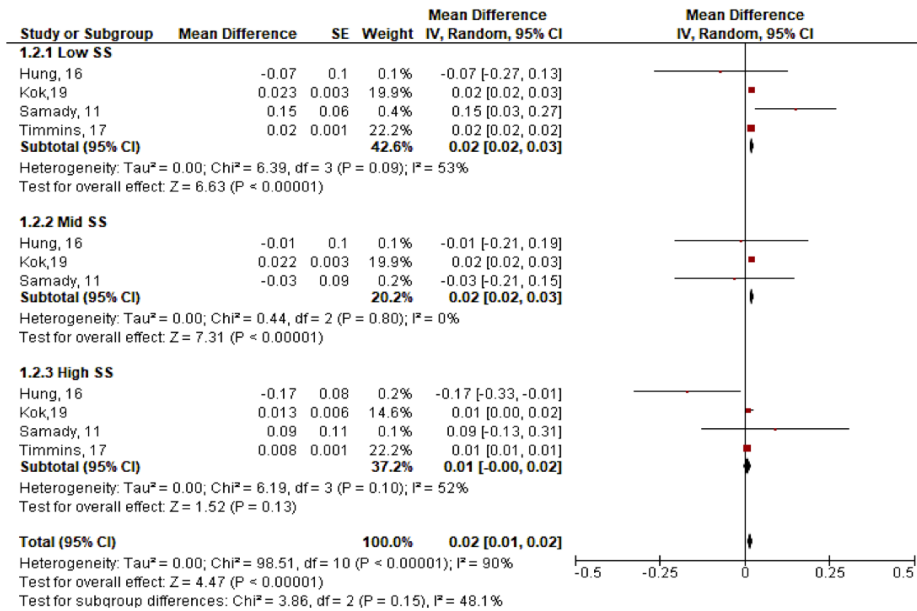


Figure 25. Mean difference in fibrous area, and fibrofatty area in the low, mid, and high shear stress groups. Forest plot analysis is represented for low, mid and high shear stress (SS) groups (from upper to lower row) according to the investigated variable (left Fibrous area, in mm²; right Fibrofatty area, in mm²).

Necrotic core area (mm²)



Dense calcium area (mm²)

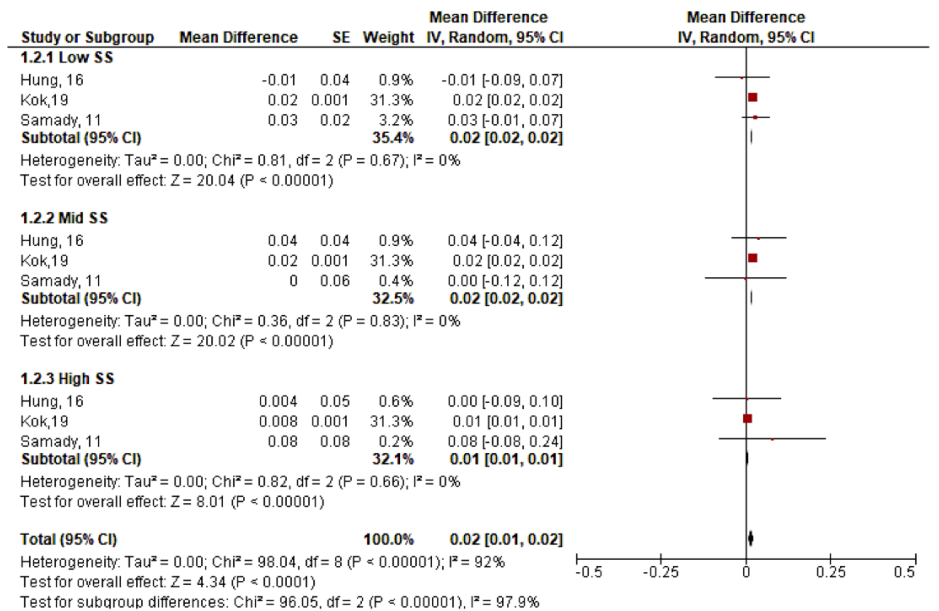


Figure 26. Mean difference in necrotic core area, and dense calcium area in the low, mid, and high shear stress groups. Forest plot analysis is represented for low, mid and high shear stress (SS) groups (from upper to lower row) according to the investigated variable (left Necrotic core area, in mm²; right Dense calcium area, in mm²).

The risk of bias was overall low to intermediate, Table 20. Visual inspection of the Funnel plots revealed no significant asymmetry, a conclusion supported by subsequent Egger's and Begg's tests for lumen area, plaque burden, and necrotic core (with p-values of 0.54 and 0.43, 0.85 and 0.72, and 0.14 and 0.17, respectively). Additionally, the fail-safe N analysis indicated a moderate to high number of studies that, if included, would result in a p-value exceeding an alpha of 0.05: 47 for lumen area, 67 for plaque burden, and 54 for necrotic core.

Results of the sensitivity analysis including only observational studies are reported on-line in the Supplementary Figures (<https://www.sciencedirect.com/science/article/pii/S0167527324006818?via%3Dihub#s0080>). Apart from the loss of significance of impact of high WSS for progression of fibrofatty area after excluding the RCT, the results of these analyses were consistent with the main one.

5.4 Discussion

In this meta-analysis, the influence of endothelial shear stress on coronary plaque progression was appraised through serial imaging assessments. The findings of the present study demonstrated that low WSS was significantly associated with a reduction in lumen area, an increase in plaque burden, and an increase in necrotic core area. In contrast, high WSS was associated with an increase in lumen area and a reduction in both fibrofatty and fibrous plaque areas. These findings suggest that endothelial shear forces play a central role in coronary plaque evolution (see Figure 27).

5.4.1 The divergent role of low and high shear forces

Current literature provides evidence supporting the association between low or high WSS and plaque growth and rupture. Physiological time-averaged WSS was initially defined as ranging from 1 to 7 Pa,¹¹ recent findings advocate for a more conservative upper WSS threshold for normality.^{11, 84} Low WSS has been linked to the development of atherosclerosis and plaque progression.¹² Conversely, higher WSS values

have been associated with plaque stabilization, as they promote the expression of endothelial genes that are protective against atherosclerosis, resulting in a more stable plaque phenotype.¹¹ However, extremely high WSS may also contribute to plaque rupture by inducing mechanical stress on the fibrous cap as well as changes in plaque composition, making it more vulnerable to damage.^{13, 86}

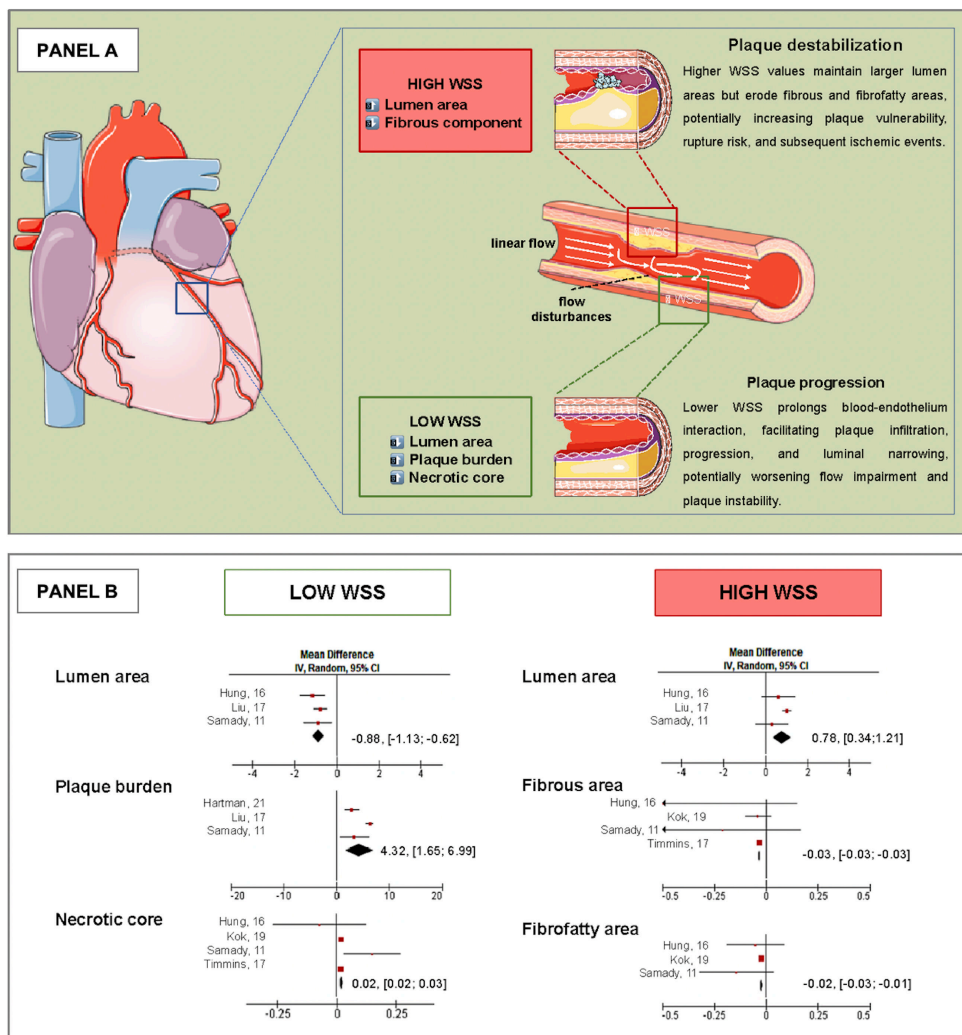


Figure 27. Graphical Abstract: Effect of translesional shear forces on coronary plaques. Wall shear stress (WSS) impacts on plaque evolution through its influence on plaque composition and progression. While lower WSS values promote plaque growth and reduce lumen area, higher WSS values, despite preserving lumen area, may adversely affect plaque stability by thinning its fibrous components. Understanding these complex interactions between WSS and plaque evolution may help to identify vulnerable plaques and guide clinical decision-making.

In regions with low WSS, slow blood flow and stasis promote endothelial cell morphology loss, increased turnover, and pro-atherogenic dysplasia with facilitation of lipoproteins and inflammatory cells infiltration into the arterial wall.⁸⁷ Consequently, lumen narrowing occurs as consequence of the growth of a lipid- and necrotic-rich plaque. The present meta-analysis, which suggests a reduction in lumen area paralleled by an increase in plaque burden and necrotic core area, aligns with the hemodynamic risk theory in interpreting the role of low WSS in plaque progression and coronary artery narrowing. On luminal surface regions undergoing high WSS, instead, the increased shear might be linked to adverse effects on the arterial wall. Detachment or "exfoliation" of endothelial cells was observed, exposing the underlying matrix and promoting platelet adhesion and thrombosis.¹⁷ Additionally, the mechanical action exerted by high WSS may contribute to fibrous cap thinning, making the plaque more vulnerable to rupture.^{13, 17} The present meta-analysis supports these adverse consequences of high WSS, demonstrating an increase in lumen area along with a reduction in fibrofatty and fibrous plaque areas, implying potential lesion destabilization and increased risk of plaque rupture.

Ultimately, it is worth noticing that predominant exposure to either low or high shear stress is associated in both cases with a higher risk of developing plaque vulnerability traits, albeit through distinct mechanisms. Low WSS appeared to lead to bulky, lipid-rich plaques, while high WSS contributes to thin fibrous caps. Despite these differences, both situations could culminate in plaque destabilization, potentially leading to acute coronary events. Yet, our current study indicates that there's a stronger evidence base supporting the findings related to low WSS compared to those for high WSS.

5.4.2 Current debate and future perspectives

This study underlines the pivotal role of WSS in predicting plaque growth and the risk of lesion destabilization due to alterations in plaque components. This understanding may have potential therapeutic implications. Unravelling the relationship between intracoronary fluid dynamics, plaque nucleation, and plaque evolution could facilitate the

development of pre-emptive medical strategies targeting WSS modulation, potentially impacting plaque rupture risk and cardiovascular event rates. Future research should focus on evaluating pharmacological and non-pharmacological interventions to optimize WSS and exploring innovative imaging techniques for improved WSS assessment in clinical settings.

While the influence of hemodynamic forces on plaque progression is widely recognized, WSS assessment is still not without uncertainty, mainly because of the lack of standardization.⁷⁹ This reflects, for example, on the identification of WSS (low, intermediate or high) threshold values. Moreover, the time-averaged WSS magnitude cannot fully capture the richness of the action of the shear stress on the endothelium throughout the cardiac cycle, characterized by high variability in instantaneous magnitude and in directionality. In this regard, several descriptors quantifying WSS multidirectionality have been introduced and a link emerged between them and altered endothelial function, gene expression,¹⁰ and adverse coronary events.⁴⁵

An added layer of complexity arises from the patient's biological context. As demonstrated in a recent study by Russo et al. (2023),⁸⁸ the relationship between WSS and gene expression, based on plaque phenotype in acute coronary conditions, was explored. This research underscores the significance of a comprehensive approach that considers both hemodynamic plaque features and gene expression modulation, particularly in the management of ACS patients.

5.4.3 Limitations

Despite the promising findings of this study, some limitations should be acknowledged. First, current CFD models may not fully capture the complex interactions between blood flow and vessel geometry *in vivo*. These models often rely on simplifications and assumptions which may introduce inaccuracies in the calculation of WSS. Second, the heterogeneity of WSS analysis among the included studies could impact on the interpretation of the results. Differences in study populations, WSS assessment methods (boundary conditions, imaging techniques), and definitions of low and high

WSS, as highlighted by Hartman et al. (2021),⁸⁴ could introduce heterogeneity. To mitigate statistical heterogeneity, we employed a random effect approach. Clinically, the selected studies showed consistency: four of them focused on patients with stable angina, and two targeted ACS patients, where WSS analysis was conducted on non-culprit coronary. This portrays a population with a harmonious risk profile. Moreover, in all but one study serial plaque assessment was performed with IVUS. Another limitation is to be found in the study selection process. To adhere to a meticulous methodology, our meta-analysis incorporated only those studies that reported data on plaque composition and morphology (e.g., plaque burden, plaque volume, necrotic core area, fibrofatty and fibrous area) both at baseline and follow-up. This allowed us to compute a difference (Δ) for comparison across all papers. The criterion here adopted represents a strength of the study, but it simultaneously poses a limitation, restricting the analysis to a subset of studies possessing the predefined requisites, with the consequence of diminishing the effect size for WSS predictions, especially regarding fibrofatty area, necrotic core, and dense calcium area. This highlights the unmet need to define standardized methods and WSS thresholds to improve the consistency and generalizability of the findings. Third, the heterogeneity and scarcity of clinical outcome assessments precluded a cross-sectional evaluation of the impact of WSS on adverse cardiovascular events. Finally, the variation in follow-up durations across the studies, with half extending to 6 months and the remainder to 12 months, could have influenced the outcomes of our analysis.

5.5 Conclusions

In conclusion, this meta-analysis highlights the relevance of translesional shear forces in predicting coronary plaque growth and adverse changes in plaque composition. The findings suggest that WSS could be a potential diagnostic marker to identify patients at increased risk of plaque rupture and subsequent cardiovascular events. Future research should concentrate on enhancing CFD models, investigating cutting-edge modalities for improved WSS assessment in clinical settings, and devising innovative therapies for mitigating WSS-related adverse flow patterns.

5.6 Tables

Table 16 – Layout of the studies included in the meta-analysis.

Study	Study design	Patient N	Inclusion criteria	Exclusion criteria	Study endpoints
Samady H et al, 2011	Prospective observational study Follow-up: 6 Months	20	Patients diagnosed with abnormal non-invasive stress test or stable anginal syndromes and found to have a nonobstructive coronary lesion requiring invasive physiological evaluation were enrolled.	Myocardial infarction, cardiogenic shock or hemodynamic instability, lesion requiring percutaneous or surgical revascularization, coronary artery bypass surgery, severe valvular heart disease, presence of visual coronary collaterals, inability to provide informed consent, serum creatinine > 1.5 mg/dL, liver disease, or significant hematologic disease	Changes in plaque area, virtual histology IVUS-derived plaque composition, and remodelling were compared according to WSS categories (low, mid, high).
Hung OY et al, 2016	Single centre double-blinded randomized controlled clinical trial Follow-up: 12 Months	24	Patients with recurrent angina symptoms and nonobstructive coronary lesions were enrolled. Investigators included patients on stable medical therapy, with presentation of stable angina or non–ST-segment elevation ACS and coronary lesion in the proximal 60 mm of an epicardial vessel which could undergo evaluation using physiology and VH-IVUS.	Cardiogenic shock, LVEF <30%, significant hepatic, hematologic, or renal impairment, history of coronary artery bypass surgery, severe valvular heart disease, inability to provide informed consent, any contraindication to b-blocker therapy, presence of lesions requiring revascularization or significant visual coronary collaterals.	Changes in plaque progression and compositions were compared according to WSS categories (low, mid, high) one year after randomization to Nebivolol 10 mg and Atenolol 100 mg cohorts.
Timmins LH et al, 2017	Prospective observational study	20	Patients diagnosed with abnormal non-invasive stress test or stable anginal syndromes and found to have a nonobstructive coronary	Myocardial infarction, cardiogenic shock or hemodynamic instability, lesion requiring percutaneous or surgical revascularization, coronary artery bypass surgery, severe	Authors investigated the role of low and oscillatory WSS in plaque transformation

	Follow-up: 6 Months		lesion requiring invasive physiological evaluation were enrolled.	valvular heart disease, presence of visual coronary collaterals, inability to provide informed consent, serum creatinine > 1.5 mg/dL, liver disease, or significant hematologic disease.	towards more vulnerable phenotype.
Liu X et al, 2017	Retrospective observational study Follow-up: 12 Months	12	Patients with age >18 years, presentation with an acute coronary syndrome (ACS, unstable angina or myocardial infarction), and right coronary artery (RCA) not planned for PCI were enrolled.	Previous PCI of RCA, coronary artery bypass surgery, renal failure, and significant hematologic disease.	Change of vascular characteristics related to WSS at the end of follow up were investigated as follows: MLA, PB, PV, coronary remodelling intended as Δ vessel area.
Kok AM et al, 2019	Prospective observational study Follow-up: 6 Months	20	Patients diagnosed with abnormal non-invasive stress test or stable anginal syndromes and found to have a nonobstructive coronary lesion requiring invasive physiological evaluation were enrolled.	Myocardial infarction, cardiogenic shock or hemodynamic instability, lesion requiring percutaneous or surgical revascularization, coronary artery bypass surgery, severe valvular heart disease, presence of visual coronary collaterals, inability to provide informed consent, serum creatinine > 1.5 mg/dL, liver disease, or significant hematologic disease.	Changes in plaque composition and size according to WSS were investigated.
Hartman EMJ, 2021	Single centre observational study Follow-up: 12 Months	40	Patients with an acute coronary syndrome (ACS) with at least one non-stented non-culprit coronary vessel were enrolled.	Previous coronary artery bypass graft surgery, 3-vessel disease, atrial fibrillation, left ventricular ejection fraction < 30%, and renal insufficiency (creatinine clearing < 50 ml/min).	Authors investigated the predictive power of low WSS for plaque progression, using four methods to define low, intermediate, and high WSS, therefore defining individual related results.

Table 16. Layout of the studies included in the meta-analysis.

Table 17 – Clinical characteristics of patients included in the selected studies.									
Study	Female (%)	Age, y	BMI, Kg/m²	HTN (%)	DM (%)	Smokers (%)	Dyslipidaemia (%)	Previous MI (%)	Previous PCI (%)
Samady H et al, 2011	7 (35)	54 (46–68)	30 (27–36)	14 (70)	7 (35)	5 (25)	-	2 (10)	-
Hung OY et al, 2016	15 (62)	52.5 ± 10.3	29.1 ± 5.8	16 (67)	4 (17)	12 (50)	18 (75)	4 (17)	-
Timmins LH et al, 2017	7 (35)	54 (46–68)	30 (27–36)	14 (70)	7 (35)	5 (25)	-	2 (10)	-
Liu X et al, 2017	6 (33)	57 (51–65)	26 (25–28)	11 (92)	5 (42)	-	-	3 (25)	4 (33)
Kok AM et al, 2019	7 (35)	54 (46–68)	30 (27–36)	14 (70)	7 (35)	5 (25)	-	2 (10)	-
Hartman EMJ, 2021	3 (7)	60±8.6	27±4.8	10 (25)	8 (20)	10 (25)	18 (45)	8 (20)	11 (28)

Table 17. Clinical characteristics of patients included in the selected studies.

Table 18 – Imaging modality, segmentation and wall shear stress (WSS) cut-offs of the included studies.					
Study	Imaging modality for CFD	Vessel	N. of segments	Lower WSS cut-off	Higher WSS cut-off
Samady H et al, 2011	IVUS	LAD	2'249	1.0 Pa	2.5 Pa
Hung OY et al, 2016	Angiography + IVUS	23 LAD 1 LCx	1'843	1.0 Pa	2.5 Pa
Timmins LH et al, 2017	Angiography + IVUS	LAD	14'235	1.0 Pa	2.5 Pa
Liu X et al, 2017	CCTA	RCA	365	Patient-specific lower tertile	Patient-specific mid and higher tertile
Kok AM et al, 2019	Angiography + IVUS	LAD	2'488	1.0 Pa	2.5 Pa
Hartman EMJ, 2021	CCTA + IVUS	15 LAD 10 LCx 16 RCA	10'205	1.0 Pa	2.5 Pa

Table 18. Imaging modality, segmentation and wall shear stress (WSS) cut-offs of the included studies.

Table 19. Changes (delta, Δ) of anatomical plaque characteristics from the baseline to the follow-up evaluation.								
Study	Imaging modality	Δ plaque burden (%)	Δ plaque area (mm ²)	Δ lumen area (mm ²)	Δ necrotic core area (mm ²)	Δ dense calc. area (mm ²)	Δ fibrofatty area (mm ²)	Δ fibrous area (mm ²)
Samady H et al, 2011	VH-IVUS	3.39 $\pm$ 6.06 vs. -1.34 $\pm$ 6.93	0.12 $\pm$ 0.78 vs. -0.16 $\pm$ 1.17	-0.9 $\pm$ 1.52 vs. 0.3 $\pm$ 1.56	0.15 $\pm$ 0.26 vs. 0.09 $\pm$ 0.51	0.03 $\pm$ 0.09 vs. 0.08 $\pm$ 0.34	0.01 $\pm$ 0.09 vs. -0.14 $\pm$ 0.44	0.14 $\pm$ 0.56 vs. -0.21 $\pm$ 0.83
Hung OY et al, 2016	VH-IVUS	-	0.47 $\pm$ 1.37 vs. -0.56 $\pm$ 2.77	-1.17 $\pm$ 1.24 vs. 0.61 $\pm$ 2.15	-0.07 $\pm$ 0.71 vs. -0.17 $\pm$ 0.88	-0.01 $\pm$ 0.22 vs. 0.04 $\pm$ 0.26	0.04 $\pm$ 0.30 vs. -0.05 $\pm$ 0.35	0.21 $\pm$ 0.76 vs. -0.47 $\pm$ 1.64
Timmins LH et al, 2017	VH-IVUS	-	0.007 $\pm$ 0.01 vs. -0.03 $\pm$ 0.007	-	0.02 $\pm$ 0.004 vs 0.01 $\pm$ 0.004	-	-	-0.002 $\pm$ 0.01 vs. -0.03 $\pm$ 0.01
Liu X et al, 2017	CCTA	6.28 $\pm$ 0.96 vs. -2.23 $\pm$ 2.53	-	-0.79 $\pm$ 0.16 vs.1.01 $\pm$ 0.38	-	-	-	-
Kok AM et al, 2019	VH-IVUS	-	-0.002 $\pm$ 0.02 vs. -0.04 $\pm$ 0.02	-	0.02 $\pm$ 0.013 vs 0.01 $\pm$ 0.013	0.02 $\pm$ 0.006 vs 0.01 $\pm$ 0.005	-0.03 $\pm$ 0.02 vs. -0.02 $\pm$ 0.02	-0.012 $\pm$ 0.01 vs. -0.04 $\pm$ 0.01
Hartman EMJ, 2021	CCTA and IVUS	2.9 (1.5-4.2) vs. 0.2 (-1.6-2.1)	-	-	-	-	-	-

Table 19. Changes (delta, Δ) of anatomical plaque characteristics from the baseline to the follow-up evaluation. Results are reported for the lower vs. higher WSS groups (upper and lower row, respectively).

Table 20 – Risk of bias assessment (low, intermediate, or high).						
	Selection bias	Performance bias	Attrition bias	Detection bias	Reporting bias	Overall bias
Hartman, 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hung, 2016	Low risk	Low risk	Low risk	Low risk	Intermediate risk	Intermediate risk
Kok, 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Liu, 2017	Low risk	Intermediate risk	Low risk	Intermediate risk	Low risk	Intermediate risk
Samady, 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Timmins, 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 20. Risk of bias assessment (low, intermediate, or high) for selection, performance, attrition, detection, reporting and overall bias.

Chapter 6

Conclusions and future works

6.1 Summary and main contributions

The focus of the present doctorate thesis was to explore the interplay between hemodynamic forces and coronary plaque stability, aiming to advance the understanding, diagnosis, and treatment of coronary artery disease (CAD). The scientific research employed innovative computational fluid dynamics (CFD) methodologies, paired with advanced imaging modalities and real-world clinical data, to bridge the gap between engineering principles and clinical applications.

The key objectives of the thesis were:

1. To investigate the role of endothelial shear stress (ESS) in predicting myocardial infarction (MI) using novel computational markers derived from angiographic imaging and CFD simulations.
2. To introduce and validate in humans innovative hemodynamic descriptors, such as the Topological Shear Variation Index (TSVI), as predictors of plaque destabilization.
3. To elucidate the link between intracoronary haemodynamics, plaque morphology, and lesion vulnerability, using integrated approaches involving CFD, imaging, and clinical data.

6.1.1 Contributions by chapter:

Chapter 2: In this study, we investigated the predictive capacity of wall shear stress (WSS) descriptors, such as time-averaged wall shear stress (TAWSS) and the novel TSVI, for acute coronary events. Using CFD simulations applied to angiographic images, the study demonstrated that TSVI offers superior predictive capability for future MI compared to traditional anatomical and functional markers.

Chapter 3: The aim of the study was to explore the relationship between intracoronary hemodynamic forces and atherosclerotic plaque phenotypes. This analysis combined CFD simulations, optical coherence tomography (OCT), and biological assays to reveal that WSS patterns correlate with plaque morphology and inflammatory markers, providing insights into mechanisms of plaque destabilization.

Chapter 4: In this exploratory study on spontaneous coronary artery dissection (SCAD) we assessed the role of local anatomy and hemodynamic forces in the vessel damage leading to the dissection. The study identified distinct hemodynamic patterns and anatomical configurations that may predispose to SCAD, advancing the understanding of this enigmatic condition.

Chapter 5: In this investigation we performed the first meta-analysis and systematic review on the impact of endothelial shear stress on coronary atherosclerotic plaque progression and composition. The findings synthesised evidence from multiple studies, highlighting the central role of shear stress in modulating plaque behaviour and informing therapeutic strategies.

6.2 Future works

The promising results obtained in this thesis open several avenues for future research:

1. Validation in larger and diverse populations: Expanding the study cohort to include more patients with diverse clinical and anatomical

characteristics is essential to confirm the robustness of TSVI and other novel descriptors as predictive biomarkers.

2. Real-Time CFD integration in clinical settings: Developing AI-driven algorithms to integrate CFD simulations into real-time clinical workflows will reduce computational time, enabling immediate risk assessments during catheterization procedures.

3. Exploration of novel functional descriptors: Further investigation into the role of helical flow patterns⁸⁹ and intravascular kinetic energy dissipation⁹⁰ in atherosclerotic lesions and plaque destabilization could provide new insights into their protective or adverse effects.

4. Multimodal coronary vulnerability analysis: Combining CFD-derived hemodynamic markers with advanced imaging techniques, such as intravascular ultrasound (IVUS) and OCT, will enhance the precision of risk stratification for coronary lesions.

5. Application to alternative pathological models: Extending these methodologies to study conditions such as coronary aneurysms and ectasia will broaden the applicability of computational approaches in cardiology.

6. Understanding biological mechanisms: Investigating the cellular and molecular pathways modulated by dynamic WSS changes will provide a deeper mechanistic understanding of plaque evolution and rupture.

By addressing these directions, future research can further solidify the role of computational cardiology in transforming CAD management, bridging the gap between engineering innovations and improved patient care.

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List of publications

Count

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○ Original papers	46
○ First authorship	7, marked with (*)
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○ Reviews	6
○ Research Letters	5
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○ Book Chapter	1

Original Paper

2025

Original Paper 1. (***) Madder R.; VanOosterhout S.; Parker J.; **Candrea A.** Transatlantic Telerobotic Coronary Angiography: A Pre-clinical Feasibility Study. JACC Adv. 2025 Jan;4(1):- . doi: 10.1016/j.jacadv.2024.101456.

Original Paper 2. (*) **Candrea A.**; Huwiler J.; Gallo D.; Schweiger V.; Gilhofer T.; Leone R.; Würdinger M.; Lodi Rizzini M.; Chiastra C.;

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Original Paper 3. (*) **Candrea, A.**; Buongiorno, A. L.; Matter, M. A.; Lodi Rizzini, M. O.; Giacobbe, F.; Ravetti, E.; Giannino, G.; Carmagnola, L.; Gilhofer, T.; Gallo, D.; Chiastra, C.; Stähli, B. E.; Iannaccone, M.; Morbiducci, U.; Porto, I.; De Ferrari, G. M.; D'Ascenzo, F. Impact of endothelial shear stress on coronary atherosclerotic plaque progression and composition: A meta-analysis and systematic review. *Int J Cardiol.* 2024 Apr 17:132061. doi: 10.1016/j.ijcard.2024.132061

Original Paper 4. (*) **Candrea A.**, Lodi Rizzini M, Calò K, Pagnoni M, Munhoz D, Chiastra C, Aben JP, Fournier S, Muller O, De Bruyne B, Collet C, Gallo D, Morbiducci U. Association Between Automated 3D Measurement of Coronary Luminal Narrowing and Risk of Future Myocardial Infarction. *J Cardiovasc Transl Res.* 2024 Mar 1. doi: 10.1007/s12265-024-10500-2. Epub ahead of print. PMID: 38427153.

Original Paper 5. Gilhofer T.S.; Schweiger V.; Gehler M.; Bokemeyer V.; Chen M.; **Candrea A.**; Würdinger M.; Di Vece D.; Templin C.; Niederseer D.; Stähli B.E.; Stehli J.; Gotschy A.; Jakob P.; Ruschitzka F.; Binder R.; Nietlispach F.; Michel J.; Kasel A.M. Long-term outcomes after echocardiography versus fluoroscopy-guided left atrial appendage closure: Is there still a role for a simplified approach? *Catheter Cardiovasc Interv.* 2024 Jun;103(4):653-664. doi: 10.1002/ccd.31126.

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Original Paper 7. Sartoretti T.; Alkadhi H.; **Candrea A.**; Mergen V.; Gotschy A.; Michel J.; Templin C.; Manka R.; Stähli B.E.; Ghadri J.R. Photon-counting detector coronary CT angiography: Defining the optimal monoenergetic level for grading of calcified coronary stenosis. *J Cardiovasc Comput Tomogr*. 2024 Jun;18(3):283-294. doi: 10.1016/j.jcct.2024.06.007.

Original Paper 8. Mergen V, Rusek S, Civaia F, Rossi P, Rajagopal R, Bättig E, Manka R, **Candrea A**, Eberhard M, Alkadhi H. Virtual calcium removal in calcified coronary arteries with photon-counting detector CT—first in-vivo experience. *Frontiers in Cardiovascular Medicine*. 2024;11:1367463. doi: 10.3389/fcvm.2024.1367463. ISSN: 2297-055X.

Original Paper 9. Bruno F, de Filippo O, Sardone A, Capranzano P, Conrotto F, Sheiban I, Giacobbe F, Laudani C, Burzotta F, Saia F, Escaned J, Roubin SR, Mancone M, Templin C, **Candrea A**, Trabattini D, Wanha W, Stefanini G, Chieffo A, Cortese B, Casella G, Wojakowski W, Colombo F, De Ferrari GM, Boccuzzi G, D'Ascenzo F, Iannaccone M. Long-term impact of intravascular ultrasound-guided for percutaneous coronary intervention on unprotected left main. The IMPACTUS-LM, an observational, multicentric study. *Int J Cardiol*. 2024 Feb 14:131861. doi: 10.1016/j.ijcard.2024.131861. Epub ahead of print. PMID: 38365014.

Original Paper 10. Schweiger V, Hiller P, Utters R, Fenice A, Cammann VL, Di Vece D, Rajman K, **Candrea A**, Gotschy A, Gilhofer T, Würdinger M, Stähli BE, Seifert B, Müller SM, Templin C, Stehli J. A novel score to predict in-hospital mortality for patients with acute coronary syndrome and out-of-hospital cardiac arrest: the FACTOR

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Original Paper 11. Matter MA, **Candrea A**, Stähli BE, Heg D, Klingenberg R, Räber L, Windecker S, Rodondi N, Nanchen D, Mach F, Gencer B, Ruschitzka F, Matter CM, Templin C. Higher 1-year mortality on rest days in patients with acute coronary syndromes and decompensated heart failure-A SPUM-ACS sub-study. Catheter Cardiovasc Interv. 2024 Feb;103(2):286-294. doi: 10.1002/ccd.30938. Epub 2023 Dec 25. PMID: 38145467.

Original Paper 12. (*) **Candrea A**; Gallo D.; Munhoz D.; Rizzini M.L.; Mizukami T.; Seki R.; Sakai K.; Sonck J.; Mazzi V.; Ko B.; Nørgaard B.; Jensen J.M.; Maeng M.; Otake H.; Koo B.K.; Shinke T.; Aben J.P.; Andreini D.; Gallinoro E.; Stähli B.E.; Templin C.; Chiastra C.; De Bruyne B.; Morbiducci U.; Collet C.. Influence of intracoronary hemodynamic forces on atherosclerotic plaque phenotypes. Int J Cardiol. 2023 Dec 21:131668. doi: 10.1016/j.ijcard.2023.131668.

Original Paper 13. Skolidis I, Noirclerc N, Meier D, Luangphiphat W, Cagnina A, Mauler-Wittwer S, Mahendiran T, De Bruyne B, **Candrea A**, Collet C, Sonck J, Muller O, Fournier S. Head-to-head comparison of two angiography-derived fractional flow reserve techniques in patients with high-risk acute coronary syndrome: A multicenter prospective study. Int J Cardiol. 2024 Mar 15;399:131663. doi: 10.1016/j.ijcard.2023.131663. Epub 2023 Dec 21. PMID: 38141730.

Original Paper 14. Stähli B.E.; Varbella F.; Linke A.; Schwarz B.; Felix S.B.; Seiffert M.; Kesterke R.; Nordbeck P.; Witzendichler B.; Lang I.M.; Kessler M.; Valina C.; Dibra A.; Rohla M.; Moccetti M.; Vercellino M.; Gaede L.; Bott-Flügel L.; Jakob P.; Stehli J.; **Candrea A**; Templin C.; Schindler M.; Wischnewsky M.; Zanda G.; Quadri G.; Mangner N.; Toma A.; Magnani G.; Clemmensen P.; Lüscher T.F.; Münzel T.;

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Original Paper 16. Matter M.A.; **Candrea A.**; Stähli B.E.; Heg D.; Klingenberg R.; Räber L.; Windecker S.; Rodondi N.; Nanchen D.; Mach F.; Gencer B.; Ruschitzka F.; Matter C.M.; Templin C. Higher 1-year mortality on rest days in patients with acute coronary syndromes and decompensated heart failure-A SPUM-ACS sub-study. Catheter Cardiovasc Interv. 2023. DOI: 10.1002/ccd.30938.

Original Paper 17. (*) **Candrea A.**; Lodi Rizzini M.; Schweiger V.; Gallo D.; Montone R.A.; Würdinger M.; Stehli J.; Gilhofer T.; Gotschy A.; Frank R.; Stähli B.E.; Chiastra C.; Morbiducci U.; Templin C..Is spontaneous coronary artery dissection (SCAD) related to local anatomy and hemodynamics? An exploratory study.International Journal of Cardiology.2023;386():1-7. DOI:10.1016/j.ijcard.2023.05.006

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patients with ANOCA.EuroIntervention.2023;19(2):E155-E166.
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Original Paper 19. Lodi Rizzini M.; **Candrea A.**; Mazzi V.; Pagnoni M.; Chiastra C.; Aben J.-P.; Fournier S.; Cook S.; Muller O.; De Bruyne B.; Mizukami T.; Collet C.; Gallo D.; Morbiducci U..Blood Flow Energy Identifies Coronary Lesions Culprit of Future Myocardial Infarction.Annals of Biomedical Engineering.2023;():-.
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