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Enhanced coronary physiology assessment with endothelial shear stress predicts residual cardiovascular risk in older patients with myocardial infarction

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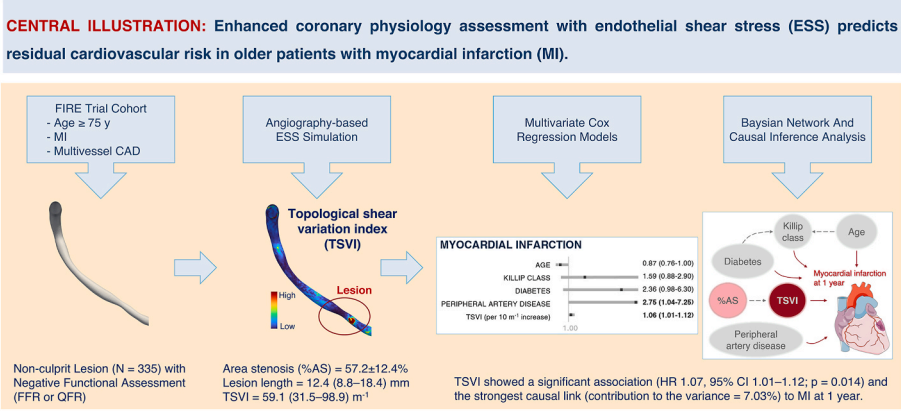
HIGHLIGHTS

- This post hoc analysis of 335 older MI patients from the FIRE trial investigated the prognostic role of endothelial shear stress (ESS)-derived metrics in residual coronary lesions with negative functional assessment.
- The topological shear variation index (TSVI), a novel marker of cyclic shear instability, was significantly associated with myocardial infarction and ischemia-driven revascularization at 1-year follow-up.
- In contrast to time-averaged ESS magnitude, TSVI captured dynamic endothelial stress patterns that better reflected vascular vulnerability and outcome risk.
- Integrating TSVI with anatomical and clinical variables significantly improved risk prediction and offers a novel framework for refining cardiovascular risk stratification in elderly CAD patients.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: The relationship between traditional risk factors, translesional hemodynamics, and plaque vulnerability remains incompletely understood. Endothelial shear stress (ESS) has recently emerged among the key players determining lesions instability and cardiovascular risk.

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Computational fluid dynamics
Endothelial shear stress
Topological shear variation index

Aims: We aimed to evaluate the prognostic value of ESS-based quantities and their interplay with anatomical and clinical factors in predicting adverse cardiovascular events in older patients with multivessel coronary artery disease (MVD).

Methods: This post hoc analysis of the Functional Assessment in Elderly MI Patients with Multivessel Disease (FIRE) trial included older patients (≥75 years) with acute myocardial infarction (MI) and MVD undergoing percutaneous coronary intervention (PCI). ESS was assessed by angiography-based computational fluid dynamics simulations and the topological shear variation index (TSVI), recently emerged as predictor of future MI measurable within a clinical framework, was computed in non-culprit coronary lesions with negative functional assessment left untreated. The primary endpoint was major adverse cardiovascular events (MACE) at one year, defined as a composite of all-cause death, non-fatal MI, stroke, and ischemia-driven revascularization. Multivariate Cox regression and causal inference analysis were used to assess the prognostic role of anatomo-functional metrics alongside traditional risk factors.

Results: A total of 335 FIRE trial patients were analyzed. The median percentage area stenosis (%AS), lesion length, time-averaged ESS, and TSVI were 57.2 %, 12.3 mm, 2.9 Pa, and 59.2 m^{-1}, respectively. Severe lesions were associated with a higher risk of the primary outcome (hazard ratio, HR, 1.024, 95 % confidence interval, CI, 1.002–1.046, p = 0.031). Longer lesions were significantly linked to an increased risk of all-cause death (HR 1.042, 95 % CI 1.009–1.077, p = 0.013), while TSVI was associated with higher risk of MI (HR 1.006, 95 % CI 1.000–1.012, p = 0.014) and ischemia-driven revascularization (HR 1.006, 95 % CI 1.000–1.012, p = 0.021). The inclusion of %AS, lesion length, and TSVI significantly improved multivariate outcome prediction. Causal inference analysis indicated that TSVI had a strong causal association with both MI and revascularization, with an information content at least equal to that of %AS.

Conclusions: TSVI, rather than absolute ESS magnitude, plays a key role in predicting acute events in older MI patients with MVD. Integrating ESS-based factors with traditional clinical and anatomical factors significantly enhances risk prediction and helps refine management strategies for this challenging patient population.

1. Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide, contributing significantly to cardiovascular events like myocardial infarction (MI) and sudden cardiac death [1].

The pathophysiology of CAD involves a complex interplay of biological, systemic, and hemodynamic factors [2], as confirmed by recent studies [3–5]. In particular, endothelial shear stress (ESS) has gained momentum [6], propelled by advances in computer simulation technologies [7]. ESS, the friction tension exerted by blood flow on the arterial endothelium, plays a crucial role in maintaining vascular homeostasis and in the development of atherosclerosis [2]. Abnormal ESS patterns have been linked to the initiation and progression of coronary atherosclerotic lesions [3,8], suggesting a connection between distinct ESS features and adverse plaque characteristics, such as increased plaque burden, necrotic core expansion, and fibrous cap thinning. [4,9,10]. Moreover, ESS has emerged as a strong predictor of atherosclerotic plaque destabilization and rupture [11–13], and, consequently, adverse cardiovascular outcomes [12–16].

The *Functional Assessment in Elderly MI Patients with Multivessel Disease* (FIRE) trial was a \guided complete revascularization versus a culprit-only strategy in older patients with MI in the context of a multivessel CAD. The trial demonstrated that a complete revascularization strategy guided by physiological assessment was associated with a lower risk of adverse cardiovascular events at one-year follow-up [17].

Aligning with emerging evidence supporting the assessment of coronary physiology in older MI patients with MVD, this sub-analysis of the FIRE trial tested two key hypotheses: (i) incorporating advanced hemodynamic and anatomical analysis into this assessment could improve the identification of patients at higher risk of complications, and (ii) that distinct ESS patterns derived from personalized computational fluid dynamics (CFD) simulations in non-culprit, no-flow limiting coronary lesions have a significant causal link to CAD outcomes in older patients. To test these hypotheses, interventional cardiologists have conducted CFD simulations using a validated framework, with computational costs compatible with clinical practice [3,18–20].

2. Methods

This study is a *post hoc* analysis of the FIRE trial, a multicenter, randomized controlled trial. In the FIRE trial patients ≥75 years with acute myocardial infarction (MI) and multivessel disease undergoing PCI of the culprit lesion were randomly assigned to receive either complete revascularization of all functionally significant non-culprit lesions (‘*complete revascularization arm*’) or no further revascularization (‘*culprit-only revascularization arm*’). All procedures in the FIRE trial adhered to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

2.1. Study population

The present study population included patients from the FIRE trial who had a negative functional assessment in all investigated non-culprit vessels (Fig. 1). Invasive fractional flow reserve (FFR) and angiography-based quantitative flow ratio (QFR) measurements (Medis QFR, Medis Medical Imaging Systems) were used to assess the functional significance of coronary lesions for patients assigned to the complete revascularization arm. For patients in the culprit-only revascularization arm, functional significance was assessed using angiography-based QFR measurements. The main trial included patients with multivessel CAD, defined as having at least one lesion in a non-culprit coronary artery with a minimum vessel diameter of 2.5 mm and a visually estimated diameter stenosis greater than 50 % [17]. Patients with prior coronary artery bypass graft surgery, significant left main disease, and severe comorbidities limiting life expectancy to less than one year were excluded. For the current sub-analysis, additional exclusion criteria included poor-quality angiographic images or incomplete coronary anatomy visualization.

2.2. Coronary angiography and blood flow simulations

Coronary angiograms were obtained using standard techniques and analyzed by an independent core laboratory (Andreas Grüntzig Clinical Research Centre, University Hospital of Zurich, Switzerland), which was blinded to clinical outcomes. Three-dimensional quantitative coronary angiography (QCA) reconstructions of the coronary arteries were

generated from two orthogonal angiographic projections, at least 30° apart, using the CAAS Workstation Wall Shear Stress software (Pie Medical Imaging, Maastricht, the Netherlands). The lesion was defined as the coronary segment containing the minimum lumen area (MLA), with its boundaries delimited proximally and distally by the intersection of the QCA vessel diameter function line with the interpolated reference line [21]. Anatomical variables for each reconstruction included percentage area stenosis (%AS) at the MLA section and lesion length. Personalized CFD simulations were performed with the Wall Shear Stress tool of the CAAS Workstation Wall Shear Stress software on the reconstructed 3D coronary geometries to model coronary blood flow along the cardiac cycle and quantify the ESS distribution on the luminal surface, as discussed elsewhere [13]. The reliability of the CFD simulations, performed in standard clinical settings by interventional cardiologists in less than 11 min on average using the CAAS Workstation Wall Shear Stress software, has been previously confirmed against high-fidelity simulations [21]. The adopted CFD simulation strategy, presented in the **Supplementary materials**, has been derived from previous studies [13,16,19,22],

2.3. Endothelial shear stress analysis

The time-averaged ESS and the topological shear variation index (TSVI), both averaged over the lesion luminal surface, were used for the quantitative analysis of the action of shear forces on the endothelium. Briefly, the time-averaged ESS measures the average ESS magnitude experienced by the endothelium along the cardiac cycle [6]. The TSVI quantifies the variability in the contraction/expansion action exerted by the ESS on the endothelium along the cardiac cycle, which may reflect variations in intracellular and cell-cell junction tensions [23]. Detailed information on the ESS-based quantities and their physical significance can be found in the **Supplementary materials**. In patients having two vessels with negative functional assessment and successful ESS analysis, only the vessel with higher percentage area stenosis was selected.

2.4. Clinical outcomes

The primary outcome of the study was the incidence of major adverse cardiovascular events (MACE), defined as a composite of death from any cause, non-fatal MI of any type, stroke and ischemia-driven coronary revascularization. Secondary outcomes included the individual components of MACE.

2.5. Statistical analysis

Continuous variables were reported in terms of mean ± standard deviation or median (interquartile range, IQR), and categorical variables in terms of frequencies and percentages. Normality was evaluated using the Shapiro-Wilk test. The associations between ESS-based quantities and clinical outcomes were assessed using univariate and multivariate Cox proportional hazards models, to identify the independent predictors after adjustment for potential confounders. For each clinical outcome, demographic, clinical, anatomical or ESS-based variables with a p-value <0.10 in the univariate analysis were included in the multivariate

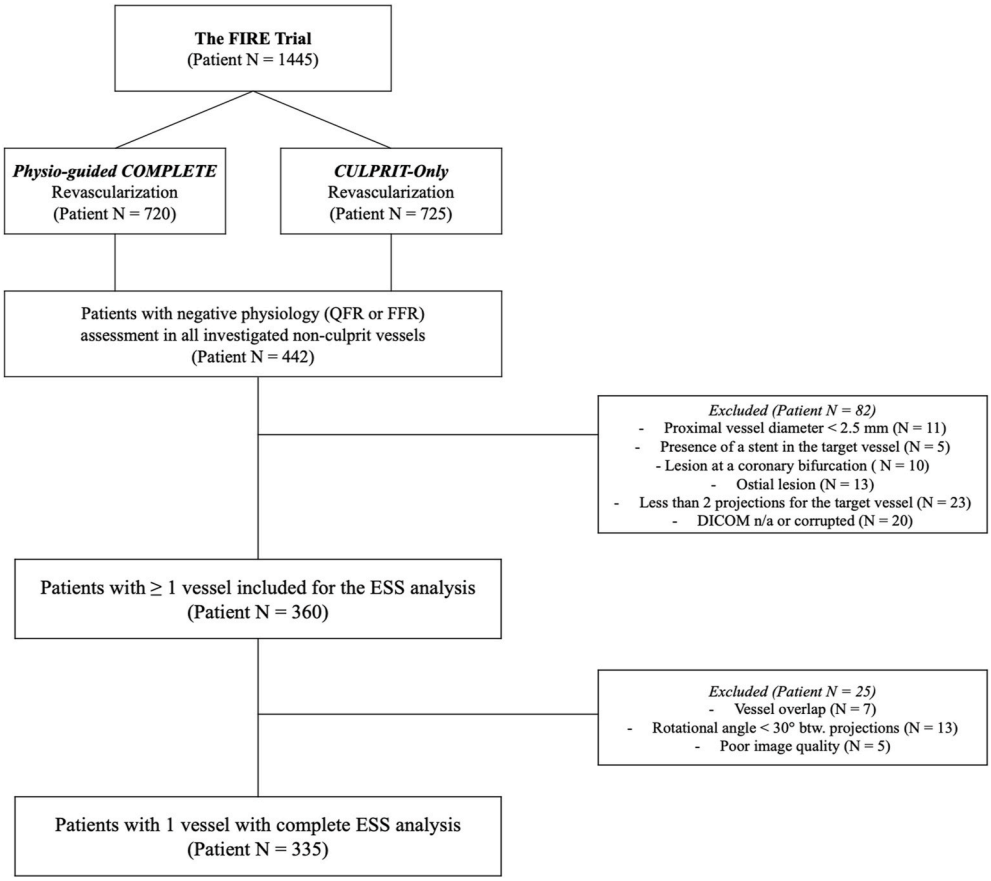


Fig. 1. – Study Workflow.
The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FIRE) trial compared the outcomes of physiology-guided versus angiography-guided coronary revascularization in elderly patients with multivessel CAD. In the present post hoc sub-analysis of the FIRE trial, only patients presenting with negative functional assessment (based either on fractional flow reserve [FFR] or quantitative flow reserve [QFR]) in all investigated non-culprit vessels were included. In patients having two vessels with negative functional assessment and endothelial shear stress (ESS) analysis, only the vessel with higher percentage area stenosis was selected.

analysis. Harrel's concordance index (C-index) was calculated to assess the predictive abilities of Cox proportional hazard models. In the multivariate analysis, the likelihood ratio test was used to evaluate the significance of adding either anatomical or ESS-based variables to clinical and demographic variables, with the goal of determining the incremental prognostic value of %AS, lesion length, time-averaged ESS, and TSVI. A p-value <0.05 was considered significant. To better capture physiologically meaningful variations in TSVI, HRs were computed for a 100 m^{-1} increase in TSVI, in line with our previous study [13]. Causal discovery and causal inference analyses were conducted to explore potential cause–and–effect relationships in the observational data [24]. For each clinical outcome predicted by ESS-based variables in the Cox regression analysis, a Bayesian network was constructed to model the causal relationship among the predictors included in the multivariate Cox proportional hazard model and the outcome of interest. The causal effect of each predictor on the clinical outcome was quantified using the Kullback-Leibler divergence, comparing the original Bayesian network with a modified network where the edge connecting the predictor to the outcome was removed [25]. The obtained Kullback-Leibler divergence values were then normalized to obtain the so-called relative strength, which indicates the percentage of the total direct causal effect attributable to each predictor. Additionally, to directly verify the causal chain of lumen narrowing → ESS-based variables → outcome, the intrinsic causal contribution of each node in the network to the variance of the outcome was calculated. This helped evaluate the 'information' added by a specific factor versus the 'information' inherited from a parent node [26]. Further details on the causal analysis can be found in the **Supplementary materials**. The analyses were performed using SPSS Statistics 29 (IBM Corp. Armonk, NY) and Python, utilizing the *lifelines* and *dowhy* packages.

3. Results

The present study included 335 patients from the FIRE trial who had a negative functional assessment in all investigated non-culprit vessels, underwent coronary angiography, and had complete CFD analysis (Fig. 1). Of these patients, 152 (45.4 %) were from the culprit-only revascularization arm of the trial, and 183 (54.6 %) were from the complete revascularization arm of the trial.

Table 1
Characteristics of the patients at baseline.

	Total (Patient N = 335)
Age, years	80 (77–84)
Female sex, no. (%)	132 (39.4)
Body mass index, kg/m^2	26.3 (23.9–29.3)
Non–ST-segment elevation myocardial infarction, no. (%)	244 (72.8)
ST-segment elevation myocardial infarction, no. (%)	91 (27.2)
Heart rate, bpm	73 (62–84)
Systolic pressure, mmHg	140.0 (120.0–150.5)
Killip Class ≥ II, no. (%)	86 (25.7)
Left ventricular ejection fraction, %	50 (41–60)
Estimated glomerular filtration rate, mL/min/1.73 m^2	61.1 (47.9–75.7)
Hemoglobin value upon admission, g/dl	13.3 (12.0–14.4)
Creatinine, mg/dL	1.06 (0.85–1.31)
Arterial hypertension, no. (%)	278 (83.0)
Dyslipidemia, no. (%)	180 (53.7)
Prior or current smoker, no. (%)	113 (33.7)
Diabetes type 2, no. (%)	109 (32.5)
Peripheral artery disease, no. (%)	66 (19.7)
Prior percutaneous coronary intervention, no. (%)	59 (17.6)

The estimated glomerular filtration rate was calculated by means of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Killip class II indicates findings consistent with mild-to-moderate heart failure, class III the presence of overt pulmonary oedema, and class IV the presence of cardiogenic shock.

3.1. Baseline patient characteristics

The baseline characteristics of the study population are presented in Table 1 and according to revascularization type arm in the Supplementary Table 1. The median age of patients was 80 years, with a slight predominance of male patients (60.6 %). The majority of patients (72.8 %) presented with non-ST segment elevation MI (NSTEMI).

3.2. Coronary angiography-derived analyses

The results of the anatomo-functional and ESS-based evaluations are presented in Table 2. The left circumflex (LCX) artery was the most frequently analyzed vessel (37.3 %). The mean %AS was 57.2 % ± 12.4 %, and lesion length was 12.4 (IQR 8.8–18.4) mm. Median FFR or QFR was 0.89 (0.86–0.94). As for ESS-based quantities, time-averaged ESS and TSVI values averaged over the lesion were 2.9 (2.0–4.2) Pa and 59.1 (31.5–98.9) m^{-1}, respectively.

3.3. Predictive role of angiography-derived anatomical and ESS-based quantities

Univariate Cox-regression analyses were initially conducted to assess the predictive significance of each covariate across all outcomes (Fig. 2). The primary outcome exhibited a significant association with lesion % AS, with a hazard ratio (HR) of 1.02 (95 % confidence interval [CI] 1.00–1.05; p = 0.031). Lesion length was significantly associated with all-cause death, with a HR of 1.04 (95 % CI 1.01–1.08; p = 0.013). Time-averaged ESS did not exhibit significant associations with the primary outcome or any of its components, while TSVI emerged as significantly associated with increased risk of MI (HR 1.01, 95 % CI 1.00–1.01; p = 0.014), and ischemia-driven revascularization (HR 1.01, 95 % CI 1.00–1.01; p = 0.021). Harrel's C-index values for the univariate Cox proportional hazards models are reported in Supplementary Table 2.

Only the outcomes with at least one anatomical or ESS-based variable achieving statistical significance at the univariate analysis were selected for further investigation. For these outcomes, the multivariate Cox regression analysis identified significant independent predictors, Fig. 3 (upper panel). Among baseline clinical characteristics, blood serum creatinine emerged as a strong predictor of the primary composite outcome (HR 1.48, 95 % CI 1.06–2.07; p = 0.020) and all-cause death (HR 1.68, 95 % CI 1.24–2.28; p < 0.001). A history of peripheral artery disease was significantly associated with a higher risk of MI at follow-up (HR 2.75, 95 % CI 1.04–7.25; p = 0.041). Additionally, %AS was independently linked to the primary endpoint (HR 1.03, 95 % CI 1.00–1.05; p = 0.018), while TSVI showed a significant association with both myocardial infarction (HR 1.01, 95 % CI 1.00–1.01; p = 0.014) and the need for revascularization at follow-up (HR 1.01, 95 % CI 1.00–1.01; p = 0.013).

Table 2
Results of the anatomo-functional evaluation.

		Total (Patient N = 335)
Type of coronary artery included in the analysis	LAD, no. (%)	107 (31.9)
	LCX, no. (%)	125 (37.3)
	RCA, no. (%)	103 (30.7)
Area stenosis, %		57.2 ± 12.4
Lesion length, mm		12.4 (8.8–18.4)
Functional assessment, FFR or QFR units		0.89 (0.86–0.94)
Time-averaged endothelial shear stress, Pa		2.9 (2.0–4.2)
Topological shear variation index, m^{-1}		59.1 (31.5–98.9)

Abbreviations: FFR = fractional flow reserve; LAD = left anterior descendent artery; LCX = left circumflex artery; QFR = quantitative flow ratio; RCA = right coronary artery.

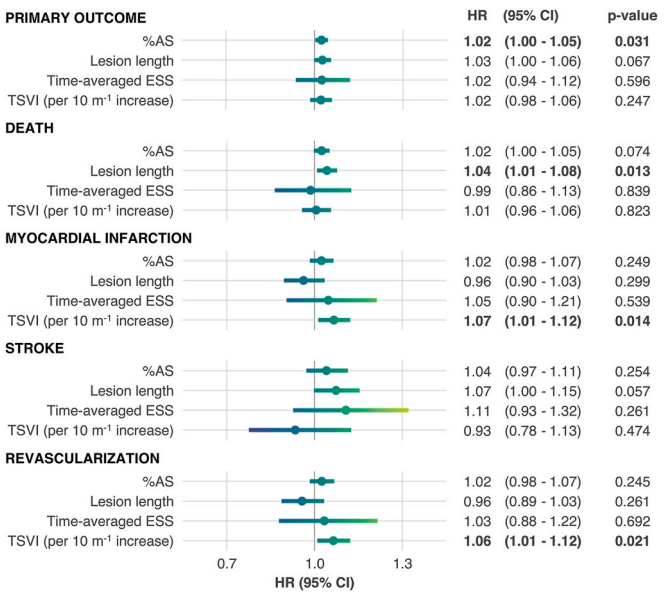


Fig. 2. Univariate Cox regression analysis of the primary outcome and its components.
Results of the Cox proportional hazard univariate models for the primary outcome and its components, based on percentage area stenosis (%AS), lesion length, time-averaged endothelial shear stress (ESS), and topological shear variation index (TSVI). Hazard ratio (HR) and 95 % confidence interval (CI) for TSVI are reported per 100 m^{-1} increase in TSVI. Significant associations are highlighted by the text in bold.

The inclusion of %AS, lesion length, or TSVI alongside clinical and demographic variables significantly improved the prognostic performance of the multivariate Cox proportional hazard models (Fig. 3, lower panel). Specifically, adding %AS to the model predicting the primary outcome increased the C-index from 0.62 to 0.64 (likelihood ratio test $p = 0.016$). Incorporating lesion length into the model for all-cause death substantially improved the C-index from 0.56 to 0.78 ($p < 0.001$). Similarly, the addition of TSVI enhanced the prediction of myocardial infarction (C-index from 0.76 to 0.79, $p = 0.032$) and ischemia-driven revascularization (C-index from 0.70 to 0.74, $p = 0.030$), demonstrating its relevance in cardiovascular risk stratification.

3.4. Causal inference analysis

The Bayesian networks summarizing the causal relationships for MI and revascularization (i.e., the outcomes influenced by TSVI according to the Cox regression analysis) are shown in Fig. 4. Among the direct causal factors of MI, TSVI was the strongest, with relative causal strength equal to 39.18 %, followed by age (32.41 %), and coexistence of peripheral artery disease (24.11 %). TSVI was the most influential factor for MI in terms of intrinsic contribution, equal to 7.03 % and about 1.55 times higher than that of %AS (4.57 %). For revascularization, the strongest direct causal factor was a history of prior MI, with relative causal strength equal to 54.44 %, while TSVI was the second strongest direct causal factor (22.08 %), followed by age (13.73 %), and the coexistence of peripheral artery disease (9.75 %). The intrinsic contribution of %AS was comparable to that of TSVI (2.83 ‰ *vs*. 2.72 ‰, respectively), confirming that, in this case as well, TSVI provides new "information", which is not merely inherited from %AS.

4. Discussion

In this *post hoc* analysis of the FIRE trial, we investigated the predictive value of various clinical, anatomical and hemodynamic factors, including ESS evaluated in clinical standard settings [27], for cardiovascular events in older MI patients with MVD. Our findings highlight three key aspects [1]: tighter and longer non-culprit lesions, even if not significantly impairing coronary flow, were associated with an increased risk of MACE and all-cause death at one year [2]; shear stress variability in the contraction/expansion action exerted on the endothelium (quantified in terms of TSVI), rather than its time-averaged magnitude, had a stronger impact on clinical outcomes, influencing the occurrence of MI and ischemia-driven revascularization at one year; and [3] TSVI, with its strong causal link with both MI and revascularization, not only propagated the information associated to lesion severity, but also contributed new insights for predicting MI or revascularization. The present study also supports recent findings, confirming that ESS evaluation can be integrated within a clinical framework and managed by interventional cardiologists.

4.1. Coronary lesion severity and residual cardiovascular risk

Emerging evidence suggests that non-culprit coronary lesions, despite not being the primary target of intervention, significantly contribute to future cardiovascular events, highlighting the need for comprehensive risk assessment and tailored therapeutic strategies [28–30]. Residual plaque vulnerability of untreated coronary lesions can be assessed anatomically. Larger plaque burden, smaller luminal area, and thin-cap fibroatheromas have been associated with an increased risk of MI and revascularization [15,31]. Our findings corroborate the added value of physiology-based intravascular metrics beyond the anatomical stenosis severity for determining the risk for MACE [32]. The quantification of lesion length adopted here may indicate a greater atherosclerotic burden, potentially harboring multiple regions of endothelial erosion [33]. Furthermore, the association between lesion length and all-cause mortality suggests that anatomical plaque burden not only impacts cardiovascular outcomes but may also reflect a more extensive systemic atherosclerotic disease burden, particularly relevant in elderly patients with multimorbidity [27].

4.2. Causal role of endothelial shear stress

A recent meta-analysis over thirty studies and more than thirty thousand patients reported that about half of the MACE cases originated from lesions that did not exhibit common high-risk features [10]. Improved prediction may arise with the incorporation of an ESS-based assessment of disturbed hemodynamics. Computational studies and clinical evidence have demonstrated that distinct, abnormal ESS patterns are critical in identifying plaques at risk for future cardiovascular events, independently of stenosis severity [6]. Low ESS magnitude has been associated with plaque growth, increased necrotic core formation, and atheroma burden expansion [11], whereas high ESS magnitude has been linked to MACE and revascularization, consequent to fibrous cap thinning and plaque rupture [4,12,19].

This study is the largest to date examining the role of ESS in determining the risk of future cardiovascular events. Here, we report that distinct features of ESS captured by TSVI accurately detect no-flow limiting lesions that were likely to progress and cause events, with a significant additive predictive value over patients' baseline characteristics. Endothelial exposure to large variability in the contraction/expansion action exerted by the streaming blood throughout the cardiac cycle —quantified by TSVI— has been previously linked to atherosclerotic plaque progression in both animal and patient studies [3,8] and to MI in 5-years follow-up [13], consistently with the present study. The mechanistic link between variability in the contraction/expansion action exerted by the ESS and plaque destabilization is multifaceted, as it involves impairment of the endothelial function, inflammatory activation, and increase of local oxidative stress, promoting high-risk plaque features, even in mild coronary stenosis [12,16,19,34]. This is consistent with our previous findings in younger patients in the setting of an acute coronary event, where high TSVI or low time-averaged ESS synergized

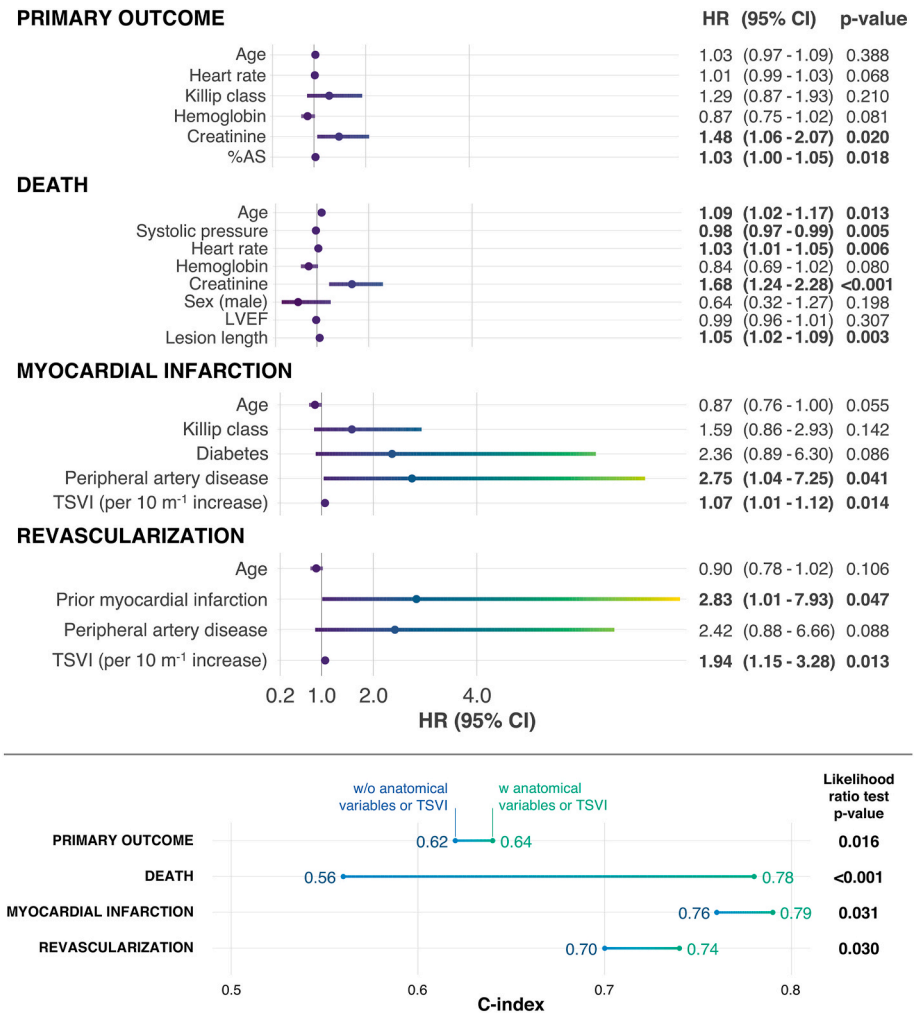


Fig. 3. Multivariate Cox regression models.
Multivariate Cox regression analysis for predicting primary outcome, all-cause death, myocardial infarction, and revascularization. Significant predictors for each outcome are shown, with inclusion of anatomical variables (percentage area stenosis [%AS] or lesion length, respectively for the primary outcome and all-cause death) or topological shear variation index (TSVI, for MI and revascularization) improving the C-index with respect to a baseline model where anatomical variables or TSVI were not included. Hazard ratio (HR) and 95 % confidence interval (CI) for TSVI are reported per 100 m^{-1} increase in TSVI. Given that no anatomical or ESS-based descriptors were significant predictors at the univariate level, no multivariate model was built for the stroke outcome.

with lipid-rich plaque (identified with intracoronary near-infrared spectroscopy) to drive plaque progression [3], further supporting the complementary role of ESS-based metrics and compositional imaging in assessing plaque vulnerability.

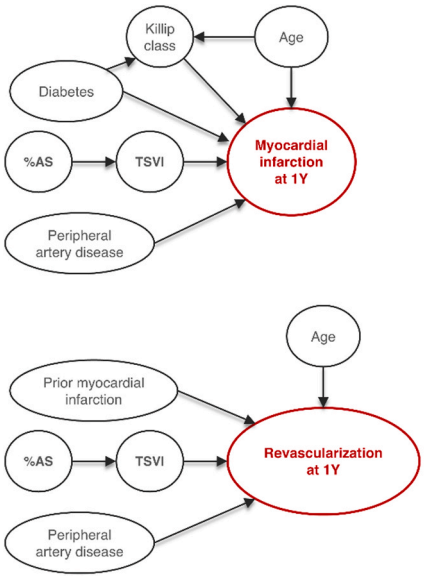
Unlike previous angiographic-based studies, which found that elevated ESS magnitude independently predicted adverse cardiovascular events [12,13,22], our findings show that time-averaged ESS magnitude does not predict any outcomes. However, the follow-up duration in this study (1 year) is shorter than in the studies mentioned above, and there are differences in the population enrolled. Additionally, this study is the first to demonstrate that distinct ESS-based quantities (TSVI) have a causal relationship with spontaneous MI and ischemia-driven revascularization, while also addressing their interaction with coronary luminal narrowing. Coronary luminal narrowing may induce flow disturbances, in turn influencing local ESS [35,36], as confirmed by the emerged association between %AS and TSVI (Pearson's $r = 0.567$, $p < 0.001$): this indicates that while %AS may not predict MI or revascularization (Fig. 2), it has an indirect effect and could still influence the outcomes through TSVI. By distinguishing the information derived from TSVI and that from %AS, the causal inference analysis reveals that TSVI is not merely a mediator or surrogate of %AS. Instead, it has a causal contribution to the outcome, explaining a portion of its variance that is comparable to or even greater than the variance explained by %AS, for MI and revascularization respectively (Fig. 4).

4.3. *Integrating systemic and local factors in cardiovascular risk stratification*

Causal inference analysis evaluates the causal relationships of established risk factors, such as age and peripheral artery disease, in relation to %AS and TSVI. This analysis provides a comprehensive conceptualization of residual risk in CAD patients by integrating systemic factors, ESS-based factors, and their interaction. This perspective not only enhances our mechanistic understanding of CAD progression but also enables more robust risk stratification and prediction.

The conceptualization described by the Bayesian networks (Fig. 4) consistently aligns with previous evidence. In elderly patients, chronic exposure to systemic risk factors like diabetes, renal dysfunction, and hypertension further impairs endothelial function, reducing the vascular reparative capacity and exacerbating plaque vulnerability [37].

Taken together, the direct detrimental impact of aberrant ESS on the vascular wall is likely modulated by systemic factors. Elderly patients with systemic comorbidities, including diabetes, chronic kidney disease, and inflammatory disorders, exhibit a more fragile endothelial



	Relative strength	Intrinsic contribution
Age	32.41%	3.25%
Killip class	0.46%	0.04%
Diabetes	3.84%	3.20%
Peripheral artery disease	24.11%	3.54%
TSVI	39.18%	7.03%
%AS	-	4.57%

	Relative strength	Intrinsic contribution
Age	13.73%	2.13‰
Prior myocardial infarction	54.44%	2.20‰
Peripheral artery disease	9.75%	2.45‰
TSVI	22.08%	2.72‰
%AS	-	2.83‰

Fig. 4. Causal Inference Analysis.
Causal inference analysis illustrating the relationships between key variables and clinical outcomes at one year (1Y). The diagrams (left panel) show the Bayesian networks conceptualizing the relationship between variables. Variables include Killip class, creatinine, age, percentage area stenosis (%AS), topological shear variation index (TSVI), prior myocardial infarction, peripheral artery disease, and diabetes. Relative strength and intrinsic contribution are tabulated in the right panel.

phenotype and impaired adaptive vascular responses [38,39]. This could amplify the detrimental effects of aberrant ESS, predisposing the endothelium to injury and subsequent plaque rupture. Advanced age and diabetes were associated with increased coronary plaque burden and vulnerability due to chronic inflammation and metabolic disturbance [40], while renal dysfunction was find to exacerbate endothelial dysfunction and accelerate atherosclerosis [41]. In this context, it is likely that shear stress patterns—such as TSVI—partially reflect a global vessel aging phenotype rather than purely lesion-specific malignancy, especially in this elderly population with diffuse vascular changes. This interpretation is further supported by the prognostic value of lesion length, a surrogate marker of disease diffuseness. Nevertheless, TSVI retained independent prognostic value for adverse outcomes, and causal modeling consistently supported its mechanistic role in plaque destabilization and event risk, even within this aged cohort.

These findings emphasize the need for a more integrative approach to cardiovascular risk assessment, where biology and local hemodynamic factors are considered together to refine risk stratification and guide treatment strategies.

4.4. Study limitations

This study has several limitations that should be acknowledged. First, the retrospective nature of this post hoc analysis may introduce selection bias, and the study population consists solely of older patients with MVD, which limits the generalizability of our findings to other patient populations. Future studies with more diverse age cohorts are needed to validate our results. Second, our analysis was conducted on a per-patient basis, but previous research on the relationship between adverse cardiovascular events and angiography-derived ESS has shown that lesion-level findings are largely consistent with patient-level findings [42]. Third, the unavailability of direct plaque imaging implies that our conclusions about plaque vulnerability are based on inferences from quantitative coronary angiography and the ESS analysis. Fourth, potential longitudinal variations and time-dependent effects of cardiovascular risk factors were not considered in this study. Changes in medication and lifestyle modifications over time could influence the observed associations and should be addressed in future research. Fifth, systematic data on LDL-C levels were not available in the trial dataset, as LDL-C measurement was not mandated by the original study protocol. While dyslipidemia was included as a surrogate variable, the absence of direct LDL-C values may have limited a more granular assessment of lipid-related risk in the present analysis. Finally, the causal inference analysis relied on some assumptions about the structure of the data and may be influenced by the presence of unmeasured confounders. This is reflected in the low value of the sum of intrinsic contributions (Fig. 4), which represents the variance explained by the factors included in the Bayesian network. However, it is important to note that these factors still show a significant relationship with the outcome (Figs. 2 and 3).

5. Conclusions

Integrating anatomical and physiology-based descriptors of the coronary environment with traditional clinical parameters improves the predictive accuracy for cardiovascular events in older patients with multivessel CAD. Patients with narrower and longer residual coronary lesions faced an increased risk of MACE and all-cause mortality, while adverse shear stress patterns were strongly associated with a higher incidence of acute plaque events and plaque progression at follow-up.

These findings highlight the interplay between systemic risk factors and local coronary hemodynamics in identifying high-risk residual non-culprit lesions and, more broadly, in determining lesion vulnerability. A more comprehensive approach to cardiovascular risk assessment—combining traditional risk stratification with detailed hemodynamic profiling—offers a promising opportunity to improve patient outcomes and optimize personalized therapeutic strategies in older CAD patients.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT (OpenAI) in order to improve manuscript readibility. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2025.120476.

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