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VIRTUAL IMAGE-BASED FFR TECHNOLOGIES

(Τεχνολογίες Εικονικής Αξιολόγησης Κλασματικής Εφεδρείας Ροής)

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Dedicated to my Family

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Περίληψη Στα Ελληνικά

Πρώτο Μέρος

Εισαγωγή : Μη επεμβατικές μέθοδοι εκτίμησης της κλασματικής εφεδρείας ροής (FFR) μελετώνται ενεργά, με στόχο να ξεπεράσουν τα προβλήματα της επεμβατικής συμβατικής εκτίμησης που απαιτεί τη χρήση ενδοαρτηριακού σύρματος μέτρησης πίεσης και τη χορήγηση φαρμάκων που προκαλούν υπεραιμία όπως η αδενοσίνη. Το FFR που προκύπτει από την αγγειογραφία με μη επεμβατικό τρόπο (FFRangio) έχει ήδη επιδείξει τη διαγνωστική του απόδοση στο πλαίσιο της σταθερής στεφανιαίας νόσου. Ωστόσο, η δεν έχει μελετηθεί στο πλαίσιο του οξέος εμφράγματος του μυοκαρδίου χωρίς ανάσπαση του διαστήματος ST (NSTEMI).

Μέθοδοι: Διεξήγαμε μια προοπτική, μονοκεντρική, διπλά τυφλή μελέτη συγκρίνοντας το FFR που υπολογίζεται από το FFRangio με το επεμβατικά μετρημένο FFR σε ασθενείς με NSTEMI. Το FFR μετρήθηκε σε όλες τις αγγειογραφία ενδιάμεσες βλάβες (30%-70% στένωση) και στη συνέχεια συγκρίθηκε με το FFRangio που υπολογίστηκε στην ίδια θέση. Οι κύριοι στόχοι ήταν η ευαισθησία και η ειδικότητα του FFRangio για την μέτρηση του FFR χρησιμοποιώντας ένα κατώτατο όριο τιμής ≤0.80.

Αποτελέσματα: Ανάμεσα σε 100 ασθενείς με NSTEMI που προσήλθαν, 46 ασθενείς με 60 αγγεία συμπεριλήφθηκαν στη μελέτη. Η μέση τιμή του FFR ήταν 0,83±0,3 με 22 (36%) να είναι ≤0.80, ενώ η μέση τιμή του FFRangio ήταν 0,82±0,1 με 22 (36%) να είναι ≤0.80. Το FFRangio επέδειξε ευαισθησία 95,5%, ειδικότητα 97,4% και διαγνωστική ακρίβεια 96,7%.

Συμπέρασμα: Το FFRangio μπορεί με ακρίβεια και μη επεμβατικά να εκτιμήσει το FFR σε NSTEMI και μπορεί να έχει ρόλο στην καθοδήγηση των αποφάσεων θεραπείας που σχετίζονται με ενδιάμεσες στεφανιαίες βλάβες στον συγκεκριμένο πληθυσμό ασθενών.

Δεύτερο Μέρος

Εισαγωγή: Τα FFRangio και QFR είναι μη επεμβατικές μέθοδοι εκτίμησης του FFR και δεν έχει αναφερθεί μέχρι σήμερα στην βιβλιογραφία καμία συγκριτική μελέτη μεταξύ τους στον ίδιο πληθυσμό ασθενών.

Μέθοδοι: Η μελέτη αυτή αποτελεί υποσύνολο μιας μεγαλύτερης προοπτικής πολυκεντρικής μελέτης με ενιαίο βραχίονα που περιλάμβανε ασθενείς που διαγνώστηκαν με NSTEMI, στους οποίους η στεφανιαία στένωση 30-70% αξιολογήθηκε με FFR. Το FFRangio και το QFR υπολογίστηκαν από 2 διαφορετικούς χειριστές και συγκρίθηκαν με το FFR. Τα δύο κύρια καταληκτικά σημεία ήταν η σύγκριση του συντελεστή συσχέτισης Pearson μεταξύ FFRangio και QFR με το FFR και η σύγκριση της μεταβλητότητας μεταξύ των παρατηρητών τους.

Αποτελέσματα: Από τους 134 ασθενείς με NSTEMI που ελέγχθηκαν, 59 ασθενείς με 84 αγγεία υποβλήθηκαν σε μετρήσεις FFR και συμπεριλήφθηκαν σε αυτήν τη μελέτη. Η μέση τιμή FFR ήταν 0,82±0,40 με 32 (38%) να είναι ≤0,80. Η μέση τιμή FFRangio ήταν 0,82±0,20 και η μέση τιμή QFR ήταν 0,82±0,30, με 27 (32%) και 25 (29%) να είναι ≤0,80 αντίστοιχα. Ο συντελεστής συσχέτισης Pearson ήταν σημαντικά καλύτερος για το FFRangio σε σύγκριση με το QFR, με τιμές R 0,76 και 0,61 αντίστοιχα (p=0,01). Η συμφωνία μεταξύ των παρατηρητών ήταν επίσης σημαντικά καλύτερη για το FFRangio σε σύγκριση με το QFR (0,86 έναντι 0,79, $p < 0,05$). Το FFRangio είχε ευαισθησία 91%, ειδικότητα 100% και ακρίβεια 96,8%, ενώ το QFR εμφάνισε ευαισθησία 86,4%, ειδικότητα 98,4% και ακρίβεια 93,7%.

Συμπέρασμα: Σε ασθενείς με NSTEMI, τα FFRangio και QFR επέδειξαν εξαιρετική διαγνωστική απόδοση. Το FFRangio φαίνεται να έχει καλύτερη συσχέτιση με το επεμβατικό FFR σε σύγκριση με το QFR.

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0. Abbreviations

ACS: Acute Coronay Syndrome

caFFR: Computational pressure-flow dynamics derived FFR

CFD: Computational fluid dynamics

CI: Confidence interval

DICOM: Digital Imaging and Communications in Medicine

FFR: Fractional flow reserve

FFRangio: Angio-based fractional flow reserve

ICA: Invasive Coronary Angiography

LAD: Left anterior descending coronary artery

LCx: Left circumflex coronary artery

LMCA: Left main coronary artery

MACE: Major adverse cardiac events

MI: Myocardial infarction

MINOCA: Myocardial Infarction with Non-Obstructive Coronary Artery Disease

NHPR: Non-hyperemic pressure ratios

NSTEMI: Non-ST-Elevation Myocardial Infarction

PCI: Percutaneous coronary intervention

Pd/Pa: Distal coronary artery pressure to aortic pressure ratio

PPV: Positive Predictive Value

QCA: Quantitative coronary angiography

QFR: Quantitative flow ratio

SD: Standard Deviation

STEMI: ST-elevation myocardial infarction

TAVR: Transcatheter Aortic Valve Replacement

vFFR: Vessel fractional flow reserve

2D QCA: 2-Dimensional quantitative coronary angiography

3D QCA: 3-Dimensional quantitative coronary angiography

1. Introduction

1.1 Background

In contemporary clinical practice, invasive coronary angiography (ICA) serves as the primary diagnostic tool for evaluating significant obstructive stenosis in patients presenting with symptoms indicative of coronary artery disease, such as exertional chest pain. Traditionally, therapeutic decision-making relied upon visual interpretation of coronary angiograms, with the percentage stenosis of an atherosclerotic lesion determined based on subjective assessment by cardiologists. However, this approach is fraught with limitations, particularly in cases of intermediate lesions, where accurate assessment becomes challenging due to factors such as inter/intra-observer variability, oculo-stenotic reflex, epicardial spasm, and vessel foreshortening or overlap. Moreover, the hemodynamic implications of coronary lesions on blood flow are multifaceted, complicating the determination of their physiological-functional significance according to the Bernoulli equation.

Fractional flow reserve (FFR) has emerged as the gold standard for invasive physiological evaluation of coronary stenoses, providing an objective and reproducible estimation of myocardial ischemia. By assessing the pressure gradient across a lesion during hyperemia, FFR effectively identifies lesions warranting percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Notably, studies have highlighted a significant discordance between treatment decisions based solely on visual estimation and those informed by FFR values, underscoring the tendency toward overtreatment of coronary lesions.

Despite its established efficacy in improving clinical outcomes, the utilization of invasive FFR guidance remains suboptimal. Barriers to widespread adoption include the need for invasive pressure guidewires and hyperemia-inducing drugs, as well as procedural costs and associated risks. Moreover, the setup, crossing of lesions, and data recording processes entail additional time and resources.

In response to these challenges, novel non-invasive FFR measurement technologies, such as FFRangio, QFR, and FFR-CT, have emerged, leveraging angiographic images to provide three-dimensional reconstructions of arterial anatomy overlaid with color-coded FFR values. By simulating blood flow dynamics and pressure gradients across coronary segments, these technologies offer a promising alternative to invasive FFR, potentially streamlining diagnostic workflows and reducing procedural risks and costs. However, their diagnostic performance, particularly in acute coronary syndromes, and direct comparisons between them remain are as of ongoing research and exploration.

1.1.1 Fractions Flow Reserve (FFR)

1.1.1.1 Definition

FFR is a quantitative measure used in cardiology to assess the severity of coronary artery stenosis, which refers to the narrowing of the coronary arteries due to plaque buildup. It is defined as the ratio of the maximal achievable blood flow in the presence of an epicardial coronary stenosis to the maximum flow that would occur in the same healthy vessel if there were no obstructive epicardial disease. In simpler terms, it quantifies the percentage of maximum blood flow that is limited by the presence of a coronary artery blockage.

To calculate FFR, the pressure in the coronary artery downstream of the stenosis (Pd) is compared to the aortic pressure (Pa) during maximal hyperemia, taking into account the central venous pressure (Pv). This comparison is expressed by the formula: FFR = (Pd - Pv) / (Pa - Pv). Maximal hyperemia, which is required for accurate FFR measurement, is typically induced by intravenous or intracoronary administration of vasodilators such as adenosine, regadenoson, or papaverine.

Adenosine, particularly when administered intracoronarily, is the preferred agent for inducing maximal hyperemia due to its rapid onset, although it may cause transient side effects such as atrioventricular block, chest discomfort, and shortness of breath. Regadenoson is an alternative vasodilator that is selective for the A2 adenosine receptor, resulting in fewer cardiac conduction side effects compared to adenosine, especially in patients with chronic obstructive pulmonary disease (COPD).

The initial threshold for FFR indicating significant stenosis was set at 0.75, but due to the ambiguity in decision-making within the range of 0.75 to 0.80, the recommended threshold has been revised to 0.80 for greater clarity. However, the decision to proceed with revascularization (e.g., percutaneous coronary intervention, or PCI) for FFR values between 0.75 and 0.80 remains contentious and should be based on individual patient factors and the risk of major adverse cardiovascular events. While FFR has traditionally been regarded as an index of epicardial ischemia, it's important to recognize its susceptibility to influence by microvascular function and resistances, often leading to elevated values. However, in patients presenting with microvascular dysfunction or experiencing myocardial infarction with non-obstructive coronary artery disease (MINOCA) alongside intermediate coronary lesions, FFR can serve as a valuable tool in excluding type 1 MI epicardial ischemia.

1.1.1.2 Technical Aspects of Measurement

The measurement of FFR plays a pivotal role in guiding PCI, providing crucial data about the hemodynamic significance of coronary artery stenoses. This procedure demands meticulous attention to technical details to ensure accurate and reliable results.

Traditionally, most PCIs utilize 6 French guiding catheters. However, modern FFR systems have been designed with low profiles, accommodating even 5 French guiding catheters. It's imperative to optimize phasic pressure recordings when using these smaller catheters, often achieved through meticulous saline flushing of the catheter system.

FFR systems typically incorporate either piezoelectric or optical sensors. These sensors function by translating pressure into a measurable signal, either through generating an electrical charge or inducing a phase delay in a reflected light beam. Recent advancements, particularly in optical pressure guidewires, have shown reduced pressure drift, enhancing the reliability of measurements. Furthermore, the latest iterations of optical pressure guidewires offer versatility by enabling their use as primary guidewires for PCI procedures, with the ability to disconnect and reconnect the FFR system as needed.

The procedural steps for FFR measurement involve several key processes. Initially, it is essential to calibrate the system by zeroing both the fluid-filled aortic pressure and the FFR pressure system to atmospheric pressure, preferably at the level of the right atrium. The pressure wire is then advanced beyond the tip of the guiding catheters, with subsequent equalization of both pressure curves achieved with the introducer needle off the Y connector. Saline flushing of the system is crucial to mitigate the dampening effect of contrast on catheter waveform pressure recordings.

Following the intracoronary administration of isosorbide dinitrate, FFR and resting microvascular resistance (NHPR) measurements are taken with the wire positioned at least 3 vessel diameters distal to the stenosis. In cases of complex lesions or diffuse disease, pull-back recordings of pressure along the vessel can identify segments with significant pressure changes, aiding in the determination of optimal PCI targets. Additionally, monitoring for potential drift

in the FFR system, deemed significant if exceeding 3 mmHg, is essential to maintain measurement accuracy.

Meticulous attention to technical details is paramount in FFR measurement to ensure accurate assessment of coronary lesions, guiding optimal decision-making in the management of patients with coronary artery disease.

1.1.1.3 Validation of FFR in the Literature

The FFR was first introduced by Pijls *et al* IN 1996 and emerged as a valuable tool in assessing the hemodynamic significance of coronary lesions. Their landmark work established an initial FFR threshold, showcasing its efficacy in reversing non-invasive stress test results post-percutaneous coronary intervention.

Subsequent trials further validated the utility of FFR in clinical decision-making. The DEFER trial, for instance, examined the safety of deferring PCI for functionally non-significant stenoses, confirming the appropriateness of this approach when FFR exceeds the defined threshold. Similarly, the FAME I trial by Tonino et al. revealed that FFR-guided PCI resulted in fewer Major Adverse Cardiovascular Events and reduced resource utilization compared to angiography-guided PCI, particularly in patients with multivessel disease using a specific threshold.

The FAME II trial, conducted by De Bruyne et al., provided further evidence supporting the integration of FFR into clinical practice. This trial demonstrated that adding FFR measurements to optimal medical therapy significantly improved outcomes compared to medical therapy alone in stable coronary artery disease patients.

Regarding non-ST-elevation acute coronary syndrome (NSTEMI), FFR-guided revascularization of non-culprit lesions during the index procedure offers a valuable strategy for evaluating the necessity of further revascularization therapy.

Moreover, meta-analyses have underscored the superiority of non-invasive stress tests in diagnosing significant CAD when compared to stress electrocardiograms. Functional imaging techniques like positron emission tomography, cardiac magnetic resonance imaging, and single-photon emission computed tomography have demonstrated superior diagnostic performance, despite limited anatomical correlation.

The literature to date consistently supports the efficacy and clinical utility of FFR in guiding revascularization decisions, optimizing patient outcomes, and enhancing resource allocation in the management of coronary artery disease.

1.1.4 Underutilization of FFR

Despite its well-documented efficacy and endorsement by prominent cardiovascular guidelines, Fractional Flow Reserve remains underutilized in clinical practice. The invasive nature of FFR procedures, necessitating the insertion of a pressure guide wire into coronary arteries, poses inherent risks to patients. Furthermore, the financial burden associated with FFR, including the costs of equipment and consumables, presents a substantial barrier to widespread adoption. Additionally, the requirement for administering hyperemic agents such as adenosine adds complexity and potential risks of adverse reactions, further limiting its application. Moreover, the time-intensive nature of FFR assessments in the catheterization laboratory results in delays in patient care and resource utilization. Lastly, the demand for specialized training and expertise to accurately interpret and perform FFR measurements underscores the challenges in integrating it into routine clinical practice.

1.1.2 Emergence of Non-invasive Angiography-Based FFR Modalities

To address the aforementioned constraints, angiography-based FFR have been developed. Initially, 2-dimensional quantitative coronary angiography (2D QCA) emerged as the pioneering angiography-based approach, but its correlation with physiological ischemic indices like FFR was found to be only modest. In contrast, 3D QCA demonstrated superior accuracy and a stronger association with FFR compared to 2D QCA, mitigating issues related to coronary lesion foreshortening and asymmetry. Advances in understanding the relationship between QCA and pressure-flow dynamics, coupled with enhancements in computational capabilities, have facilitated the development of angiography-based FFR methodologies

1.1.2.1 The Simplified Computational Fluid Dynamics Concept

Computational Fluid Dynamics (CFD) stands as the predominant technique for solving the Navier–Stokes equations, governing fluid motion. These equations yield insights into velocity and pressure distributions within the coronary artery system over time. However, due to the computational complexity and time-intensive nature of solving the Navier–Stokes equations, simplified analyses based on foundational works by Young, Tsai, and Gould have been introduced.

The challenge in virtually estimating pressure drop stems from the variability of hyperemic flow, crucial for FFR assessment, which is intricately linked to myocardial vasodilation and the patient's hemodynamic status. Nevertheless, this technology is rapidly evolving, and several approaches for FFR computation integrating simplified CFD models with 3D QCA from coronary angiography have emerged.

1.1.2.2 FFRangio

Coronary angiography-derived FFR (FFRangio; Cathworks) is a novel FDA- approved and CE-marked technology that uses 3 two- dimensional (2D) images obtained during coronary angiography acquisition to automatically build a 3D reconstruction of the coronary artery trees. FFRangio utilizes multiple angiographic projections, spaced at least 30 degrees apart, to construct a comprehensive 3D model of the coronary tree, treating each segment as an electric circuit component, enabling detailed hemodynamic assessment. This technology evaluates the impact of arterial narrowings on flow resistance, estimating pressure drops and flow rates. FFRangio generates two coronary tree models: one with stenosis and another without. The pivotal FFRangio metric is calculated as the ratio of maximal flow in the presence and absence of stenotic lesions, offering crucial insights into the functional significance of coronary artery narrowings and aiding clinical decision-making. In the FFRangio pilot study, analyzing 101 lesions in 88 patients, significant concordance with invasive FFR measurements was observed (interclass correlation coefficient = 0.97, $p < 0.001$). Moreover, subsequent trials demonstrated robust diagnostic performance and high interobserver reproducibility. The FAST-FFR trial addressed previous limitations by enrolling 301 patients, achieving notable sensitivity and specificity per vessel using FFR as a reference. Notably, FFRangio demonstrated exceptional diagnostic performance, particularly in patients with multivessel disease, as evidenced by a single-center Japanese trial. A pooled analysis of multiple prospective cohort studies revealed consistent, high diagnostic performance across various patient and lesion subgroups, with a mean difference between FFR and FFRangio of 0.00 ± 0.12 and a high correlation coefficient. Additionally, post hoc analyses from the FAST-FFR trial and real-world clinical trials underscored the clinical feasibility and safety of FFRangio-guided treatment, with outcomes aligning closely with treatment decisions based on FFRangio results. The Japan FFRangio Clinical Outcomes Study (NCT05648396), a retrospective multicenter registry, aims to further

evaluate the real-world outcomes of FFRangio-guided treatment for coronary artery disease, focusing on Japanese patients. The study's completion is anticipated in 2027, offering valuable insights into the long-term efficacy and impact of FFRangio in clinical practice.

1.1.2.3 QFR

Quantitative Flow Ratio (QFR), developed by Medis Medical Imaging System in Leiden, the Netherlands, and Pulse Medical Imaging Technology in Shanghai, China, is acquired from two diagnostic angiographic projections, with a minimum separation of 25°, to generate a 3D QCA model. In the QFR model, the pressure drop is computed for each segment using stenosis geometry and mean hyperemic flow velocity, employing the Gould formula. Blood is considered a homogeneous and Newtonian fluid, with coronary pressure assumed to remain constant in the absence of stenosis, coronary flow velocity preserved along the coronary, and steady flow specified as the boundary condition at the outlet. Thus, the mass flow rate at each location along the interrogated vessel can be determined by the mean flow velocity and vessel sizing from 3D QCA.

The FAVOR PILOT study examined 84 coronary vessels in 73 patients with intermediate coronary lesions, comparing the predictive accuracy of fixed-flow QFR (fQFR), contrast-flow QFR (cQFR), and adenosine-flow QFR (aQFR) in identifying functionally significant stenoses (FFR $\leq$ 0.80). Retrospective QFR calculations in a core-lab setting showed good correlations with standard FFR values. cQFR demonstrated superior performance to fQFR and comparable results to aQFR. The FAVOR II China study involved 308 patients, showcasing the diagnostic efficacy of online QFR computation in identifying hemodynamically significant coronary stenosis, with consistent correlation and agreement with FFR. Additionally, the WiFi II study,

involving 362 patients, emphasized QFR's strong correlation with FFR, particularly in non-obstructive CAD cases.

A meta-analysis of four trials (FAVOR Pilot, FAVOR II China, FAVOR II E-J, and WIFI II) further underscored QFR's diagnostic performance, despite some limitations such as incomplete data on factors affecting QFR and the absence of cost-benefit analyses. Choi et al.'s study in Korea reaffirmed QFR's effectiveness in diagnosing and predicting outcomes for coronary artery disease over a 2-year period, especially in ACS scenarios. The FAVOR III China trial, involving 3,825 patients, highlighted the significant reduction in major adverse cardiac events (MACE) with QFR-guided PCI compared to angiography-guided PCI. Subsequent analyses revealed improved clinical outcomes, particularly in cases where the treatment strategy aligned with QFR measurements.

Moreover, ongoing trials like FAVOR III Europe Japan, FAVOR4-QVAS, and PIONEER-IV are further evaluating the effectiveness of QFR-guided PCI across diverse patient populations, while trials like QFR-STEMI and QUOMODO focus on managing non-culprit lesions in STEMI patients. Additionally, the AQVA trial explored the feasibility of QFR-based virtual PCI, demonstrating its superiority in achieving optimal post-PCI physiological results compared to conventional angiography-based PCI. However, limitations persist, particularly in acute MI settings and the need for further validation of new QFR-derived techniques.

1.1.2.4 vFFR

Vessel fractional flow reserve (vFFR), developed by CAAS, Pie Medical Imaging, Maastricht, the Netherlands, is obtained from two angiographic views with at least a 30° difference in rotation/angulation to generate the 3D QCA. Within the CAAS workstation, a CFD approach models flow using a simplified Navier–Stokes equation, applying boundary conditions such as

a constant parabolic flow profile at the inlet, a stress-free outlet, rigid-wall non-slip conditions, and a Newtonian fluid approximation of blood. The pressure drop is calculated by applying physical laws, including viscous resistance and separation loss effects present in coronary flow behavior, as described by Gould and Kirkeeide (Gould & Kirkeeide, 1992). Maximum hyperemic blood flow is empirically determined from clinical data and assumes that proximal coronary velocity is preserved along the coronary artery. The algorithm applies automated and harmonized optimal end-diastolic frame selection in the two orthogonal projections by ECG triggering and allows physiological lesion assessment of a specific target segment or vessel of interest, precluding the need to perform an assessment of the full cardiac tree or manual frame counting.

In the VIRTU-FAST study, Morris et al. introduced an innovative method for calculating virtual fractional flow reserve (vFFR) using a "pseudotransient" analysis protocol based on angiographic images and steady-state CFD. The computation time is significantly reduced to 189 seconds compared to over 24 hours required for transient analysis, while maintaining an error less than 1% compared to full-transient CFD. The precision and diagnostic accuracy were assessed across various cases. In all scenarios, the "pseudotransient" method exhibited a mean error of 0.0070 ± 0.0045, and the steady method showed a mean error of 0.0044 ± 0.0044. Subgroup analysis based on FFR values demonstrated consistent precision for both methods. Applying a more diligent FFR threshold of 0.75, the vFFR displayed excellent performance. VIRTU-FAST addressed limitations of VIRTU-1, including generic boundary conditions, software availability, and computational time, by deducing coronary microvascular resistance parameters from invasive measurements and focusing on real-time application and subgroup-specific analysis.

1.1.2.5 caFFR

Computational pressure-flow dynamics derived FFR (caFFR), developed by Rainmed Ltd in Suzhou, China, is a technique based on the 3D reconstruction of the vessel from two angiographic projections at angles of ≥ 30°. The resting coronary flow velocity is determined using the TIMI frame count, while the aortic pressure is recorded by the FlashPressure pressure transducer connected to the guide catheter and transmitted to the FlashAngio console. The console automatically determines the mean aortic pressure over the third to eighth cycles following angiography.

Both the flow velocity and the mean aortic pressure serve as inputs for the FlashAngio software, which calculates the pressure drop along the generated mesh of the coronary artery. Compared to previous software, caFFR employs real-time invasive pressure coupled with computational flow modeling to determine the pressure drop across a stenosis. This approach accounts for the dynamic nature of blood pressure, rather than relying on a static value for aortic pressure, and also considers energy loss in the lumen areas proximal and distal to the stenosis. The data are further processed using CFD techniques, which provide insights into the characteristics of intravascular blood flow and the pressure field. This enables the computation of the pressure gradient between the inlet and outlet of the studied coronary segment. In terms of efficiency, the time required for computation was highlighted in FLASH FFR, indicating that caFFR analysis necessitated a total operation time of less than 5 minutes, with computation taking less than 1 minute.

2. Rationale of the Study

2.1 Rationale

The assessment of coronary artery physiology has significantly advanced, demonstrating notable improvements in patient outcomes across diverse patient cohorts. However, these advancements often entail invasive procedures and the administration of hyperemic agents, potentially inducing side effects. Despite the emergence of non-invasive angiography-derived technologies, such as QFR and FFRangio, their applicability in certain patient subsets remains underexplored.

1) While FFRangio has exhibited promising diagnostic performance in chronic coronary disease, its efficacy in the context of NSTEMI patients remains uncharted.

2) Although QFR has been extensively researched, its accuracy in measuring FFR has not been directly compared to another non-invasive angiography-derived modality like FFRangio.

2.2 Hypothesis

We hypothesize that:

1) FFRangio will demonstrate comparable reliability in predicting FFR in NSTEMI patients as it has shown in chronic coronary syndrome cases documented in existing literature.

2) There are potential disparities in diagnostic accuracy among different angiography-derived FFR technologies, such as FFRangio and QFR.

2.3 Aims

1) We sought to assess the diagnostic performance of FFRangio exclusively in patients presenting with NSTEMI, for the first time in published literature, utilizing invasive FFR as the gold standard reference.

2) We aim to conduct a head-to-head comparison between QFR and FFRangio in the same patient population, which has not been previously documented in the literature.

3. Part 1: Diagnostic Performance of Angiography-Derived Fractional Flow Reserve in Patients with NSTEMI

3.1 Methods

3.1.1 Study Population

This study is a prospective, single-center, single-arm, double-blinded validation study. It represents a sub-study of a main study protocol whose design and rationale has been previously published, evaluating the diagnostic performance of computed tomography-derived FFR (FFR-CT) in NSTEMI patients. In this protocol, FFR was invasively measured in every 30%-70% stenosis by visual estimation.

Of all patients included in the main FFR-CT study, the present study specifically included adult patients presenting with NSTEMI, with at least one stenosis 30%-70% by visual estimation in at least one vessel. The main exclusion criteria for the main study were: patients presenting with STEMI, left main disease (stenosis ≥50%), severe renal failure, pregnant and breast-feeding women, patients with prior CABG or previous stenting, or known severe heart failure. Importantly, patients with one or more very high-risk criteria as defined by current European and American NSTEMI guidelines were excluded. All patients provided written informed consent prior to enrollment in the main study. Detailed inclusion/exclusion criteria of the study are reported in **Table 1.**

Inclusion criteria:

- ≥18 years old patients
- Presenting a rise and/or fall of high-sensitive cardiac troponins T (hs-cTnT) values measured in CHUV on at least 2 timepoints with at least one value above the 99th percentile of the URL and with at least one of the following:
    - Symptoms of ischemia
    - New or presumed new significant ST-segment–T wave (ST–T) changes
- Informed consent signed
- Presumed availability for follow-up up to 1 year (i.e. patients only transiting through Switzerland for travel purpose are de facto excluded)
- Wire-based FFR with hyperemic stimulus was assessed in at least one vessel.

Exclusion Criteria:

- STEMI patients
- Estimated glomerular filtration rate (eGFR) of <45 ml/min
- Presence of very high-risk criteria:
    - Hemodynamic instability or cardiogenic shock
    - Recurrent or ongoing chest pain refractory to medical treatment
    - Life-threatening arrhythmias or cardiac arrest
    - Mechanical complications of MI
    - Acute heart failure
    - Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation
- Pregnant and breast-feeding women (women of child bearing potential must have a negative urine or blood pregnancy at screening)
- Contra-indication to beta-blocker and/or nitro-glycerine
- Patients transferred from another hospital where diagnosis was made using a troponin dosage other than hs-cTnT
- Patients with prior coronary artery bypass grafting (CABG)
- Patient with known severe heart failure (i.e Ejection fraction of left ventricle of <30%)
- Patient incapable of judgement or under tutelage
- Patient in emotional distress or other unstable psychical condition incompatible with informed consent signature

Table 1. Complete list of inclusion/exclusion criteria

3.1.2 Study procedures

Diagnostic coronary angiography was performed as per standard practice according to local procedures at a cine frame rate of at least 10 frames per second. For a given stenosis of 30-70%, operators were instructed to acquire three different projections separated by a minimum of 30° before proceeding to FFR. The exact inclination of the C-arm was left to the discretion of the operator. FFR was measured in the respective lesions by an interventional cardiologist blinded to the FFR results. According to the operator's discretion, FFR was measured in every lesion with a visual diameter stenosis 30%-70% using the PressureWire™ X Guidewire (Abbott, Chicago, Illinois, USA) and following a predetermined protocol. Initial equalization of the pressure wire and of the aortic pressure was achieved at the tip of the guide catheter prior to all measurements, followed by advancement of the pressure wire distal to the stenosis and by inducing hyperemia using intracoronary adenosine (150 mcg for the right coronary artery and 200 mcg for the left descending or the circumflex coronary arteries. The absence of a drift was confirmed after a pull-back of the pressure to the same location as the initial equalization at the end of the procedure.

The different DICOM (Digital Imaging and Communications in Medicine) files were transferred directly via internal PACs system to the FFRangio console (Cathworks Ltd., Kfar Saba, Israel) and the FFRangio was measured on site for all patients by physician-operator who was blinded to the FFR result. More specifically, the physician entered the mean aortic pressure of the patient, selected the artery of interest by designating the responsible lesion and identified the three most optimal frames of each DICOM according to cardiac phase synchronization and visibility of the lesion. The FFRangio system then automatically created a 3D reconstruction of the coronary arteries designated by the operator based on the previous parameters.

FFRangio was measured in the same position as FFR by the blinded physician and a hemodynamically significant lesion was defined as a lesion with an FFR value of ≤0.80. Finally, the results of FFRangio and FFR were compared.

3.1.3 Endpoints

The study primary endpoints were the sensitivity and specificity of FFRangio in predicting if the FFR of the lesion was ≤0.80.

Secondary endpoints were the following: diagnostic performance (accuracy, positive and negative predictive value) of FFRangio in comparison to FFR as the standard of reference in the 'gray zone' of FFR values [0.75–0.85] as well as the specific performance in each vessel (LAD, LCX, and RCA). In addition, the correlation between the diagnostic accuracy of FFRangio and FFR was calculated.

3.1.4 Statistical methods

Continuous variables were expressed as mean ± SD, and continuous variables were expressed as absolute numbers and percentages. Categorical patient characteristics were presented as percent frequency, and continuous characteristics were presented as mean mean ± SD or median with interquartile range. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy of FFRangio were calculated, using FFR as the gold standard. The FFRangio result for each lesion was classified as true/false positive or true/false negative using FFR as the reference standard and a value of ≤0.80 as the threshold for functionally significant lesions for both modalities. To explore the agreement between

FFRangio and FFR, Bland–Altman analyses were plotted, and the 95% limits (1.96 ∗ SD) of agreements were calculated. The performance of FFRangio for identifying hemodynamically significant lesions in each of the three coronary arteries was compared by the Chi-square test. A Pearson correlation coefficient between FFR and FFRangio was reported.

A p value <0.05 was considered statistically significant. Statistical analysis was performed with the SPSS Statistics (version 28.0.1, SPSS Inc., Chicago, Illinois, United States).

3.2 Results

Between August 2019 and December 2021, a total of 100 NSTEMI patients were included in the main study (FFR-CT) and were automatically screened for inclusion in the current prospective, single center, double-blinded study. Of the 100 patients screened, 46 patients had one or more intermediate coronary lesion (diameter stenosis of 30-70%) evaluated using FFR, as per **Figure 1**. The baseline clinical characteristics of these patients are displayed in **Table 2**. The mean age was 64 ±13.3, 71% were male, and the mean body mass index was 27 ±3.7 kg/m2.

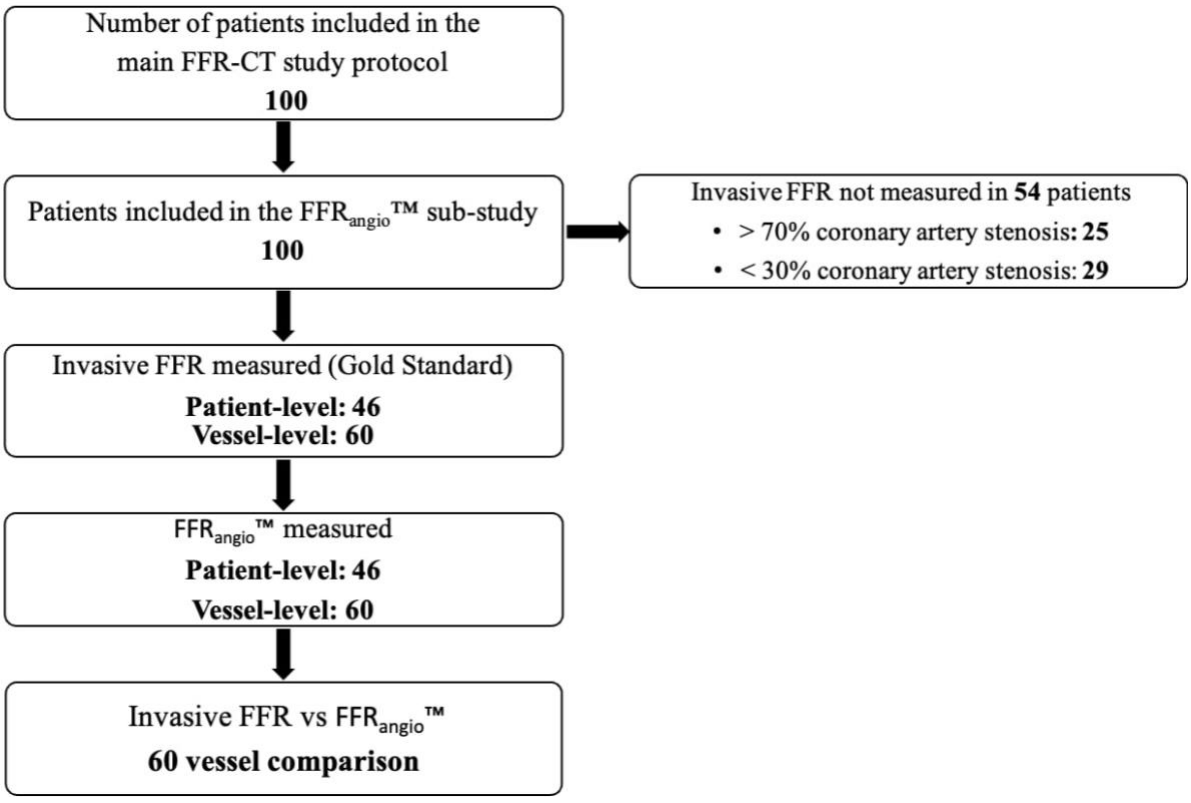

Figure 1. Flow-chart for patients included in the study. FFR, fractional flow reserve measured by pressure guidewire; FFRangio fractional flow reserve measured by FFRangio device

Table 2. Baseline Characteristics	
Characteristic	**n (%)**
Age, y	64 ±13.3
Male gender, n (%)	33 (71.7)
Body mass index, kg/m2	27 ±3.7
Hypertension, n (%)	26 (56.5)
Hypercholesterolemia, n (%)	32 (69.5)
Smoking (current or former), n (%)	33 (71.7)
Diabetes mellitus (Type I or Type II), n (%)	8 (17.3)
Dyslipidemia, n (%)	32 (69.5)

Table 2. Baseline characteristic. Data are presented as n (%) where appropriate.

Among the 46 patients finally included in the study, a total of 60 lesions underwent physiological assessment (FFR). The same 60 lesions were also functionally evaluated with FFRangio. FFR was measured in 1.4 vessels per patient and 17 patients had FFR measured in more than one vessel. The artery most frequently evaluated by FFR was the left anterior descending (40%), followed by the right coronary artery and the left circumflex artery (both 30%). The procedural characteristics of the vessels are reported in **Table 3**.

Table 3. Procedural Characteristics	n (%)
Lesions per patient	1.4±0.12
Target vessel	
LAD	24(40)
RCA	18(30)
LCX	18(30)
% Diameter stenosis range	30-70

Table 3. Procedural Characteristics. Data are presented as n (%) where appropriate. FFR, fractional flow reserve; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

3.2.1 FFR values

The physiological assessment summary of the vessels is displayed in **Table 4**. Of the 60 lesions included, the mean value of FFR was 0.83±0.3 and the median value was 0.88 (0.78-0.93). Out of the total of 22 lesions (36%) with pathological FFR values (FFR $\leq$ 0.80), 13 (59%) were found in the LAD, 3 (14%) in the LCX and 6 (27%) in the RCA. In addition, 17 FFR values were inside the gray zone of 0.75–0.85.

Table 4. Physiological Assessment	n (%)
Mean invasive FFR	0.83±0.3
Median invasive FFR	0.88 (0.78-0.93)
FFR ≤0.80	22(36)
LAD	13(59)
LCX	3(14)
RCA	6(27)
FFR = [0.75–0.85]	17(28)
Mean FFR_{angio}^{TM}	0.82±0.12
Median FFR_{angio}^{TM}	0.86 (0.74-0.92)
FFR_{angio}^{TM} ≤0.80	22(36)
LAD	13(59)
LCX	4(18)
RCA	5(23)
FFR_{angio}^{TM} = [0.75–0.85]	12(20)

Table 4. Physiological Assessment. Data are presented as n (%) where appropriate. FFR, fractional flow reserve measured by pressure guidewire; FFRangio, fractional flow reserve measured by FFRangio device; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

3.2.2 FFRangio values

The mean FFRangio value was 0.82±0.12, with a median of 0.86 (0.74-0.92) and 22 vessels (36%) had pathological FFRangio values (≤ 0.80). Pathological FFRangio values were found most frequently in the LAD (59%), followed by the RCA (23%) and the LCX (18%).

3.2.3 FFRangio diagnostic performances

The performance of FFRangio per vessel was as follows: sensitivity of 95.5% (95% confidence interval [CI]: 77.1% to 99.9%), specificity of 97.4% (95% CI: 86.2% to 99.9%) and diagnostic accuracy of 96.7% (95% CI: 88% to 99.6%) **(Table 5)**. The positive predictive value was 95.5% (95% CI: 75.2% to 99.3%), the negative predictive value was 97.4% (95% CI: 84.5% to 99.6%) and the diagnostic accuracy was 96.7% (95% CI: 88% to 99.6%).

3.2.4 Correlation between FFR and FFRangio

The Pearson correlation coefficient between invasive FFR and FFRangio was 0.82 ($p < 0.001$). **Figure 2**. Additionally, the Bland–Altman plot demonstrated 95% confidence limits between −0.12 and 0.10 for the absolute differences **Figure 3**.

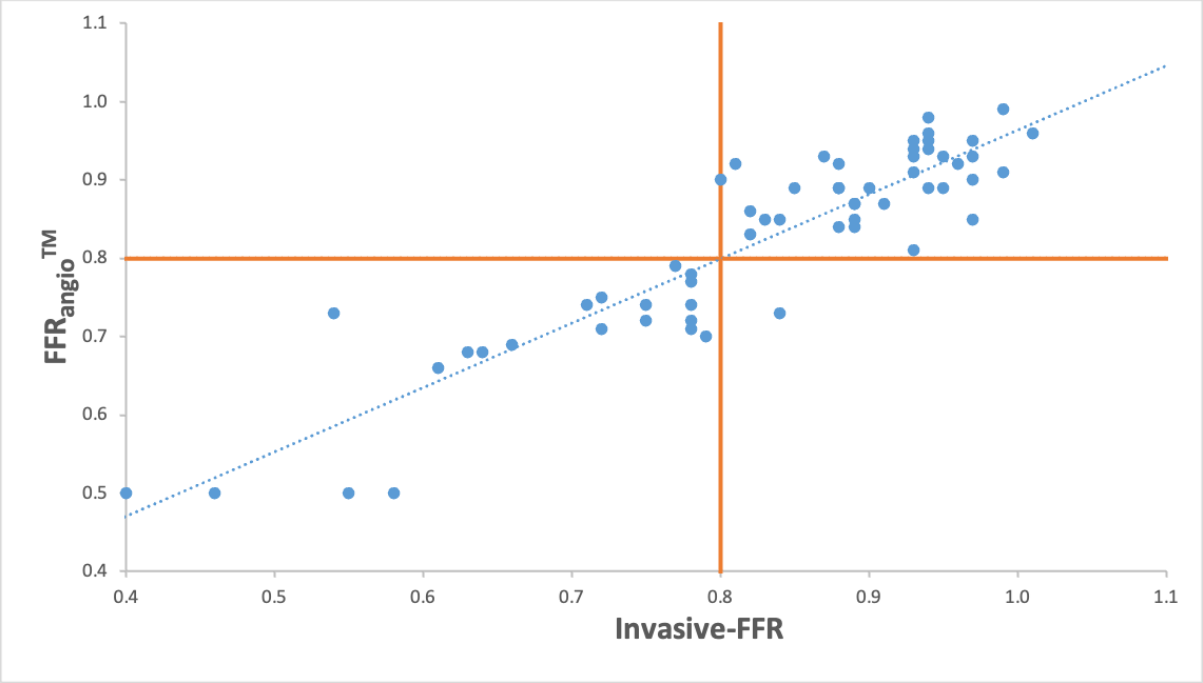

Figure 2. Correlation between FFR and FFRangio. Correlation scatter plot with linear regression, Pearson's r=0.82, P<0.001. FFR, fractional flow reserve measured by pressure guidewire; FFRangio, fractional flow reserve measured by FFRangio device.

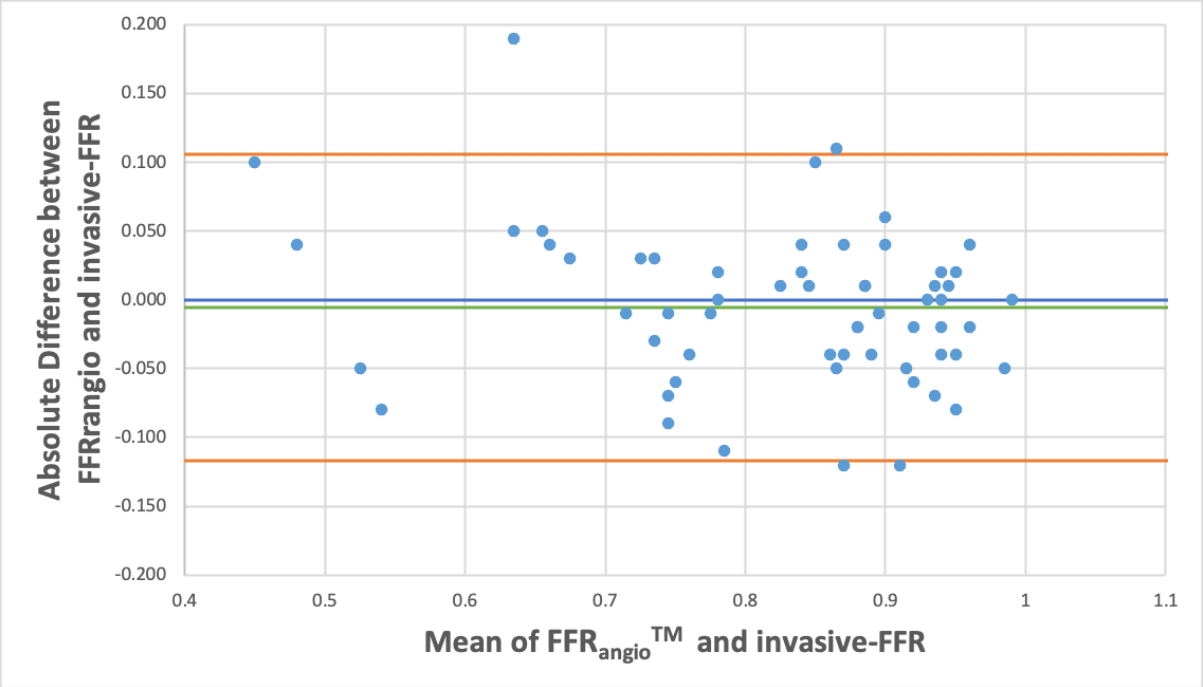

Figure 3. Bland–Altman plot. Bland–Altman plot with 95% confidence limits between −0.12 and 0.10 for the absolute differences. FFR, fractional flow reserve measured by pressure guidewire; FFRangio, fractional flow reserve measured by FFRangio device.

3.2.5 FFRangio diagnostic performances according to vessel

The per coronary artery analysis of FFRangio diagnostic performance was calculated. For the LAD, FFRangio demonstrated a sensitivity of 100% (95% CI: 75.3% to 100%), a specificity of 100% (95% CI: 71.5% to 100%) and a diagnostic accuracy of 100% (95% CI: 85.8% to 100%). The LCX demonstrated a sensitivity of 100% (95% CI: 29.2% to 100%), a specificity of 93.3% (95% CI: 68.1% to 99.8%) and a diagnostic accuracy of 94.4% (95% CI: 72.7% to 99.9%) The RCA demonstrated a sensitivity of 83.3% (95% CI: 35.8% to 99.6%), a specificity of 100% (95% CI: 73.5% to 100%) and a diagnostic accuracy of 94.4 (95% CI: 72.7% to 99.9%) **(Table 5).**

3.2.6 FFRangio diagnostic performances in gray zone of FFR values [0.75–0.85]

Within the gray zone, FFRangio had a sensitivity of 80.0 (95% CI: 28.4% to 99.5%), a specificity of 85.7 (95% CI: 42.1% to 99.6%) and a diagnostic accuracy of 83.3 (95% CI: 44.6% to 96.9%) **(Table 5).**

Of note, the only false positive and the only false negative of the whole study were found inside the gray zone of FFR (0.75–0.85). Regarding the false negative result, the invasive FFR was at 0.80, exactly at the limit of positivity, and the FFRangio was at 0.90. This discrepancy was possibly attributed to a tortuosity compared with vessel overlapping in one of the 3 images that were used for the FFRangio measurement. When only considering values outside of the gray zone (<0.75, >0.85), FFRangio demonstrated a diagnostic accuracy, sensitivity and specificity of 100%.

Table 5. Diagnostic performance of FFRangio

Per lesion analysis	**% (95% CI)**
Sensitivity	95.5 (77.1 to 99.9)
Specificity	97.4 (86.2 to 99.9)
Diagnostic Accuracy	96.7 (88.0 to 99.6)
Positive Predictive Value	95.5 (75.2 to 99.3)
Negative Predictive Value	97.4 (84.5 to 99.6)
Per artery analysis	
LAD	
Sensitivity	100 (75.3 to 100)
Specificity	100 (71.5 to 100)

Diagnostic Accuracy	100 (85.8 to 100)
LCX	
Sensitivity	100 (29.2 to 100)
Specificity	93.3 (68.1 to 99.8)
Diagnostic Accuracy	94.4 (72.7 to 99.9)
RCA	
Sensitivity	83.3 (35.9 to 99.6)
Specificity	100 (73.5 to 100)
Diagnostic Accuracy	94.4 (72.7 to 99.9)
Gray zone of FFR = [0.75–0.85]	
Sensitivity	80.0 (28.4 to 99.5)
Specificity	85.7 (42.1 to 99.6)
Diagnostic Accuracy	83.3 (44.6 to 96.9)
Beyond gray zone of FFR (<0.75, >0.85)	
Sensitivity	100 (80.5 to 100)
Specificity	100 (88.8 to 100)
Diagnostic Accuracy	100 (92.6 to 100)

Table 5. Diagnostic performance of FFRangio. Per lesion and per coronary artery analysis for the total of sample size as well as analysis of the gray zone of FFRangio = [0.75–0.85] Results are % and 95% CI. FFR, fractional flow reserve measured by pressure guidewire; FFRangio, fractional flow reserve measured by FFRagio technology; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

3.3 Discussion

In this prospective, single center, double blinded validation study in NSTEMI patients, FFRangio displayed high diagnostic performance with values for sensitivity, specificity, positive predictive value, negative predictive value and accuracy all being greater than 95% compared to FFR. **(Figure 4)**

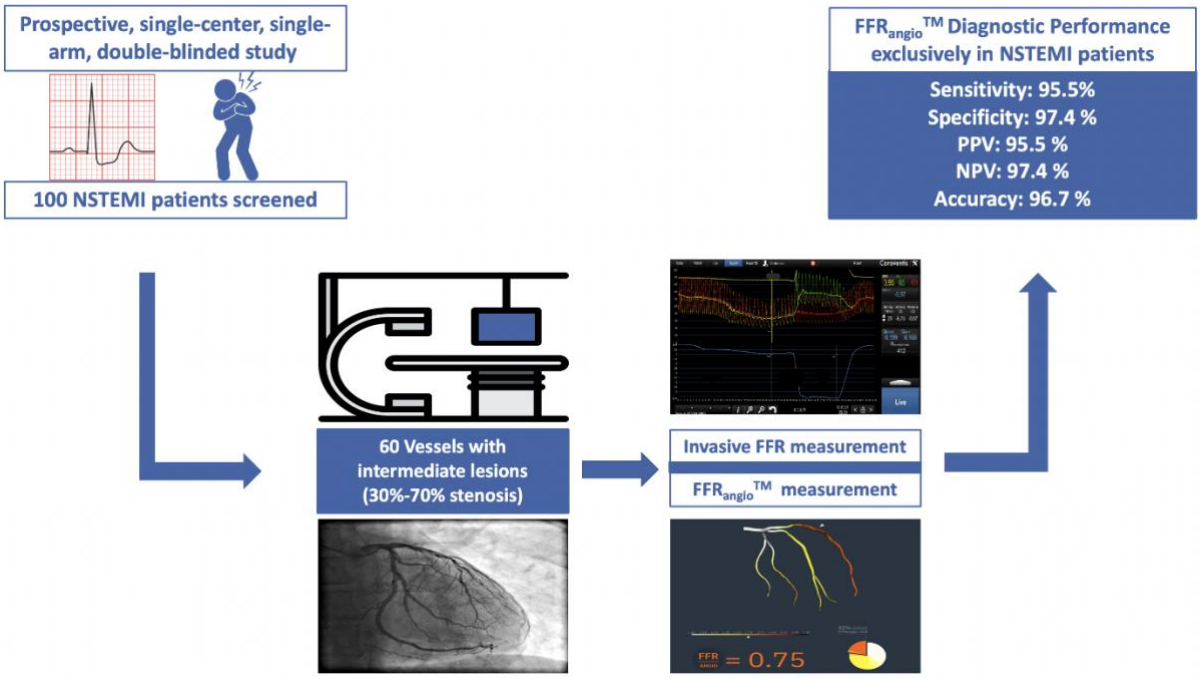

Figure 4. FFRangio Performance in NSTEMI patients. A prospective, single-center, single-arm, double-blinded study showing excellent diagnostic performance of FFRangio in patients presenting with NSTEMI compared to the invasive-measured FFR as gold standard.

To the best of our knowledge, this is the first study focusing on the validation of FFRangio in patients with NSTEMI. FFRangio exhibited a strong correlation with FFR , with a performance that was slightly greater than seen in previous validation studies that included predominantly

patients with stable coronary artery disease. In addition, FFRangio exhibited a strong correlation with FFR.

Despite the fact that previous studies have demonstrated the good diagnostic performance of FFRangio in ACS patients, these studies included both unstable angina and NSTEMI patients. To date, no study has specifically addressed the performance of FFRangio in a population of only NSTEMI patients. For example, a pooled analysis by Witberg et al confirm the excellent performance of FFRangio with a sensitivity of 91% and a specificity of 94%. However, only 10.7% of the included patients had a diagnostic of NSTEMI. Moreover, the FAST-FFR study also enrolled patients with stable coronary disease and ACS (unstable angina and NSTEMI) and found a sensitivity and specificity at 94% and 91% respectively. Nevertheless, only 28 NSTEMI patients were included in the study and the accuracy in this population wasn't evaluated separately. In 2020, Kobayashi et al performed a post-hoc analysis of the FAST-FFR study in order to investigate whether specific patient/lesion characteristics affect the diagnostic performance. Among patients presenting with ACS (unstable angina and NSTEMI) the sensitivity was 93.8% and the specificity was 88.2%, but again without measuring performance specifically in NSTEMI patients. To summarize, previous studies have demonstrated the impressive performance of FFRangio in mixed ACS populations containing both NSTEMI and UA, but without evaluating performance in NSTEMI patients alone like in the present study.

The results of the present study, demonstrate the potential of FFRangio as a tool that could be used to guide treatment decisions in NSTEMI patients with angiographically intermediate coronary artery lesions. Our study suggests that FFRangio introduces an easy, fast and precise alternative to FFR that could result in an improved uptake of physiological testing among patients evaluated in the catherization laboratory, with more lesions being evaluated per patient, whilst avoiding the risks associated with FFR. The treatment of culprit lesions in

NSTEMI patients can be time consuming and the possibility to use FFRangio “offline” after PCI to assess the hemodynamic impact of non-culprit lesions is of particular interest.

Future randomized trials evaluating FFRangio-guided treatment of coronary artery disease (stable or ACS) are now needed to defnitively establish the role of FFRangio in the physiological assessment of coronary lesions.

3.4 Limitations

The present study has several limitations. First of all, the total sample size was relatively small as its population presented a subgroup of patients recruited for the FFR-CT study, with the same inclusion and exclusion criteria as this main study, thus limiting the number of NSTEMI patients that could potentially be included. Supplemental Material The main reasons for exclusion from the study were: previous stents, CABG, renal insufficiency, and elevated heart rate (>60 beats per second) which affected the feasibility and quality of the CT scan. On the other hand, although restricting the sample size, it also gives credibility to the current prospective study that followed respectfully a constructive and meticulous research protocol, the design and rationale of which has been previously published. Moreover, the total amount of FFRangio measurements were calculated by the same blinded physician. Measurement by different users could potentially reproduce slight variations for the FFRangio result. Even though FFRangio system and algorithm are mainly automated, there is a final user-dependent correction phase during the calculation of FFRangio. Finally, the study does not report the time needed to complete the FFRangio measurement, from the beginning of the image transfer to the final FFRangio report. In spite of the fact that the blinded physician using the FFRangio

machine had already completed the measurement before the invasive method estimation, a more time-focused head-to-head comparison of the two different methods could be of interest.

3.5 Conclusion

FFRangio represents a modern, noninvasive method of estimating FFR that has demonstrated excellent diagnostic performance among patients presenting with NSTEMI when compared with the gold standard, FFR, especially outside of the gray zone 0.75–0.85. The current study strengthens the growing body of evidence for the excellent diagnostic performance of FFRangio, thus providing more confidence in the use of FFRangio for the physiological assessment of angiographically intermediate coronary artery lesions in NSTEMI patients. Future randomized control trials comparing FFRangio-guided treatment with FFR-guided treatment in the setting of NSTEMI are required to confirm the performance and role of FFRangio in the management of this specific population.

4. Part 2: Head-to-Head Comparison of Two Angiography-Derived Fractional Flow Reserve Techniques in Patients with High-Risk Acute Coronary Syndrome: A Multicenter Prospective Study

4.1 Methods

4.1.1 Study population

We performed a prospective, multicenter (University of Crete, Greece, Lausanne University Hospital, Switzerland and OLV Aalst, Belgium), single-arm, double-blinded study. The present work is a post-hoc analysis of a study whose design has been previously published, aiming to evaluate the diagnostic performance of computed tomography-derived FFR (FFR-CT) in high-risk ACS patients. In brief, the main study enrolled adult patients admitted with a suspicion of high-risk ACS with positive cardiac biomarkers and symptoms of ischemia. Main exclusion criteria were STEMI, severe renal failure, pregnant and breast-feeding women, patients with prior coronary artery bypass grafting (CABG) or previous stenting, or known severely reduced left ventricular ejection fraction. Importantly, patients with one or more very high-risk criteria as defined by current European and American high-risk ACS guidelines were excluded. The present sub-study included only patients with at least one stenosis 30%-70% by visual estimation. All patients provided written informed consent prior to enrollment. Detailed inclusion/exclusion criteria of the study are reported in the **Table 1.**

4.1.2 Study procedures

The standard procedure for diagnostic coronary angiography was carried out in accordance with local guidelines. The cine frame rate was set at a minimum of 10 frames per second. To

ensure accuracy, operators were advised to capture three different projections with a minimum 30-degree separation for a stenosis ranging between 30-70% before proceeding with FFR. The C-arm's exact angle was left to the operator's discretion. FFR was measured in the respective lesions by an interventional cardiologist according to standard practice. The PressureWire™ X Guidewire (Abbott, Chicago, Illinois, USA) was used to measure FFR in each lesion with a visual diameter stenosis between 30%-70%. Prior to all measurements, the pressure wire and aortic pressure were equalized at the guide catheter's tip. Afterward, the pressure wire was advanced distal to the stenosis, and hyperemia was induced using intracoronary adenosine (150 mcg for the right coronary artery and 200 mcg for the left descending or the circumflex coronary arteries).

4.1.3 FFRangio measurement

The DICOM (Digital Imaging and Communications in Medicine) files were transferred directly via internal PACs system to the FFRangio console. The FFRangio was measured offline for all patients twice (by two physician operators who were blinded to the FFR results and blinded to the results of each other). More specifically, the operators entered the mean aortic pressure of the patient, which was specifically the one recorded immediately prior to the administration of intracoronary adenosine for the invasive FFR measurement, selected the artery of interest by designating the responsible lesion and identified the three most optimal frames of each DICOM according to cardiac phase synchronization and visibility of the lesion. The FFRangio system then automatically created a 3D reconstruction of the coronary arteries designated by the operator based on the previous parameters.

4.1.4 QFR measurement

The DICOM angiograms were transferred directly via internal PACs system to the software package QAngio XA 3D. The QFR was measured offline for all patients twice (by the same two physician operators who were blinded to the FFR results and to the results each other). Two angiographic projections at least 25 degrees apart were selected according to each target vessel. The investigators identified 1 or 2 anatomic landmarks (e.g., bifurcations) as reference points for matching location information in the 2 frames and subsequently indicated the most proximal site and the most distal site of the vessel. Vessel contours were automatically detected and manually corrected if needed. The software reconstructed a 3D anatomic vessel model without its side branches for the 3D quantitative coronary angiographic analysis and for the QFR computation. Final QFR values were obtained computing 3D-QCA and TIMI frame counting.

4.1.5 Definitions

FFRangio and QFR were measured in the same position as FFR using the recorded position of the pressure wire. FFRangio and QFR values were defined as the average value measured offline by the two blinded operators (that had equal experience in using both software) and were then compared to the FFR result for each lesion. A hemodynamically significant lesion was defined as a lesion with an FFR value of ≤ 0.80.

4.1.6 Endpoints

The two co-primary endpoints were the comparison of the Pearson correlation coefficient between FFRangio and QFR with FFR and well as the comparison of their inter-observer variability.

The usual key performance indicators (accuracy, sensitivity, specificity, positive and negative predictive value) of FFRangio and QFR compared to FFR were also reported and the diagnostic performance of FFRangio and QFR in the "grey zone" of FFR values [0.75-0.85] was also investigated.

4.1.7 Statistical methods

Continuous variables were expressed as mean ± SD, and continuous variables were expressed as absolute numbers and percentages. Categorical patient characteristics were presented as percent frequency, and continuous characteristics were presented as mean mean ± SD or median with interquartile range. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy of FFRangio and QFR were calculated, using FFR as the gold standard. The FFRangio and QFR results for each lesion were classified as true/false positive or true/false negative (using FFR as the reference standard and a value of ≤0.80 as the threshold for functionally significant lesions for both modalities). To explore the agreement between FFRangio QFR and FFR, Bland–Altman analyses were plotted, and the 95% limits (1.96 ∗ SD) of agreements were calculated. A Pearson correlation coefficient between FFR, FFRangio and QFR was reported and values were compared using the Fisher's r to z transformation, a statistical method widely used for the purpose of comparing correlation coefficients. A p value <0.05 was considered statistically significant. Statistical analysis was performed with the SPSS Statistics (version 28.0.1, SPSS Inc., Chicago, Illinois, United States).

4.2 Results

Between August 2019 and March 2022, a total of 134 HIGH-RISK ACS patients were included in the main study and were screened for inclusion in the current study. Of the 134 patients screened, 59 patients had one or more intermediate coronary lesion (diameter stenosis of 30-70%) evaluated using FFR. The baseline clinical characteristics of these patients are displayed in **Table 6**. The mean age was 64 ±9.3, 68% were male, and the mean body mass index was 28 ±4.3 kg/m^2.

Characteristic	**n (%)**
Age, y	64±9.3
Male gender, n (%)	40 (67.7)
Body mass index, kg/m2	28 ±4.3
Hypertension, n (%)	33 (55.9)
Hypercholesterolemia, n (%)	39 (66.1)
Smoking (current or former), n (%)	43 (72.8)
Diabetes mellitus (Type I or Type II), n (%)	14 (23.7)
Dyslipidemia, n (%)	40 (67.7)

Table 6. Baseline characteristics. Data are presented as n (%) where appropriate.

Among the 59 patients included in the study, a total of 84 lesions underwent physiological assessment (FFR). The same 84 lesions were also functionally evaluated with FFRangio and QFR. FFR was measured in 1.4 vessels per patient and 23 patients had FFR measured in more than one vessel. The artery most frequently evaluated was the left anterior descending (41%), followed by the right coronary artery (33%) and the left circumflex artery (26%). The procedural characteristics of the vessels are reported in **Table 7.**

Angiographic findings	**n (%)**
Lesions per patient	1.4±0.16
Target vessel	
LAD	34 (41)
RCA	28 (33)
LCX	22 (26)
% Diameter stenosis range	30-70

Table 7. Angiographic Characteristics. Data are presented as n (%) where appropriate. FFR, fractional flow reserve; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

4.2.1 FFR values

The physiological assessment summary of the vessels is displayed in **Table 8.** Of the 84 lesions included, the mean value of FFR was 0.82±0.40. Out of the total of 32 lesions (38%) with pathological FFR values (FFR $\leq$ 0.80), 17 (53%) were found in the LAD, 7 (22%) in the LCX and 8 (25%) in the RCA. In addition, 20 FFR values were inside the grey zone of 0.75–0.85.

Method used	**n (%)**
Invasive FFR	
Mean invasive FFR	0.82±0.4
FFR ≤0.80	32 (38)
LAD	17 (53)
LCX	7 (22)
RCA	8 (25)
InvasiveFFR = [0.75–0.85]	20 (24)
FFRangio	
Mean FFRangio	0.82±0.2
FFRangio ≤0.80	27 (32)
LAD	15 (56)
LCX	6 (22)
RCA	6 (22)
FFRangio = [0.75–0.85]	19 (22)
QFR	
Mean QFR	0.82±0.3
QFR ≤0.80	25 (36)
LAD	13 (52)
LCX	6 (24)
RCA	6 (24)
QFR = [0.75–0.85]	16 (19)

Table 8. Physiological Assessment. Data are presented as n (%) where appropriate. FFR, fractional flow reserve measured by pressure guidewire; FFRangio, fractional flow reserve

measured by FFRangio device; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; QFR, fractional flow reserve measured by quantitative flow ratio

4.2.2 FFRangio values

The mean FFRangio value was 0.82±0.2 and 27 vessels (32%) had pathological FFRangio values (≤ 0.80). Pathological FFRangio values were found most frequently in the LAD (56%), followed by the RCA and the LCX (22% each). In addition, 19 FFRangio values were inside the grey zone of 0.75–0.85. (**Table 8)**

4.2.3 FFRangio diagnostic performances

The performance of FFRangio per vessel was the following: sensitivity of 84.4% (95% confidence interval [CI]: 67.2% to 94.7%), specificity of 100 % (95% CI: 93.2% to 100%) and diagnostic accuracy of 94.1% (95% CI: 86.7% to 98.1%) **(Table 9).** The positive predictive value was 100% (95% CI: 87.2% to 100%) and the negative predictive value was 91.2% (95% CI: 80.7% to 97.1%). The Pearson correlation coefficient between FFR and FFRangio was 0.76 (**Figure 5A**). Additionally, the Bland–Altman plot demonstrated 95% confidence limits between −0.13 and 0.11 for the absolute differences **(Figure 6A).** In total, 5 (5.9%) lesions were misclassified and all of them were false negative (positive FFR but negative FFRangio), 3 of them belonging to the grey zone of FFR.

Performance parameter	FFRangio	QFR
Per lesion analysis % (95% CI)		
Sensitivity	84.4 (67.2 to 94.7)	75 (56.6 to 88.5)
Specificity	100 (93.2 to 100)	98.1 (89.7 to 99.9)
Diagnostic Accuracy	94.1 (86.7 to 98.1)	82.3 (80.6 to 94.9)
Positive Predictive Value	100 (87.2 to 100)	96 (79.7 to 99.9)
Negative Predictive Value	91.2 (80.7 to 97.1)	86.4 (75.1 to 93.9)
Grey zone of FFR = [0.75–0.85]		
Sensitivity	72.7 (39.1 to 93.9)	63.64 (30.8 to 89.1)
Specificity	100 (66.4 to 100)	100 (63.1 to 100)
Diagnostic Accuracy	85 (62.1 to 96.8)	78.9 (54.4 to 93.9)

Table 9. Diagnostic performance. Per lesion and per coronary artery analysis for the total of sample size as well as analysis of the grey zone of FFRangio = [0.75–0.85] Results are % and 95% CI. FFR, fractional flow reserve measured by pressure guidewire; FFRangio, fractional flow reserve measured by FFRangio device; QFR, fractional flow reserve measured by quantitative flow ratio, LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery, QFR, fractional flow reserve measured by quantitative flow ratio

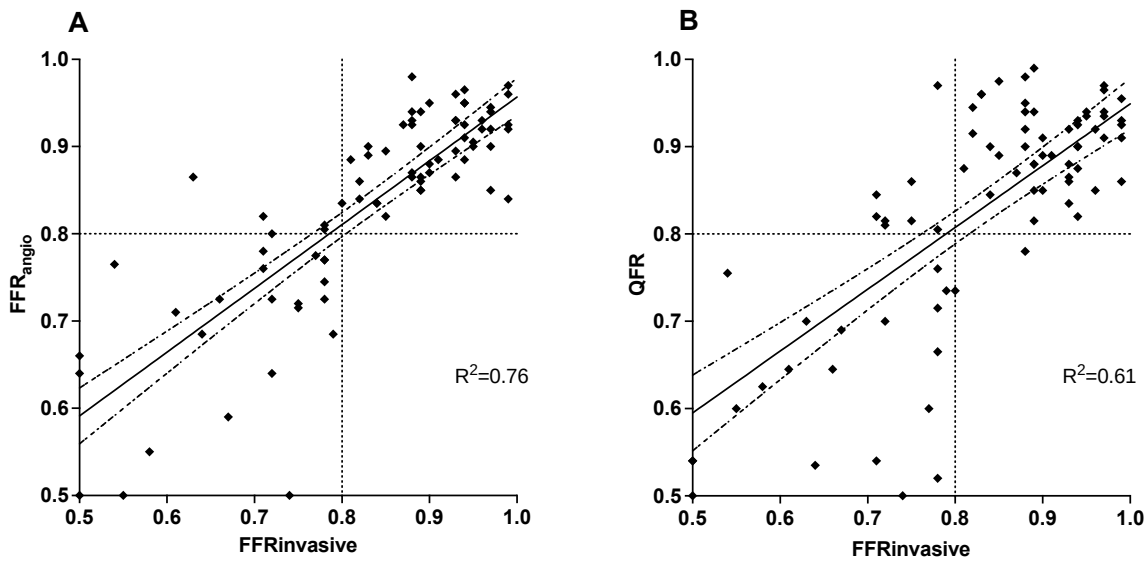

Figure 5. Correlation between FFR and FFRangio (A) and correlation between FFR and QFR (B). Figures 1A and 1B display the correlation scatter plot with a linear regression and 95% CI, the Pearson coefficient is reported. FFRangio; fractional flow reserve measured by FFRangio device; QFR, fractional flow reserve measured by quantitative flow ratio

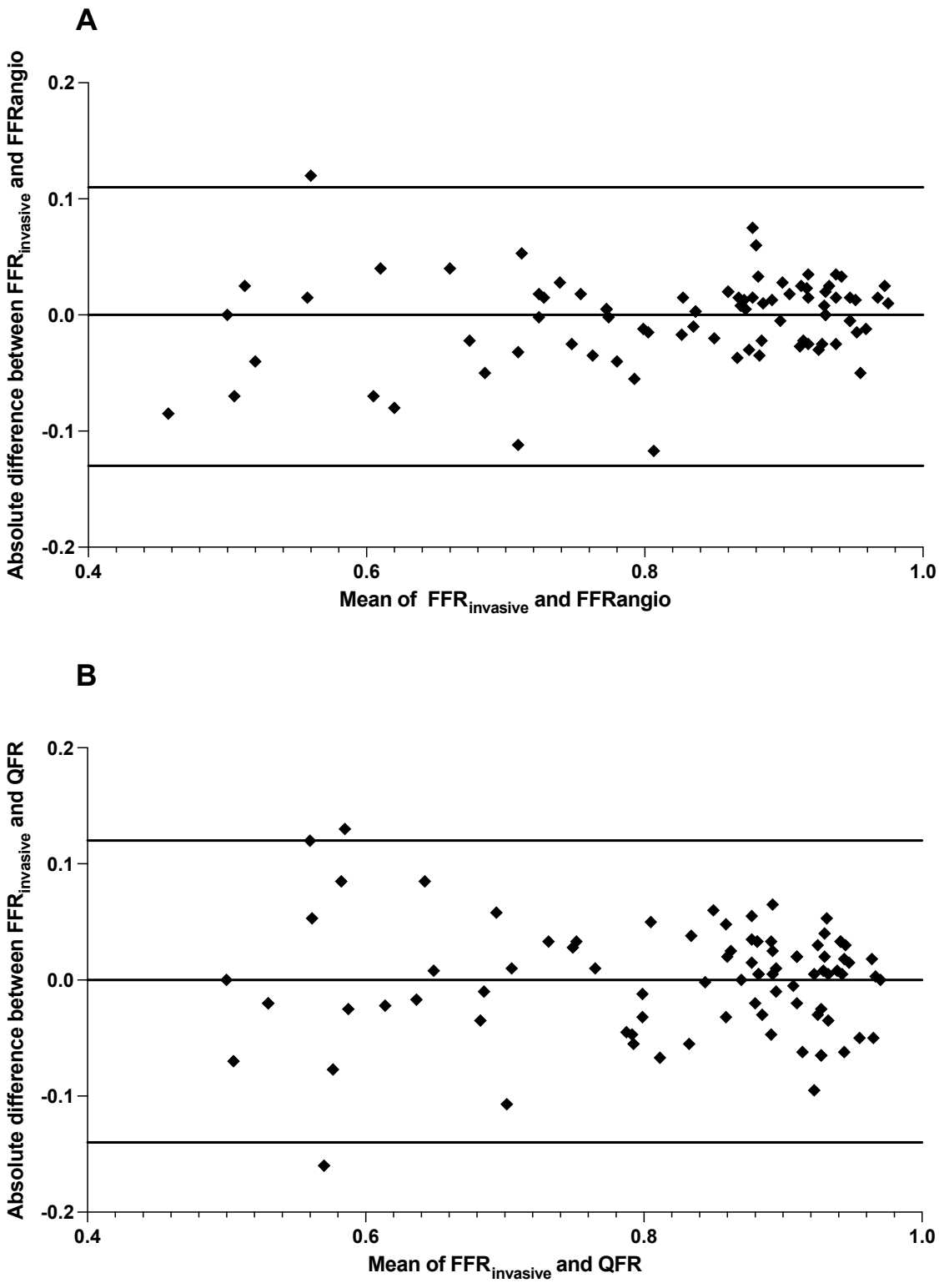

Figure 6. Bland–Altman plot for FFR and FFRangio (A) and for FFR and QFR (B).

Bland–Altman plot with 95% confidence limits between for the absolute differences

4.2.4 FFRangio diagnostic performances in grey zone of FFR values [0.75–0.85]

Within the grey zone, FFRangio had a sensitivity of 72.7% (95% [CI]: 39.1% to 93.9%), a specificity of 100% (95% [CI]: 66.4% to 100%) and a diagnostic accuracy of 85% (95% [CI]: 62.1% to 96.8%) **(Table 8)**.

4.2.5 QFR values

The mean QFR value was 0.82±0.2 and 27 vessels (32%) had pathological QFR values (≤ 0.80). Positive QFR values were found most frequently in the LAD (52%), followed by the RCA and the LCX (24% each). Moreover, 16 QFR values were inside the grey zone of 0.75–0.85. (**Table 8)**

4.2.7 QFR diagnostic performances

The performance of QFR per vessel was the following: sensitivity of 75% (95% confidence interval [CI]: 56.6% to 88.5%), specificity of 98.1 % (95% CI: 89.7% to 99.9%) and diagnostic accuracy of 94.1% (95% CI: 86.7% to 98.1%) **(Table 9).** The positive predictive value was 96% (95% CI: 79.7% to 99.9%) and the negative predictive value was 89.4% (95% CI: 75.1% to 93.9%). The Pearson correlation coefficient between invasive FFR and QFR was 0.61 ($p < 0.001$). (**Figure 5B**). Additionally, the Bland–Altman plot demonstrated 95% confidence limits between −0.14 and 0.12 for the absolute differences **(Figure 6B).** In total, 9 lesions (10.7%) were misclassified. Out of them, 8 were false negative (positive FFR) with 7 of them belonging to the grey zone of FFR.

4.2.8 QFR diagnostic performances in grey zone of FFR values [0.75–0.85]

Within the grey zone, QFR had a sensitivity of 63.6% (95% [CI]: 30.8% to 89.1%), a specificity of 100% (95% [CI]: 66.4% to 100%) and a diagnostic accuracy of 78.9% (95% [CI]: 54.4% to 93.9%) **(Table 9)**.

4.2.9 Comparison between FFRangio and QFR correlation

The Pearson correlation coefficient demonstrated a significantly higher value for FFRangio compared to QFR (0.76 vs 0.61, $p < 0.001$). The inter-observer agreement was also significantly better for FFRangio compared to QFR (0.86 vs 0.79, $p < 0.05$). **(Figure 5)**

4.3 Discussion

This is the first study comparing these 2 different angiography-derived FFR modalities. FFRangio and QFR have been evaluated in a growing number of studies assessing their performance in various context including high-risk ACS. In this context, prior studies demonstrated good diagnostic performance for both modalities, but no head-to-head comparison has been reported to date. In this prospective, multi center, double blinded validation study, the 2 most studied angiography-derived FFR techniques, showcased high diagnostic performance and even demonstrated higher specificity compared to previous studies in the literature. Here, interestingly, FFRangio showed a significantly better correlation to invasive FFR in comparison to the one of QFR with a better inter-observer agreement, even if the number of misclassified stenoses appears to be comparable.

The high specificity observed in this study has implications for clinical practice. By reducing the likelihood of unnecessary invasive procedures in patients without hemodynamically significant lesions, these angiography-derived FFR tools can contribute to improved patient safety and resource allocation. Unnecessary invasive procedures not only pose potential risks and complications to patients but also increase healthcare costs.

Regarding the misclassification of lesions, it is noteworthy that almost all the misclassified lesions were false negatives, indicating a failure to identify hemodynamically significant lesions. However, it is important to consider that most of these misclassified lesions were within the grey zone of FFR values (0.75-0.85), where the decision to proceed with revascularization or adopt a conservative treatment approach is less clear-cut. In these cases, a conservative treatment strategy could still be considered. Finally, while our study design does not allow us to definitively determine why one technique outperforms the other, we can offer plausible explanations based on the technical aspects of each method. It is important to note that FFRangio and QFR employ fundamentally different approaches to calculate non-invasive FFR, which might contribute to the observed performance differences.

A key technical distinction is that FFRangio requires three diagnostic coronary angiography projections for its calculation, whereas QFR typically uses only two. This additional projection in FFRangio allows for a more comprehensive vessel analysis, including detailed assessment of de novo lesions, ostium localization, and thorough contouring of the lesion as well as the proximal and distal segments of the analyzed vessel. This approach, by incorporating more measurements, potentially offers a more robust analysis, minimizing the margin of error and enhancing the accuracy of the FFR estimation.

4.4 Limitations

The current study has a certain number of limitations. Importantly, the sample size was limited since these patients represent a subset of a larger study. The main reasons for exclusion from the study were previous stents, CABG, renal insufficiency, and elevated heart rate (>60 beats per second), which affected the feasibility and quality of the CT scan (main study). This rigorous patient selection however strengthens the findings these patients come from a homogenous population systematically selected according to a previously published research protocol. Further studies including a larger number of ACS patients will be reassuring and would more confidently support a potential superiority of FFRangio vs QFR in this setting. As this study was designed with the specific intent of conducting FFRangio and QFR measurements, coronary angiography was performed accordingly. It's important to acknowledge that our results may not readily apply to measurements conducted offline or retrospectively, especially when coronary angiography was not initially planned for non-invasive FFR assessment. This potential limitation stems from variations in measurement conditions and procedural objectives, impacting the generalizability of our results. It must also be noted that the time required to complete the QFR and FFRangio measurement, from the start of the image transfer to the final result was not recorded. Moreover, unlike QFR, FFRangio requires a mean arterial pressure value, which can fluctuate during the procedure, especially with nitroglycerine administration. The optimal pressure for routine FFRangio measurements remains undefined and could potentially affect the result. Furthermore, possible limitation stems from the microvascular involvement in ACS, which is not accounted for by FFrangio. It would be expected to result in positive invasive FFR but negative FFRangio. While theoretical expectations align with our study's 100% PPV and 91% NPV, this specific scenario occurred only five times (resulting in five false negatives), making it challenging to extrapolate general conclusions from this limited dataset. Finally, it would be of interest to compare the potentially

different learning curves between the two modalities among different operators in order to evaluate the level of user-dependency and familiarity.

4.5 Conclusion

In this head-to-head comparison of the diagnostic performance of QFR and FFRangio, both demonstrated excellent diagnostic performance among patients presenting with high-risk ACS compared to invasive FFR. There was a significant difference in the correlation coefficient in favor of FFRangio. The current study reinforces the existing evidence regarding the diagnostic performance of angiography-derived FFR. This might foster the application of physiological evaluation in angiographically intermediate coronary artery lesions among high-risk ACS patients.

5. Cumulative Discussion

Acknowledging the fact that FFR is currently underutilized due to its invasive nature, which necessitates the administration of hyperemic agents, incurs significant costs, and demands considerable time, we embarked on a comprehensive endeavor in 2019. This prospective, double-blinded validation and comparison study sought to address the pressing need for alternative, non-invasive angiography-based techniques. These emerging methodologies hold immense promise in overcoming the inherent limitations associated with traditional FFR procedures. Over the course of approximately five years, spanning from the initial submission of protocols to the ethical committee to the meticulous analysis and subsequent publication of findings, our research endeavor unfolded. This extensive timeline allowed us to delve deeply into the nuances of novel non-invasive angiography-derived FFR technologies, providing invaluable insights that could potentially revolutionize clinical practice.

Our study cohort comprised a diverse range of patients admitted to the hospital with NSTEMI, a population particularly vulnerable to the challenges posed by invasive procedures. The meticulous design of our study, meticulously outlined and formally published in the International Journal of Cardiology: Heart & Vasculature in 2020, laid the groundwork for a rigorous examination of these groundbreaking technologies (Meier D, Skalidis I et al. Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS admitted in the emergency department with chest pain, study design and rationale. Int J Cardiol Heart Vasc. 2020 Mar).

In our Part 1 phase, we set out to evaluate the diagnostic performance of FFRangio exclusively within the NSTEMI population, marking a pioneering endeavor in the annals of medical literature. The results yielded remarkable insights, showcasing exemplary diagnostic accuracy with commendably high sensitivity, specificity, and accuracy. Notably, even within the

nebulous terrain of FFR gray zones (ranging from 0.75 to 0.85), FFRangio exhibited remarkable proficiency, demonstrating a robust correlation with invasive FFR measurements. These findings were not only instrumental in expanding the existing body of evidence but also shed light on the potential of FFRangio in navigating the complexities of acute coronary syndrome without ST elevation.

Building upon the results our Part 1 phase, we endeavored to broaden the scope of our study by collaborating with esteemed institutions such as the Aalst Heart Center of Belgium. This collaborative effort transformed our study into a multicentric endeavor, marking a significant milestone in the realm of cardiac research. By amalgamating data from multiple centers and augmenting our patient cohort, we aimed to achieve a more comprehensive understanding of the comparative efficacy of non-invasive angiography-derived FFR modalities. Moreover, our Part 2expansion entailed a meticulous refinement of methodologies, including the introduction of a second operator for QFR and FFRangio measurements. This strategic enhancement not only fortified the analytical robustness of our study but also underscored our unwavering commitment to methodological rigor and scientific integrity.

The culmination of our efforts, encapsulated in the results of our multicentric study, reaffirmed the reliability and efficacy of non-invasive angiography-derived FFR modalities in the context of NSTEMI. Both FFRangio and QFR demonstrated unparalleled performance metrics, surpassing the benchmarks set by previous studies in the literature. While both modalities exhibited commendable specificity and positive predictive value, FFRangio emerged as the frontrunner, boasting superior sensitivity and negative predictive value. Noteworthy, the correlation coefficient analysis further accentuated the superiority of FFRangio over QFR, highlighting its robust correlation with invasive FFR measurements. Furthermore, the absence of significant inter-observer variability, observed across both FFRangio and QFR measurements, underscores the reproducibility and consistency of these cutting-edge

technologies. This remarkable consistency, irrespective of operator experience, bodes well for the widespread adoption and clinical integration of non-invasive angiography-derived FFR modalities

5.1 Overall Limitations

Our study encountered several limitations, consistent across both parts. Notably, the sample size was constrained as the patients involved constituted a subset of a larger study on FFR-CT. Exclusion criteria were stringent, including prior stents, CABG, renal insufficiency, and elevated heart rate (>60 beats per second), due to their impact on the feasibility and quality of the CT scan in the main study. Despite these limitations, the rigorous selection process led to a cohort of patients homogeneously selected according to a predefined research protocol, enhancing the internal validity of the findings. Future investigations incorporating a larger cohort of patients with ACS would provide additional reassurance and stronger evidence to support any potential superiority of FFRangio over QFR in this clinical context. It's important to note that our study was specifically designed to conduct FFRangio and QFR measurements, with coronary angiography performed accordingly. Thus, the applicability of our results to offline or retrospective measurements, particularly when coronary angiography was not initially planned for non-invasive FFR assessment, may be limited due to variations in measurement conditions and procedural objectives, which could impact the generalizability of our findings. Furthermore, the time taken to complete QFR and FFRangio measurements, from image transfer initiation to obtaining final results, was not documented, which could have provided valuable insights into procedural efficiency. Lastly, investigating potential differences in the learning curves between the two modalities among different operators would be beneficial for evaluating user-dependency and familiarity levels, thus enhancing the understanding of these technologies' clinical implementation and outcomes.

5.2 Scientific Milestones

After extensive research and analysis, the findings of our study were published in reputable peer-reviewed journals and presented at major international cardiology conferences. The Part 1 of our study was published at the Catheterization and Cardiovascular Interventions journal in December 2022, where we reported the outcomes of our study evaluating the diagnostic performance of FFRangio in patients with NSTEMI (Skalidis I et al. Diagnostic performance of angiography-derived fractional flow reserve in patients with NSTEMI. Catheter Cardiovasc Interv. 2022 Dec 28). Regarding this publication, the preliminary and final results were showcased at EuroPCR 2022 in Paris, France, and the European Society of Cardiology Congress 2022 in Barcelona, Spain, respectively. Our research garnered praise from prominent figures in interventional cardiology, including Dr. Morton Kern, Professor at the University of California, who commended our work with an editoral (Kern MJ, Seto AH. Validating angiographically derived FFR in the NSTEMI patient: An important step forward. Catheter Cardiovasc Interv. 2023 Feb 7). Additionally, it was honored with the Otto Hess Trainee Award by the Swiss Society of Cardiology, recognizing it as the best research project in Switzerland led by a cardiology trainee under 32 years old.

In the Part 2 phase of our study, we embarked on comparing the diagnostic accuracy of two distinct non-invasive FFR techniques, FFRangio and QFR, for the first time in scientific literature. Initial findings were presented at the Transcatheter Cardiovascular Therapeutics (TCT) congress in Boston, Massachusetts, in October 2022, and at the Swiss Society of Cardiology Annual Congress in Basel, Switzerland, in June 2023. The final results, incorporating data from patients treated at the Cardiovascular Center of Aalst in Belgium to enhance the multicentric nature of our study, were unveiled at the European Society of Cardiology Congress in Amsterdam, Netherlands, in August 2023. Moreover, our study was recognized as one of the best abstracts at the Panhellenic Congress of Cardiology by the

Hellenic Society of Cardiology in Thessaloniki, Greece, in October 2023. The conclusive outcomes of our multicentric prospective double-blinded study were formally published in the International Journal of Cardiology in December 2023 (Skalidis I et al. 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, Epub 2023 Dec 21).

6. Future Perspectives

The field of non-invasive image-based angiography-derived FFR modalities is currently experiencing a surge of interest within the interventional cardiology community. These modalities offer promising avenues for research, particularly in their application to chronic coronary syndrome and NSTEMI settings, where existing data supports their accuracy.

6.1 Angiography-derived FFR in Severe Aortic Stenosis

An intriguing area ripe for investigation is their efficacy in cases of valvular heart disease, particularly severe aortic stenosis. A debate exists regarding the reliability of FFR in accurately assessing the hemodynamic severity of coronary lesions when severe aortic stenosis is present. In this context, there's significant interest in exploring the performance of FFRangio and QFR. FFRangio incorporates mean aortic pressure into its algorithm for FFR measurement, which may be influenced by the presence of aortic stenosis. On the other hand, QFR does not rely on this parameter, potentially making it less sensitive to aortic stenosis and thereby enabling more reliable evaluation of CAD before aortic valve replacement. An study by Sehr-Hansen et al. demonstrated promising diagnostic performance of pre- TAVR QFR using post-TAVR FFR as a reference. Currently, a study is underway at the University Hospital of Lausanne in Switzerland to compare FFRangio and QFR specifically in the context of severe aortic stenosis,

with invasive FFR serving as the exclusive reference point in the pre-TAVR setting. The results of this study are anticipated to be available in late 2024.

6.2 Learning curves of angiography-derived FFR

It would be interesting to compare the learning curve of FFRangio and QFR for coronary artery disease physiology evaluation to understand observer dependence and to discern potential differences in accuracy among different health professionals, including interventional cardiologists, fellows, residents, nurses, and medical students. Reduced operator dependence would enhance trust and credibility in these technologies. A sub-study of our project is currently in the analysis phase at the University Hospital of Lausanne in Switzerland, where we aim to compare the learning curve of FFRangio and QFR for coronary artery stenosis assessment based on the progression in analysis speed and accuracy relative to actual invasive results over time. A group of 5 investigators, blinded to invasive values and comprising 2 nurses, 1 medical student, and 2 physicians in training, received similar basic standardized teaching with the two technologies. In total, 270 analyses (54 coronary lesions in 44 patients, from the Part 1 study) were conducted in the same order with QFR and FFRangio. For each analysis, the time to finalize the case and the angiography-based FFR value were recorded, the latter being compared with the invasive gold standard. The results will be published at the European Society of Cardiology Congress in London, United Kingdom, in September 2024.

6.3 Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS

High-risk ACS patients pose a significant diagnostic challenge in cardiology. Clinical assessment and electrocardiograms alone often fall short in confirming or excluding diagnosis. Thus, the inclusion of blood tests, such as troponin, remains pivotal for early diagnosis and subsequent treatment. The advent of high-sensitive troponin (hs-Tn) has revolutionized patient management by enabling early diagnosis. However, nearly 50% of patients with troponin elevations ≤ 3 times the upper limit of normal will have normal coronary angiograms, leading to unnecessary resource utilization and exposure to potential medication side effects. Identifying a non-invasive method to accurately discern patients who may forego coronary angiography could offer substantial resource savings. While FFR-CT is established for diagnosing coronary artery disease in stable angina patients, its application in high-risk ACS cases amidst the hs-Tn era remains unexplored.

The findings from this main study, which encompassed the entire patient cohort and served as the foundation for all the above studies, have been integrated into a larger multicenter patient dataset. A total of 190 patients (102 from Lausanne, 29 from Aalst, 53 from Monzino, and 6 from Brussels) were included, with 570 vessels analyzed using FFR-CT. Among these, 90 patients with 160 vessels underwent invasive FFR measurement that will be the standard of reference. The cardiac CT and FFR-CT results for these vessels are currently undergoing evaluation by an independent CoreLab. The final results will be presented as a late-breaking trial at the European Society of Cardiology Congress in London, United Kingdom, in September 2024.

7. Final Conclusion

Our study contributes to the expanding body of evidence supporting the reliability and precision of novel non-invasive image-based FFR technologies in assessing the hemodynamic severity of coronary artery lesions. Both FFRangio and QFR showcased great diagnostic performance in patients presenting with NSTEMI, slightly surpassing findings from previous studies, and exhibited minimal interobserver variability. Notably, FFRangio demonstrated a stronger correlation with the invasive gold standard FFR compared to QFR. Further investigations with larger sample sizes are necessary to thoroughly explore their performance and establish their significance in advancing the physiological assessment of coronary artery lesions in routine clinical practice within the catheterization laboratory.

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9. Publications in Peer Reviewed Journals

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Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS admitted in the emergency department with chest pain, study design and rationale

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ABSTRACT

Background: In the era of High-sensitive troponin (hs-Tn), up to 50% of patients with a mild increase of hs-Tn will finally have a normal invasive coronary angiogram. Fractional Flow Reserve (FFR) derived from coronary computed tomographic angiography (FFR-CT) has never been used as a non-invasive tool for the diagnosis of coronary artery disease in patients with high-risk acute coronary syndrome without ST segment elevation (NSTE-ACS).
Aims: The study aims to determine the role of coronary CT angiography and FFR-CT in the setting of high-risk NSTE-ACS.
Methodology: We will conduct a prospective trial, enrolling 250 patients admitted with high-risk NSTE-ACS who will rapidly undergo a coronary CT angiography and then a coronary angiography with FFR measurements. Results of coronary CT, FFR-CT and coronary angiography (± FFR) will be compared.
Potential significance: In conclusion, non-invasive identification of patients with high-risk NSTE-ACS who could avoid coronary angiography would reduce procedure related risks and medical costs.

1. Introduction

Patients admitted to the emergency department (ED) for chest pain are a top priority, the early diagnosis of a myocardial infarction (MI) being key for the prognosis of the patient. Unlike myocardial infarction with ST segment elevation (STEMI) where the diagnosis is usually straightforward after electrocardiogram (ECG) analysis, acute coronary syndrome without ST segment elevation (NSTE-ACS) patients represent a major diagnostic challenge. Indeed, clinical assessment and ECG alone are not sufficient to confirm or exclude diagnosis in most patients. Therefore, the addition of blood test such as troponin remains the cornerstone of an early diagnosis and subsequent adequate treatment especially regarding the decision to send the patient to the catheterization laboratory for a coronary angiography. The recent introduction of high-sensitive troponins (hs-Tn) has considerably improved diagnostic sensitivity of NSTE-AC. However, this comes at a cost as a high proportion of these patients will finally have a 'normal' invasive angiography (up to 50% among patients with an increase of troponins of ≤3x the upper range limit (URL) according to the recent fourth universal definition of myocardial infarction from the European guidelines [1]).

As troponin alone seems to be insufficient to correctly identify patients in real need of a coronary angiography, alternative diagnostic strategies are critically needed in order to avoid multiple unnecessary exams. In that sense, the identification on a non-invasive tool able to identify patients in whom coronary

Abbreviations: AE, Adverse Event; ACS, Acute coronary syndrome; CT, Computed tomography; ECG, Electrocardiogram; ED, Emergency department; FFR, Fractional Flow Reserve; FFR-CT, FFR derived from coronary CT; Hs-Tn, High-sensitive troponins; MACE, Major adverse cardiac events; MI, Myocardial infraction; CMRI, Cardiac Magnetic resonance imaging; NSTE-ACS, Acute coronary syndromes without ST-segment elevation; NSTEMI, Non-ST-elevation myocardial infarction; PCI, Percutaneous Coronary Intervention; STEMI, ST-elevation myocardial infarction; URL, Upper Range Limit.

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ORIGINAL ARTICLE - CLINICAL SCIENCE

WILEY

Diagnostic performance of angiography-derived fractional flow reserve in patients with NSTEMI

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Funding information
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Abstract

Noninvasive methods of estimating invasively measured fractional flow reserve ($FFR_{invasive}$) are actively being explored, aiming to avoid the use of an invasive pressure wire and the administration of hyperemia-inducing drugs. Coronary angiography-derived FFR (FFR_{angio}) has already demonstrated its diagnostic performance in the context of stable coronary artery disease. However, its applicability in the context of non-ST-segment elevation myocardial infarction (NSTEMI) has yet to be established. We sought to determine the diagnostic performance of FFR_{angio} exclusively in patients presenting with NSTEMI. We performed a prospective, single-center, single-arm, double-blinded study comparing FFR calculated by FFR_{angio} to $FFR_{invasive}$ in NSTEMI patients. $FFR_{invasive}$ was measured in all angiographically intermediate lesions (30%–70% stenosis) and was then compared to FFR_{angio} which was calculated at the same position, by a blinded operator. The primary endpoints were the sensitivity and specificity of FFR_{angio} for predicting $FFR_{invasive}$ using a cut-off value of ≤0.80. Among 100 NSTEMI patients who were screened, 46 patients with 60 vessels in total underwent $FFR_{invasive}$ and were included in the study. The mean value of $FFR_{invasive}$ was 0.83 ± 0.3 with 22 (36%) being ≤0.80 while the mean FFR_{angio} was 0.82 ± 0.1 with 22 (36%) being ≤0.80. FFR_{angio} exhibited a sensitivity of 95.5%, a specificity of 97.4%, and a diagnostic accuracy of 96.7%. FFR_{angio} can precisely and noninvasively estimate $FFR_{invasive}$ in acute coronary syndromes and may have a role in guiding treatment decisions related to angiographically intermediate coronary lesions in this context.

What is known: FFR_{angio} has demonstrated its diagnostic performance in validation studies, as a noninvasive and cost-effective method in the context of stable coronary artery disease but its performance has never been exclusively evaluated in NSTEMI patients.

Abbreviations: ACS, acute coronary syndrome; FFR, fractional flow reserve; FFR_{angio}, fractional flow reserve derived from coronary angiography; FFR-CT, computed tomography-derived FFR; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; NSTEMI, no-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Ioannis Skalidis and David Meier contributed equally to this study.

Commentary: Expert Article Analysis for: Validating angiographically derived FFR in the NSTEMI patient: An important step forward

Skalidis I, Meier D, De Bruyne B, Collet C, Sonck J, Mahendiran T, Rotzinger D, Qanadli SD, Eeckhout E, Muller O, Fournier S. Diagnostic performance of angiography-derived fractional flow reserve in patients with NSTEMI. Catheter Cardiovasc Interv. 2022 Dec 28. doi: 10.1002/ccd.30526

Catheterization and Cardiovascular Interventions homepage

COMMENTARY | Full Access

Validating angiographically derived FFR in the NSTEMI patient: An important step forward

This article relates to:

Diagnostic performance of angiography-derived fractional flow reserve in patients with NSTEMI

Ioannis Skalidis MD, David Meier MD, Bernard De Bruyne MD, PhD, Carlos Collet MD, PhD, Jeroen Sonck MD, PhD, Thabo Mahendiran MD, David Rotzinger MD, PhD, Salah Dine Qanadli MD, PhD, Eric Eeckhout MD, PhD, Olivier Muller MD, PhD, Stephane Fournier MD, PhD

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Morton J. Kern MD, MSCAI, FACC, FAHA, Arnold H. Seto MD, MPA, FACC, FSCAI

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Head-to-head comparison of two angiography-derived fractional flow reserve techniques in patients with high-risk acute coronary syndrome: A multicenter prospective study

Ioannis Skalidis [a,b,1], Nathalie Noirclerc [a,1], David Meier [a], Wongsakorn Luangphiphat [a], Aurelien Cagnina [a], Sarah Mauler-Wittwer [a], Thabo Mahendiran [a], Bernard De Bruyne [a,c], Alessandro Candreva [d], Carlos Collet [c], Jeroen Sonck [c], Olivier Muller [a], Stephane Fournier [a,*]

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ABSTRACT

Background: FFRangio and QFR are angiography-based technologies that have been validated in patients with stable coronary artery disease. No head-to-head comparison to invasive fractional flow reserve (FFR) has been reported to date in patients with acute coronary syndromes (ACS).
Methods: This study is a subset of a larger prospective multicenter, single-arm study that involved patients diagnosed with high-risk ACS in whom 30–70% stenosis was evaluated by FFR. FFRangio and QFR – both calculated offline by 2 different and blinded operators – were calculated and compared to FFR. The two co-primary endpoints were the comparison of the Pearson correlation coefficient between FFRangio and QFR with FFR and the comparison of their inter-observer variability.
Results: Among 134 high-risk ACS screened patients, 59 patients with 84 vessels underwent FFR measurements and were included in this study. The mean FFR value was 0.82 ± 0.40 with 32 (38%) being ≤0.80. The mean FFRangio was 0.82 ± 0.20 and the mean QFR was 0.82 ± 0.30, with 27 (32%) and 25 (29%) being ≤0.80, respectively. The Pearson correlation coefficient was significantly better for FFRangio compared to QFR, with R values of 0.76 and 0.61, respectively ($p = 0.01$). The inter-observer agreement was also significantly better for FFRangio compared to QFR (0.86 vs 0.79, $p < 0.05$). FFRangio had 91% sensitivity, 100% specificity, and 96.8% accuracy, while QFR exhibited 86.4% sensitivity, 98.4% specificity, and 93.7% accuracy.
Conclusion: In patients with high-risk ACS, FFRangio and QFR demonstrated excellent diagnostic performance. FFRangio seems to have better correlation to invasive FFR compared to QFR but further larger validation studies are required.

1. Introduction

Invasive physiological assessment has become a fundamental aspect of clinical decision-making in the management of coronary artery disease (CAD). It is indeed well-established that angiographic evaluation of lesion severity does not correlate well with functional significance [1,2] and that even mild angiographic stenoses, in vessels supplying a large myocardial territory can be associated with ischemia and future adverse vascular events [3]. Fractional Flow Reserve (FFR) has been validated to assess the functional significance of coronary stenosis and select the most adequate revascularization strategy, thus improving patient outcomes [1,2]. Despite the clinical evidence, FFR remains however underutilized [4]. This may be related to several factors, such as the additional time needed to perform the measurements, technical issues and risks associated with wiring of the coronary artery, or the potential side effects related to the use of some hyperemic agents.

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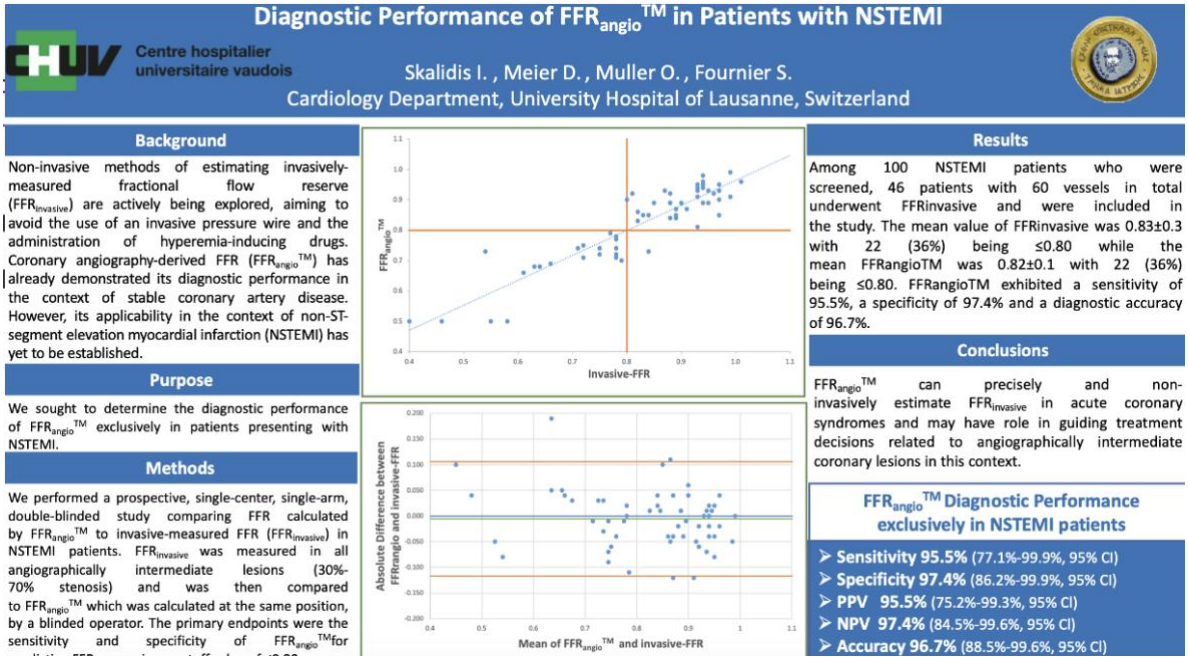
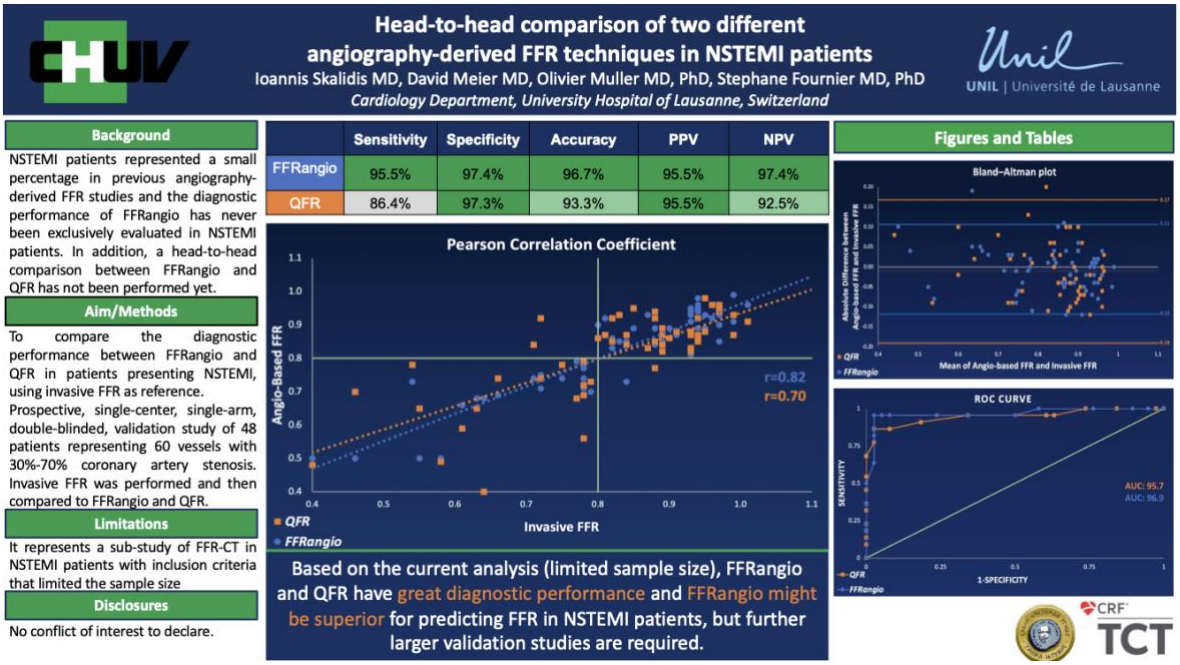
10. Presentations in International Congresses

Skalidis I, Meier D, Muller O, Fournier S. Diagnostic Performance of FFRangio in NSTEMI patients. EuroPCR. May 2022, Paris, France.

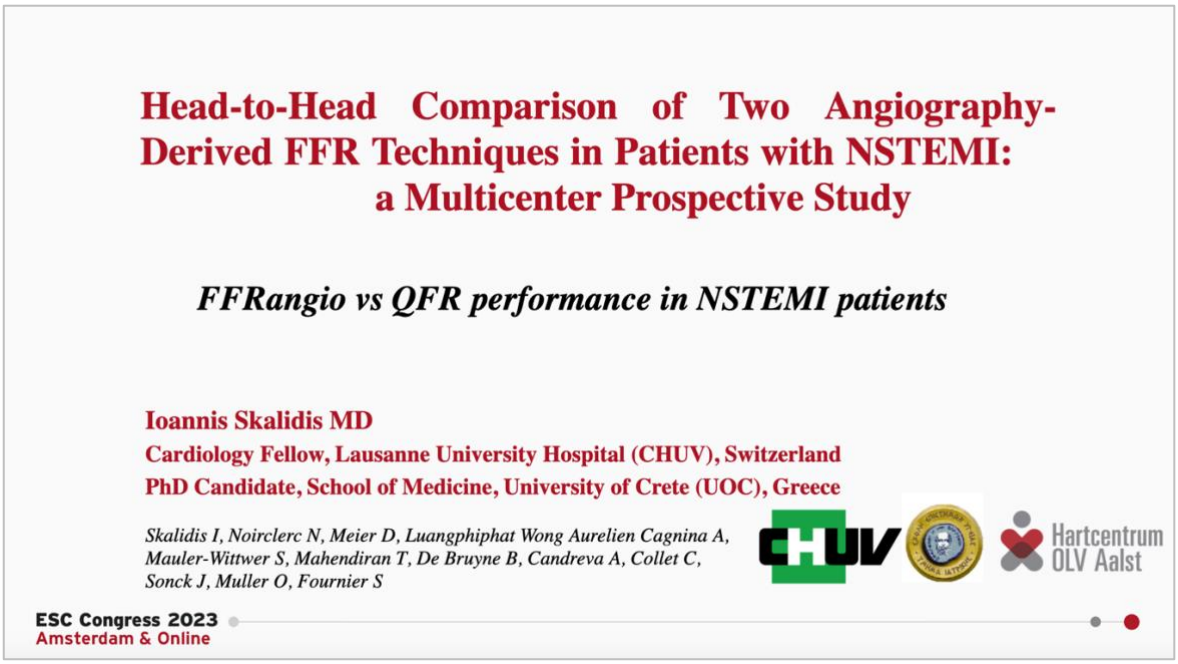


Skalidis I, Meier D, Muller O, Fournier S. Diagnostic Performance of angiography-derived FFR in patients presenting with NSTEMI. ESC Congress 2022, Barcelona, Spain.

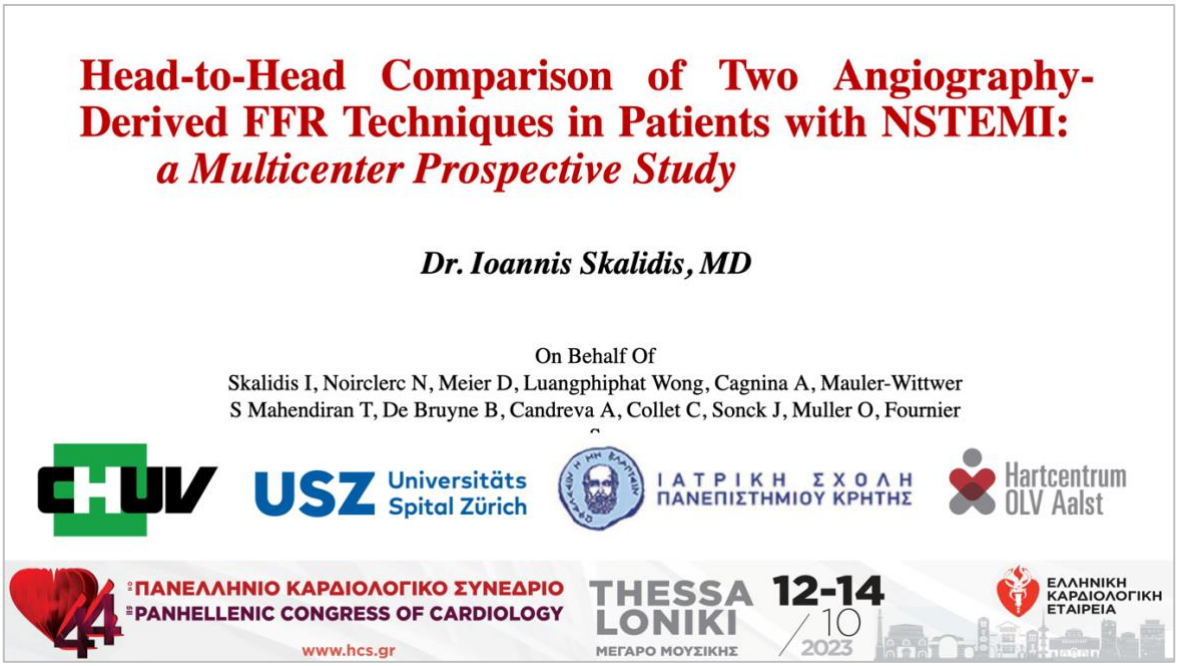


Skalidis I, Meier D, Muller O, Fournier S. Head-to-head comparison of two different angiography-derived FFR techniques in NSTEMI patients. TCT Congress 2022. September 2022, Boston, USA

Skalidis I, Meier D, Mahendiran T, Collet C, De Bruyne B, Eeckhout E, Muller O, Fournier S. Head-to-head comparison of two different angiography-derived FFR techniques in NSTEMI patients. Congress of Swiss Society of Cardiology, June 2023, Basel, Switzerland.



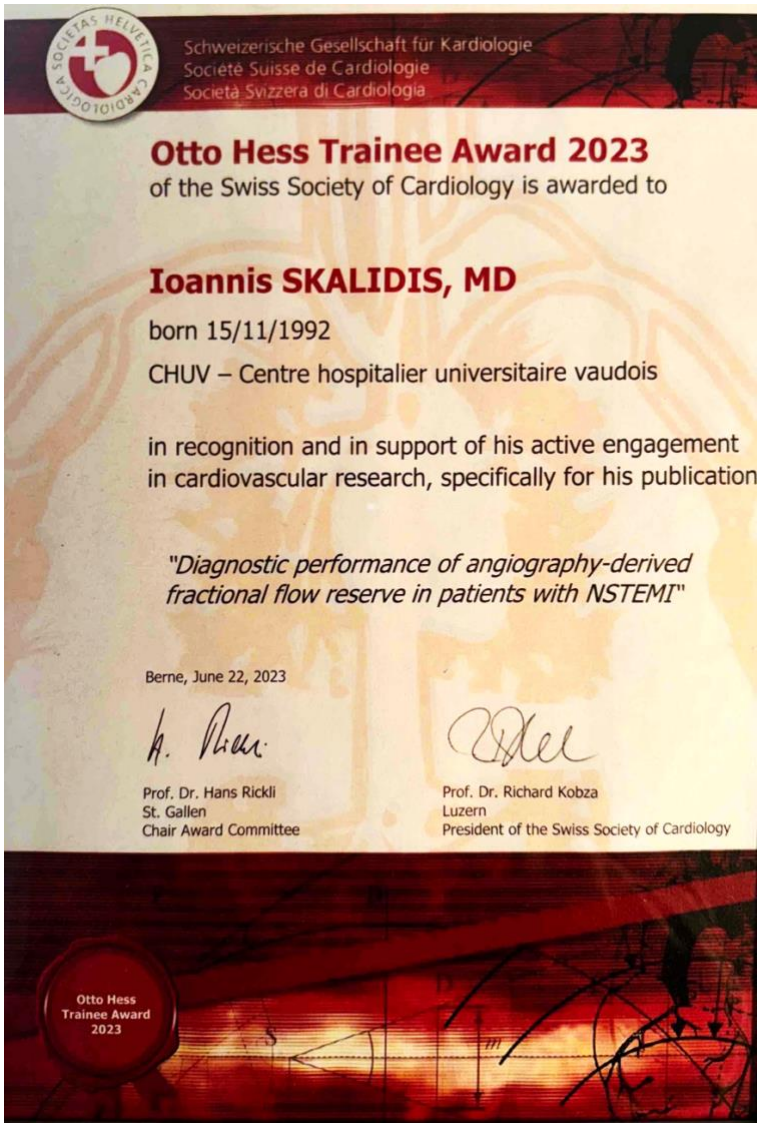
Skalidis I, Meier D, Mahendiran T, Cagnina A, Noirclerc N, Collet C, De Bruyne B, Eeckhout E, Muller O, Fournier S Comparison of two angiography-based FFR techniques in NSTEMI Patients: A Multicenter Study. ESC Congress 2023. September 2023 Amsterdam, Netherlands



Skalidis I, Noirclerc N, Meier D, Luangphiphat W, Cagnina A, Mauler-Wittwer S, Mahendiran T, De Bruyne B, Candreva 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. 44th Panhellenic Cardiology Congress. October 2023, Thessaloniki, Greece

11. Prizes

The <u>Otto Hess Trainee Award</u> of the Swiss Society of Cardiology for a young trainee in Cardiology with active involvement in research



Schweizerische Gesellschaft für Kardiologie
Société Suisse de Cardiologie
Società Svizzera di Cardiologia

Otto Hess Trainee Award 2023

of the Swiss Society of Cardiology is awarded to

Ioannis SKALIDIS, MD

born 15/11/1992

CHUV – Centre hospitalier universitaire vaudois

in recognition and in support of his active engagement in cardiovascular research, specifically for his publication

"Diagnostic performance of angiography-derived fractional flow reserve in patients with NSTEMI"

Berne, June 22, 2023

Prof. Dr. Hans Rickli
St. Gallen
Chair Award Committee

Prof. Dr. Richard Kobza
Luzern
President of the Swiss Society of Cardiology

Otto Hess Trainee Award 2023

SwissCardio

Otto Hess Trainee Award de la SSC

Avec le Otto Hess Trainee Award, la Société Suisse de Cardiologie soutient les futurs cardiologues au début de leur carrière de chercheur et récompense leurs performances.

Award

Les lauréats reçoivent un prix de 5'000 CHF.

Lauréates et lauréats des prix

2023 Ioannis Skalidis, Lausanne

12. Supplementary Material

12.1 Translated Patient Informed Consent in English Language

Capacity of FFR-CT to detect the absence of significant coronary lesions among patients with high-risk acute coronary syndrome,

This project is organized by: Cardiology Department of CHUV

Madam, Sir,

We invite you to participate in our research project. This information sheet describes the research project in detail.

Detailed Information

1. Objectives of the research project

In hospitalized patients with high-risk acute coronary syndrome, where by definition we suspect narrowing in one of the 3 coronary arteries that supply blood and therefore oxygen to the heart muscle, we want to know to what extent coronary CT angiography with measurement of fractional flow reserve (FFR-CT) can predict patients in whom coronary angiography (currently the gold standard examination) will not find narrowing requiring treatment. In other words, we aim to identify the population for whom coronary CT angiography with measurement of fractional flow reserve could replace coronary angiography, potentially avoiding invasive and costly examinations for patients.

2. Selection of eligible participants

Participation is open to all adults admitted to the Cardiology Department of CHUV with a diagnosis of high-risk acute coronary syndrome. Patients with significant renal insufficiency, those requiring coronary angiography within 24 hours (due to a presentation deemed very high risk based on a list of criteria according to international recommendations), pregnant or lactating women, patients with contraindications to certain medications (beta-blockers, nitroglycerin), those with a history of coronary artery bypass grafting, and those with severe heart failure cannot participate in the study.

3. General information about the project

The project aims to determine the performance of FFR-CT measurement in identifying high-risk acute coronary syndrome patients without coronary lesions requiring treatment, thus potentially avoiding coronary angiography. This is a project developed by the Cardiology Department of CHUV and exclusively conducted at CHUV. It is a diagnostic accuracy study, which aims to compare, in the same patient, FFR measurement by coronary angiography (standard method) and by coronary CT angiography (method evaluated by the study and performed just before coronary angiography). The results of the CT scan will be compared to the results of coronary angiography to calculate the performance of the CT scan compared to the gold standard examination, which is coronary angiography. Coronary CT angiography is a well-known technique used routinely at CHUV in patients with valvular heart diseases or in those suspected of coronary artery disease but with a certainty level too low to justify immediate coronary angiography. FFR calculation from CT images is a rapidly expanding technique worldwide as it is very promising, but it is not yet used at CHUV currently. A sub-part of the project is also dedicated to the use of software (FFRangio), currently in testing phase

at CHUV, allowing simulation of fractional flow reserve based solely on coronary angiography images. The total duration of the project is 3 years, and it is planned to enroll approximately 250 patients. We conduct this project in accordance with Swiss legislation. The competent cantonal ethics committee has reviewed and authorized the project.

4. Procedure for participants

If you agree to participate in the study, you will first undergo a coronary CT angiography. This is a painless radiology examination aimed at visualizing your coronary arteries. The examination will require the administration of an additional dose of medications also used subsequently for routine management (a beta-blocker and nitroglycerin) to optimize your heart rate for good image quality. Coronary CT angiography will be the only additional examination to the standard management of patients with a pathology like yours. The results of the scan will not be disclosed (neither to you nor to your doctor) during your hospitalization to avoid interference with your management, which must strictly adhere to international recommendations. Then, your management will follow the normal process with the performance of coronary angiography (ideally within 24 hours of diagnosis, but this delay may sometimes extend to 48 hours, especially on weekends or in cases of unusually high patient influx requiring coronary angiography), followed by hospitalization in our department for monitoring and initiation of medical treatment. After discharge from the hospital, you will need to attend 3 follow-up visits at 1, 6, and 12 months for a total follow-up duration of 12 months. These visits are part of the standard management after a heart attack (they aim to ensure the good tolerance of medications, absence of recurrence of concerning symptoms, and to ensure, through echocardiography, that your heart function remains normal after acute coronary syndrome), with the particularity that yours will need to be done at CHUV. At the end of these 3 visits, you will of course be free to continue your follow-up with the cardiologist of your

choice. It is possible that we may have to exclude you from the study before the scheduled end. This situation may occur if your condition deteriorates before the CT scan (appearance of very high-risk criteria) and coronary angiography consequently needs to be performed immediately.

5. Benefits for participants

Your participation in the project will not bring you any direct benefit. However, on a larger scale, the results of the project could be important in the future for people affected by the same disease as you.

6. Participant rights

You are free to accept or refuse to participate in the project. If you choose not to participate or if you choose to participate and then change your mind during the course of the project, you do not have to justify yourself. This will not change anything in your usual medical management. You may ask any necessary questions about the study at any time. Please address the designated person at the end of this information sheet for this purpose.

7. Participant Obligations

As a participant in the project, you will be required to:

- Follow the medical instructions given by the project management. These instructions are limited since the only addition to your standard care will be the coronary scan. Besides that, you must attend 3 follow-up visits after your heart attack at 1, 6, and 12 months. These visits are part of the standard follow-up in your situation but must specifically take place at CHUV.
- Inform your investigator doctor/project management of any changes in your condition, any new symptoms, or any new issues.

- Inform your investigator doctor/project management of all medications you may be taking.

8. Risks

The only difference from standard care is the completion of a scan, so the only risks associated with your participation in the project are those arising from this examination. Thus, undergoing a scan exposes you to:

- A small additional dose of X-rays, estimated at 2.5 mSv, which should not have an impact on your health. This dose is a little less than the annual radiation dose to which everyone is exposed, which is 5.8 mSv on average in Switzerland.
- An additional dose of contrast agent, which theoretically could pose a risk of transiently altering your kidney function (a phenomenon called acute kidney injury, which is rapidly reversible in almost all cases).

If you are pregnant or breastfeeding, you cannot participate in the study.

9. Discoveries during the Project

The investigator doctor will inform you during the study of any new discoveries that may affect the study's benefits or your safety, and thus your consent to participate. In the case of incidental findings that could contribute to the prevention, diagnosis, and treatment of existing or probable diseases in the future, the project doctor will inform you once a diagnosis and final treatment have been made regarding your current reason for admission (such as a heart attack).

10. Data Confidentiality

For the needs of the study, we will record your personal and medical data. Only a limited number of people can access your data in an unencoded form, and solely to perform tasks

necessary for the project's progress. Data collected for research purposes are coded at collection. Coding means that all data allowing your identification (e.g., name, date of birth, etc.) are replaced by a code. The code remains permanently within the hospital. Persons not knowing this code cannot link this data to you. In the case of publication, aggregated data cannot be attributed to you as an individual. Your name will never appear on the internet or in a publication. Sometimes, scientific journals require the transmission of individual data (raw data). If individual data must be transmitted, they are always coded and therefore cannot identify you as a person. All persons involved in the study in any way are bound by professional secrecy. All data protection guidelines are respected, and you have the right to access your data at any time. Some of your data will be sent in encoded form to the United States to a company named Heart Flow, based in California (https://www.heartflow.com), where it will be used to carry out this research project and to improve this technology. Sending your data to this company is a prerequisite since it is the only company in the world currently capable of performing this type of analysis. Another portion of the data (some of the images from your coronary angiography) will be sent to Israel to a company named CathWorks (https://cath.works), which has developed the FFRangio technology mentioned in the introduction and holds the exclusive rights. This sending is also necessary to ensure high-quality data analysis by experienced personnel. The only entity with access to the relevant codes is the Cardiology Service of the CHUV where your data will be stored for 10 years. Recipient foreign institutions must meet standards and requirements at least equivalent to those to which this study is subject in Switzerland. Compliance with national and international data protection provisions is the responsibility of the project management.

Your health-related data may be used in future research projects or sent for analysis in Switzerland or abroad to be used in other research projects. However, this database must comply with the same standards and requirements as the database of this project. These future

projects must obtain approval from the Ethics Commission in advance. If you agree to this reuse, please check the appropriate box in the consent form at the end of this information sheet. You have the right to change your decision at any time without having to justify yourself.

During its course, the project may be subject to inspections. These may be carried out by the ethics commission responsible for its initial control and authorization, but may also be mandated by the institution that initiated it (the Cardiology Service of the CHUV). The project management may need to disclose your personal and medical data for the purposes of these inspections. In the event of damage, a representative of the CHUV may also need to consult your data. However, this can only concern elements absolutely necessary for the investigation of the case. All involved persons are bound by professional secrecy. We guarantee compliance with all data protection directives and will not disclose your name in any report or publication, in print or online. In the future, the physician responsible for the study/project management may contact your future treating physician to obtain information about your health status. This may occur mainly if for any reason you do not attend the scheduled follow-up visits without informing us.

11. Withdrawal from the Project

You may withdraw from the study at any time if you wish. Medical data collected up to that point will still be analyzed, to ensure the overall value of the study is not compromised. After analysis, we will anonymize your data, permanently erasing the code linking them to you. After that, no one will be able to know that this data belongs to you. If for any reason you do not attend the scheduled follow-up visits without informing us, we will contact your treating physician or a family member to ensure your health status.

12. Participant Remuneration

If you participate in this project, you will not receive any remuneration for it. Your participation will have no financial consequences for you or your health insurance. If, unexpectedly, you suffer from adverse effects during the study, such as hospital expenses, additional tests, or transportation costs directly resulting from it (excluding the 3 standard follow-up visits), these will be reimbursed. Regarding the 3 follow-up visits, which must be carried out by a cardiologist anyway, if coming to CHUV involves expenses related to traveling to a city other than your treating cardiologist's, these will be reimbursed.

13. Compensation for Damages

In case of potential damages caused to participants in the study, the CHUV will be responsible for them as the sponsor in accordance with applicable legal provisions. If you have suffered damage, please contact the responsible project physician.

14. Project Funding

The study is primarily funded by the Vaudoise Foundation for Interventional Cardiology, which has no conflicts of interest related to this project.

15. Contacts

In case of doubt, fear, or emergencies during or after the study, you can contact any of the following representatives at any time:

Project Manager

Dr. Stéphane Fournier

Centre Hospitalier Universitaire Vaudois (CHUV), Cardiology Department

Rue du Bugnon 46, 1011 Lausanne, Switzerland

Tel: +41 79 556 82 05

Email: stephane.Fournier@chuv.ch

Project Co-Manager

Dr. Ioannis Skalidis

Centre Hospitalier Universitaire Vaudois (CHUV), Cardiology Department

Rue du Bugnon 46, 1011 Lausanne, Switzerland

Tel: +41 79 556 99 21

Email: ioannis.skalidis@chuv.ch

Consent Declaration

Written Consent Declaration for Participation in a Research Project

- Please read this form carefully.

- Do not hesitate to ask questions if you do not understand something or if you would like further clarification.

BASEC Project Number :	2019-00392
Study Title :	Ability of FFR-CT to detect the absence of significant coronary lesions among patients with high-risk acute coronary syndrome
Responsible Institution :	Cardiology Service of CHUV Rue du Bugnon 46, 1011 Lausanne, Switzerland
Lieu de réalisation du projet :	CHUV, Lausanne, Cardiology Service
Project Site Director:	Dr Stéphane Fournier

Participant:

Name and surname in printed characters:	.....
Date of birth:	.....
	☐ Female ☐ Male

- I declare that I have been informed, orally and in writing, by the investigator doctor / by the person providing the information, about the objectives and conduct of the project as well as the presumed effects, benefits, possible disadvantages, and potential risks.
- I am participating in this study voluntarily and I accept the contents of the information sheet provided to me regarding the aforementioned project. I have had sufficient time to make my decision.
- I have received satisfactory answers to the questions I have asked regarding my participation in the project. I will retain the information sheet and receive a copy of my written consent declaration.
- I agree that competent specialists from the institution, the project sponsor, and the Ethics Commission responsible for this study may access my raw data for checks, provided that the confidentiality of this data is strictly ensured.
- I will be informed of (incidental) discoveries directly impacting my health.
- I am aware that my personal data may be transmitted for research purposes within the scope of this project only and in encoded form, also abroad.
- I agree that my data may be reused for other studies in Switzerland or abroad:

  yes ☐ no ☐

  provided that the standards and requirements of the concerned database are at least equivalent to Swiss standards. All legal provisions regarding data protection will be respected.

- In the event of subsequent treatment outside the project site, I authorize my physician(s) to provide the responsible project physician / project management with relevant post-treatment data for the project.
- I may revoke my consent to participate in the study at any time and without having to justify myself, without this having any adverse effect on the continuation of my usual medical care. I understand that medical data collected up to that point will, however, be analyzed.
- I agree that if I do not attend the scheduled follow-up visits within the study framework without informing the study coordinators, they may contact my treating physician or a family member to inquire about my health status.
- In the event of potential damages to participants in the study, the CHUV will be liable for them as the sponsor in accordance with applicable legal provisions. I am aware that the obligations mentioned in the participant information sheet must be respected

throughout the study. The study management may exclude me at any time in the interest of my health.

Location, date	Signature of the participant

Investigator/Information Provider Attestation: I hereby certify that I have explained to the participant the nature, significance, and scope of the project. I declare that I fulfill all obligations related to this project in accordance with applicable law. If I become aware, at any time during the project, of any information that may affect the participant's consent to participate in the project, I undertake to inform them immediately.

Location, date	First and last name of the investigator doctor / person providing information to participants in printed characters. Signature of the investigator doctor / person providing the information

12.2 Original Patient Informed Consent in French Language

Capacité du FFR-CT à détecter l'absence de lésion coronarienne significative, parmi les patients avec un syndrome coronarien aigu à haut risque,

Ce projet est organisé par : Service de cardiologie du CHUV

Madame, Monsieur,

Nous vous proposons de participer à notre projet de recherche. Cette feuille d'information décrit le projet de recherche de façon détaillée.

Information détaillée

1. Objectifs du projet de recherche

Chez les patients hospitalisés avec un syndrome coronarien aigu à haut risque chez qui par définition nous avons une suspicion de rétrécissement dans l'une des 3 artères coronaires qui apportent le sang et donc l'oxygène au muscle cardiaque, nous voulons savoir dans quelle mesure le scanner coronarien avec mesure de la réserve de flux coronarien (en anglais FFR-CT) est capable de prédire les patients chez qui la coronarographie (qui est actuellement l'examen de référence) ne retrouvera pas de rétrécissement nécessitant un traitement. En d'autres termes, nous visons à identifier la population pour laquelle le scanner coronarien avec mesure de la réserve de flux coronarien pourrait remplacer la coronarographie, et ainsi potentiellement éviter aux patients un examen invasif et coûteux.

2. Sélection des personnes pouvant participer au projet

La participation est ouverte à toutes les personnes majeures, qui sont admises dans le Service de Cardiologie du CHUV avec un diagnostic de syndrome coronarien aigu à haut risque.

Les patients présentant une insuffisance rénale importante, ceux nécessitant une coronarographie dans un délai de moins de 24h (en raison d'une présentation jugée à très haut risque, basée sur une liste de critères selon les recommandations internationales), les femmes enceintes ou qui allaitent, les patients avec une contre-indication à certains médicaments (bétabloquant, nitroglycérine), ceux avec un antécédent de pontage aorto-coronarien et ceux avec une insuffisance cardiaque sévère ne peuvent pas participer à l'étude.

3. Informations générales sur le projet

Le projet a donc pour but de déterminer la performance de la mesure de FFR-CT pour identifier les patients avec syndrome coronarien aigu à haut-risque ne présentant pas de lésion

coronarienne nécessitant un traitement et pouvant donc éviter l'angiographie coronaire. Il s'agit d'un projet développé par le Service de Cardiologie du CHUV et se déroulant exclusivement au CHUV.

Il s'agit d'une étude de précision diagnostique, qui vise à comparer chez un même patient la mesure du FFR par coronarographie (méthode standard) et par scanner coronaire (méthode évaluée par l'étude et qui sera réalisée juste avant la coronarographie). Les résultats du scanner seront comparés aux résultats de l'a coronarographie afin de pouvoir calculer les performances du scanner par rapport à l'examen de référence qu'est la coronarographie.

Le scanner coronarien est une technique bien connue utilisée en routine au CHUV chez des patients présentant des maladies des valves cardiaques ou encore chez ceux chez qui l'on suspecte une maladie des coronaires mais avec un degré de certitude trop bas pour justifier une angiographie coronarienne d'emblée. Le calcul de la FFR à partir des images du scanner est une technique en pleine expansion mondiale car très prometteuse, mais qui n'est pas encore utilisée au CHVU actuellement. Une sous-partie du projet est par ailleurs dédiée à l'utilisation d'un logiciel (FFRangio), actuellement utilisé en phase de test au CHUV et permettant une simulation de la réserve de flux coronarien en se basant uniquement sur les images de la coronarographie.

La durée totale du projet est de 3 ans et il est prévu d'enrôler environ 250 patients.

Nous effectuons ce projet dans le respect des prescriptions de la législation suisse. La commission cantonale d'éthique compétente a contrôlé et autorisé le projet.

4. Déroulement pour les participants

Si vous acceptez de participer à l'étude, vous allez dans un premier temps rapidement avoir un scanner coronarien. Il s'agit d'un examen de radiologie indolore, visant à visualiser vos artères coronaires. L'examen va nécessiter l'administration d'une dose supplémentaire de médicaments utilisés aussi par la suite pour la prise en charge de routine (un bétabloquant et de la nitroglycérine) afin d'optimiser votre rythme cardiaque pour assurer une bonne qualité d'images. Le scanner coronarien sera le seul examen ajouté à la prise en charge standard des patients souffrant d'une pathologie comme la vôtre. Les résultats du scanner ne seront pas divulgués (ni à vous, ni à votre médecin) durant votre hospitalisation afin d'éviter que cette méthode, encore en cours de validation, n'interfère avec votre prise en charge qui doit respecter strictement les recommandations internationales.

Ensuite votre prise en charge suivra le processus normal avec la réalisation d'une coronarographie (idéalement dans les 24h suivant la pose du diagnostic mais ce délai peut parfois atteindre 48h, notamment le week-end ou en cas d'affluence inhabituellement importante de patients nécessitant une coronarographie), puis une hospitalisation dans notre service pour surveillance et mise en place du traitement médicamenteux.

Après votre sortie de l'hôpital, vous devrez vous présenter à 3 visites de contrôle à 1, 6 et 12 mois pour une durée totale de suivi de 12 mois. Ces visites font de toute manière partie de la prise en charge standard après un infarctus (elles visent à s'assurer de la bonne tolérance des médicaments, de l'absence de récidive de symptômes inquiétants ainsi qu'à s'assurer au moyen d'une échographie cardiaque que la fonction de votre cœur reste normale après le syndrome

coronarien aigu), avec la particularité que les vôtres devront se faire au CHUV. A la fin de ces 3 visites, vous serez bien entendu libre de poursuivre votre suivi chez le cardiologue de votre choix.

Il se peut que nous devions vous exclure de l'étude avant le terme prévu. Cette situation peut se produire si votre situation devait se dégrader avant la réalisation du scanner (apparition de critères de très haut risque) et que la coronarographie devait en conséquence être réalisée immédiatement.

5. Bénéfices pour les participants

Votre participation au projet ne vous apportera aucun bénéfice. Néanmoins, à une échelle plus large, les résultats du projet pourraient se révéler importants par la suite pour les personnes touchées par la même maladie que vous.

6. Droits des participants

Vous êtes libre d'accepter ou de refuser de participer au projet. Si vous choisissez de ne pas participer ou si vous choisissez de participer et revenez sur votre décision pendant le déroulement du projet, vous n'aurez pas à vous justifier. Cela ne changera rien à votre prise en charge médicale habituelle. Vous pouvez à tout moment poser toutes les questions nécessaires au sujet de l'étude. Veuillez-vous adresser pour ce faire à la personne indiquée à la fin de la présente feuille d'information.

7. Obligations des participants

En tant que participant au projet, vous serez tenu :

- de suivre les instructions médicales de la direction du projet. Ces instructions sont en nombre limité puisque le seul élément ajouté à votre prise en charge standard sera le scanner coronarien. Pour le reste vous devrez vous présenter à 3 visites de contrôle après votre infarctus à 1, 6 et 12 mois. Ces visites font de toute façon partie du suivi standard dans votre situation mais devront se dérouler spécifiquement au CHUV.
- d'informer votre médecin-investigateur / direction du projet de l'évolution de la maladie et de signaler tout nouveau symptôme, tout nouveau trouble et tout changement dans votre état ;
- d'informer votre médecin-investigateur / direction du projet de tous les médicaments que vous pourriez prendre.

8. Risques

La seule différence avec la prise en charge habituelle étant la réalisation d'un scanner, les seuls risques liés à votre participation au projet sont ceux qui découlent de la réalisation de cet examen. Ainsi, la réalisation d'un scanner nécessite l'administration de produit de contraste qui est également requise pour la réalisation d'une coronarographie (autrement dit, vous recevrez également du produit de contraste si vous ne participez pas à l'étude, mais en plus petite quantité).

Le fait de réaliser un scanner en plus de la prise en charge habituelle vous expose :

- à une petite dose de rayons X supplémentaire, estimée à 2.5 mSv qui ne devrait pas avoir d'impact sur votre santé. Cette dose correspond à un peu moins de la dose de radiation à laquelle toute personne est exposée annuellement, soit 5.8 mSv en moyenne en Suisse et
- à une dose supplémentaire de produit de contraste, qui pourrait théoriquement présenter un risque d'altérer transitoirement le fonctionnement de vos reins (phénomène appelé insuffisance rénale aiguë, qui est, dans la quasi-totalité des cas, rapidement réversible).

Si vous êtes enceinte ou allaitez, vous ne pouvez en aucun cas prendre part à l'étude.

9. Découvertes pendant le projet

Le médecin-investigateur vous avisera pendant l'étude de toute nouvelle découverte susceptible d'influer sur les bénéfices de l'étude ou votre sécurité, et donc sur votre consentement à y participer. En cas de découvertes fortuites qui, chez vous, pourraient contribuer à la prévention, au diagnostic et au traitement de maladies existantes ou probables dans le futur, le médecin du projet vous en informera une fois qu'un diagnostic et un traitement final auront été réalisés concernant votre raison d'admission actuelle (infarctus par exemple)

10. Confidentialité des données

Pour les besoins de l'étude, nous enregistrerons vos données personnelles et médicales. Seul un nombre limité de personnes peut consulter vos données sous une forme non codée, et exclusivement afin de pouvoir accomplir des tâches nécessaires au déroulement du projet. Les données recueillies à des fins de recherche sont codées lors de leur collecte. Le codage signifie que toutes les données permettant de vous identifier (p. ex. le nom, la date de naissance, etc.) sont remplacées par un code. Le code reste en permanence au sein de l'hôpital. Les personnes ne connaissant pas ce code ne peuvent pas lier ces données à votre personne. Dans le cas d'une publication, les données agrégées ne vous sont donc pas imputables en tant que personne. Votre nom n'apparaîtra jamais sur Internet ou dans une publication. Parfois, les journaux scientifiques exigent la transmission de données individuelles (données brutes). Si des données individuelles doivent être transmises, elles sont toujours codées et ne permettent donc pas de vous identifier en tant que personne. Toutes les personnes impliquées dans l'étude de quelque manière que ce soit sont tenues au secret professionnel. Toutes les directives relatives à la protection des données sont respectées et vous avez à tout moment le droit de consulter vos données.

Certaines de vos données seront envoyées sous forme codée aux Etats-Unis à une compagnie nommée Heart Flow, basée en Californie (https://www.heartflow.com) où elles seront exploitées pour permettre la réalisation de ce projet de recherche et pour permettre l'amélioration de cette technologie. L'envoi de vos données à cette société est un prérequis puisqu'il s'agit de la seule société au monde actuellement capable de réaliser ce type d'analyses. Une autre fraction des données (une partie des images de votre coronarographie) sera envoyée en Israël à une société nommée CathWorks (https://cath.works), qui a mis au point la technologie FFRangio évoquée en introduction et en détient l'exclusivité. Cet envoi est également nécessaire afin de garantir une analyse de haute qualité des données, par du personnel expérimenté. Le seul organisme à avoir un droit d'accès aux codes concernés est le Service de Cardiologie du CHUV où vos données seront stockées 10 ans. Les institutions étrangères destinataires doivent répondre à des normes et exigences au moins équivalentes à

celles auxquelles est tenue la présente étude en Suisse. Le respect des dispositions nationales et internationales relatives à la protection des données relève de la responsabilité de la direction du projet.

Il se peut que les données liées à votre santé soient ultérieurement exploitées dans de futurs projets de recherche ou envoyées à des fins d'analyse en Suisse ou à l'étranger pour être aussi exploitées dans d'autres projets de recherches. Cette base de données doit toutefois obéir aux mêmes normes et exigences que la base de données du présent projet. Ces futurs projets devront obtenir l'accord de la Commission d'Ethique au préalable. Si vous êtes d'accord avec cette réutilisation, nous vous prions de cocher la case qui convient dans le consentement à la fin de cette feuille d'information. Vous aurez le droit de revenir sur votre décision à tout moment sans avoir à vous justifier.

Durant son déroulement, le projet peut faire l'objet d'inspections. Celles-ci peuvent être effectuées par la commission d'éthique qui s'est chargée de son contrôle initial et l'a autorisé, mais aussi être mandatées par l'organisme qui l'a initié (le Service de cardiologie du CHUV). Il se peut que la direction du projet doive communiquer vos données personnelles et médicales pour les besoins de ces inspections. En cas de dommage, un représentant du CHUV peut également être amené à consulter vos données. Cela ne peut toutefois concerner que les éléments absolument nécessaires à l'instruction du dossier. Toutes les personnes impliquées sont tenues au secret professionnel. Nous garantissons le respect de toutes les directives de la protection des données et ne ferons apparaître votre nom dans aucun rapport ou publication, imprimé ou en ligne.

Il se peut que dans le futur le médecin responsable de l'étude / la direction du projet contacte votre futur médecin traitant, afin d'obtenir des renseignements sur votre état de santé. Ce cas de figure se présentera essentiellement si pour une raison ou une autre vous ne vous présentez pas aux visites de suivi sans nous en avoir prévenu.

11. Retrait du projet

Vous pouvez à tout moment vous retirer de l'étude si vous le souhaitez. Les données médicales recueillies jusque-là seront tout de même analysées, ceci afin de ne pas compromettre la valeur de l'étude dans son ensemble. Après l'analyse nous rendrons vos données anonymes, en effaçant définitivement le code les reliant à votre personne. Après cela, plus personne ne pourra savoir que ces données sont les vôtres.

Si pour une raison ou une autre vous ne vous présentez pas aux visites de suivi prévues, sans nous en avoir informé, nous prendrons contact avec votre médecin traitant, ou un membre de votre famille, afin de nous assurer de votre état de santé.

12 Rémunération des participants

Si vous participez à ce projet, vous ne recevrez pour cela aucune rémunération. Votre participation n'aura aucune conséquence financière pour vous ou votre assurance maladie. Si pour une raison imprévue vous deviez souffrir d'effets indésirables survenus durant l'étude, les dépenses, telles que les frais hospitaliers, les analyses supplémentaires ou les frais de transport, qui en découleraient directement, (ne sont en principe pas compris les 3 visites qui font partie

du suivi standard) vous seraient remboursées. Concernant les 3 visites de suivi, qui doivent de toute façon être assurées par un cardiologue, si le fait de venir au CHUV implique des frais liés à un déplacement dans une ville autre que celle de votre cardiologue traitant, ceux-ci vous seront remboursés.

13 Réparation des dommages subis

En cas de dommages éventuels causés aux participants dans le cadre de l'étude, le CHUV répondra de ces derniers en sa qualité de promoteur conformément aux dispositions légales applicables. Si vous avez subi un dommage, veuillez-vous adresser au médecin responsable du projet.

14 Financement du projet

L'étude est majoritairement financée par la Fondation Vaudoise de Cardiologie Interventionnelle, qui n'a aucun conflit d'intérêt relatif à ce projet.

15 Interlocuteurs

En cas de doute, de craintes ou d'urgences pendant ou après l'étude, vous pouvez vous adresser à tout moment à l'un des interlocuteurs suivants :

Responsable du projet

Dr Stéphane Fournier

Centre Hospitalier Universitaire Vaudois (CHUV), Service de Cardiologie

Rue du Bugnon 46, 1011 Lausanne, Suisse

Tél : 079 556 82 05

Email : stephane.Fournier@chuv.ch

Co-responsable du projet

Dr Ioannis Skalidis

Centre Hospitalier Universitaire Vaudois (CHUV), Service de Cardiologie

Rue du Bugnon 46, 1011 Lausanne, Suisse

Tél : 079 556 99 21

Email : ioannis.skalidis@chuv.ch

Déclaration de consentement

Déclaration de consentement écrite pour la participation à un projet de recherche

- Veuillez lire attentivement ce formulaire.
- N'hésitez pas à poser des questions lorsque vous ne comprenez pas quelque chose ou que vous souhaitez avoir des précisions.

Numéro BASEC du projet :	2019-00392
Titre de l'étude :	Capacité du FFR-CT à détecter l'absence de lésion coronarienne significative, parmi les patients avec un syndrome coronarien aigu à haut risque,
Institution responsable :	Service de Cardiologie du CHUV Rue du Bugnon 46, 1011 Lausanne, Suisse
Lieu de réalisation du projet :	CHUV, Lausanne, Service de Cardiologie
Directeur du projet sur le site :	Dr Stéphane Fournier
Participant / participante :	
Nom et prénom en caractères d'imprimerie :	.....
Date de naissance :	.....
	☐ femme ☐ homme

- Je déclare avoir été informé, par le médecin investigateur / par la personne assurant l'information soussigné(e), oralement et par écrit, des objectifs et du déroulement du projet ainsi que des effets présumés, des avantages, des inconvénients possibles et des risques éventuels.
- Je prends part à cette étude de façon volontaire et j'accepte le contenu de la feuille d'information qui m'a été remise sur le projet précité. J'ai eu suffisamment de temps pour prendre ma décision.
- J'ai reçu des réponses satisfaisantes aux questions que j'ai posées en relation avec ma participation au projet. Je conserve la feuille d'information et reçois une copie de ma déclaration de consentement écrite.
- J'accepte que les spécialistes compétents de l'institution, du mandataire du projet, de la Commission d'éthique compétente pour cette étude, puissent consulter mes données brutes afin de procéder à des contrôles, à condition toutefois que la confidentialité de ces données soit strictement assurée.

- Je serai informé des découvertes (fortuites) ayant une incidence directe sur ma santé.
- Je sais que mes données personnelles peuvent être transmises à des fins de recherche **dans le cadre de ce projet uniquement** et sous une forme codée, également à l'étranger.
- J'accepte que mes données soient réutilisées dans le cadre d'autres études en Suisse ou à l'étranger :

  oui ☐ non ☐

  à condition que les normes et exigences de la base de données concernée soient au moins équivalentes aux normes et exigences suisses. Toutes les dispositions légales relatives à la protection des données seront respectées.

- En cas de traitement ultérieur en dehors du lieu de réalisation de ce projet, j'autorise mon ou mes médecins à fournir au médecin responsable du projet / à la direction du projet les données post-traitements pertinentes pour le projet.
- Je peux, à tout moment et sans avoir à me justifier, révoquer mon consentement à participer à l'étude, sans que cela n'ait de répercussion défavorable sur la suite de ma prise en charge médicale usuelle. Je sais que les données médicales qui ont été recueillies jusque-là seront cependant analysées.
- J'accepte que, si je ne me présente pas aux visites de suivi prévues dans le cadre de l'étude, sans en informer les référents de l'étude, ceux-ci contactent mon médecin traitant ou un membre de ma famille pour s'enquérir de mon état de santé.
- En cas de dommages éventuels causés aux participants dans le cadre de l'étude, le CHUV répondra de ces derniers en sa qualité de promoteur conformément aux dispositions légales applicables..Je suis conscient que les obligations mentionnées dans la feuille d'information destinée aux participants doivent être respectées pendant toute la durée de l'étude. La direction de l'étude peut m'en exclure à tout moment dans l'intérêt de ma santé.

Lieu, date	Signature du participant / de la participante

Attestation du médecin investigateur /de la personne assurant l'information : Par la présente, j'atteste avoir expliqué au participant / à la participante la nature, l'importance et la portée du projet. Je déclare satisfaire à toutes les obligations en relation avec ce projet conformément au droit en vigueur. Si je devais prendre connaissance, à quelque moment que ce soit durant la réalisation du projet, d'éléments susceptibles d'influer sur le consentement du participant / de la participante à prendre part au projet, je m'engage à l'en informer immédiatement.

Lieu, date	Nom et prénom du médecin investigateur / de la personne assurant l'information aux participants en caractères d'imprimerie. Signature du médecin investigateur / de la personne assurant l'information

12.3 Main Study Ethical Committee Protocol in French Language

canton de vaud
COMMISSION CANTONALE
D'ÉTHIQUE DE LA RECHERCHE
SUR L'ÊTRE HUMAIN
CER-VD
Av. de Chailly 23
1012 Lausanne

Dr Stéphane Fournier
CHUV
Service de cardiologie
Rue du Bugnon 46
1011 Lausanne

Lausanne, le 3 septembre 2019
Réf. PAM/ccg/cc

Décision de la Commission cantonale (VD) d'éthique de la recherche sur l'être humain (CER-VD)

Project-ID	2019-00392
Titre du projet	Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk ACS admitted in the emergency department with chest pain: a diagnostic accuracy prospective study
Investigateur principal	Dr Stéphane Fournier
Promoteur	Dr Stéphane Fournier
Centres	Dr Stéphane Fournier, CHUV, Lausanne

Décision

- ☒ Autorisation accordée
- ☐ Autorisation avec charges
- ☐ En l'état, l'autorisation ne peut pas être accordée
- ☐ Autorisation non accordée
- ☐ Non entrée en matière

Remarques :

La date du début de l'étude n'a pas été actualisée dans le formulaire de soumission.

Les deux DTA font référence à la loi fédérale sur la protection des données alors que le CHUV relève du droit cantonal. De plus, ils indiquent que le CHUV reste propriétaire des données, alors que celles-ci appartiennent en fait aux patients (et non aux donneurs comme indiqué dans les deux documents). Veuillez en tenir compte dans les futurs contrats.

Classification

☒ Projet de recherche au sens de l'ORH Catégorie : B

- ☒ recherche sur des personnes
- ☐ réutilisation du matériel biologique ou des données personnelles liées à la santé
- ☐ sur des personnes décédées
- ☐ sur des embryons et des fœtus
- ☒ avec rayonnements ionisants

Procédure de décision

☐ Procédure ordinaire ☐ Procédure simplifiée ☒ Procédure présidentielle

La Commission certifie se conformer aux principes ICH GCP.

Voies de recours

La présente décision peut faire l'objet d'un recours au Tribunal cantonal, Cour de droit administratif et public. L'acte de recours doit être déposé auprès du Tribunal cantonal dans les **30 jours** suivant la communication de la décision attaquée ; il doit être signé et indiquer les conclusions et motifs du recours. La décision attaquée est jointe au recours. Le cas échéant, ce dernier est accompagné de la procuration du mandataire.

Signature

p.o.

Prof. Pierre-André Michaud
Vice-président

Annexes: -Obligations du requérant
-Signification des décisions possibles
-Liste des documents soumis les 27 février 2019, 24 avril 2019, 20 mai 2019 et 26 août 2019

Annexes

Obligations du requérant (promoteur ou investigateur) :

Soumission de documents : les documents modifiés et les nouveaux documents relatifs à l'étude/au projet de recherche sont soumis via le dossier existant. Les documents qui ne sont plus valides sont effacés et remplacés par les nouveaux. Les documents révisés doivent être soumis une fois en mode « suivi des modifications » et une fois en mode « modifications acceptées » (« track changes » et « clean »). Les documents d'information et de consentement ainsi que le protocole doivent être transmis dans un format permettant la recherche (PDF navigable) ou scannés avec une fonction OCR (Optical Character Recognition). Le cas échéant, les documents révisés sont également mis à disposition des autorités compétentes pour approbation.

Remarque: La commission d'éthique compétente examine, dans le cadre du processus d'autorisation, les feuilles d'information et déclarations de consentement dans une des langues officielles suisses: allemand, français ou italien. La commission d'éthique ne fait qu'accuser réception des feuilles d'information et déclarations de consentement écrites dans d'autres langues. Le promoteur ou la direction du projet est responsable de la traduction correcte des documents.

Obligations d'annonce : Les obligations d'annonce (p.ex d'évènements indésirables, d'interruption d'étude) et de soumission pour autorisation des modifications essentielles obligatoires s'appliquent (Ordonnances). Le rapport final est à remettre à la commission d'éthique compétente dans un délai d'une année à compter de la fin ou de l'arrêt de l'étude.

Devoir d'enregistrement : Le promoteur d'un essai clinique doit procéder à l'enregistrement dans un registre primaire reconnu par l'OMS ou dans le registre de la bibliothèque médicale nationale des Etats-Unis d'Amérique (clinicaltrials.gov) puis indiquer le numéro de l'étude sur le portail BASEC. Le transfert des données vers le Swiss National Clinical Trials Portal (SNCTP) est effectué automatiquement suite à l'autorisation de l'étude par la commission d'éthique, sous réserve de l'accord du requérant. Les données relatives à l'essai clinique figurant sur les deux registres sont accessibles au public. Swissethics publie également sur son site des informations sur chaque étude ayant reçu une autorisation, à l'exception des essais cliniques de phase I.

Signification des décisions possibles

Autorisation accordée : L'étude peut commencer selon le plan de recherche accepté. Elle doit être menée dans le cadre des dispositions légales en vigueur. D'autres obligations d'autorisation (Swissmedic/OFSP) doivent être respectées.

Autorisation avec charges : L'étude peut commencer selon le plan de recherche accepté. Elle doit être menée dans le cadre des dispositions légales en vigueur. Les charges doivent être remplies dans un délai de 30 jours. Les documents modifiés seront réévalués en procédure présidentielle. D'autres obligations d'autorisation (Swissmedic/ OFSP) doivent être respectées

En l'état, l'autorisation ne peut pas être accordée : L'étude ne peut pas commencer. Prière de répondre point par point aux conditions de la commission d'éthique et de nous faire parvenir les documents révisés avec les modifications apparentes et la mention de la date de la nouvelle version.

Autorisation non accordée : L'étude ne peut pas commencer dans sa forme actuelle. Une nouvelle soumission reste possible.

Non entrée en matière : Justification, voir ci-dessus, par exemple la commission d'éthique n'est pas juridiquement compétente pour accorder une autorisation ou l'étude ne nécessite pas d'autorisation

Liste des documents soumis

Dr Stéphane Fournier, CHUV, Lausanne

nom du fichier	date du fichier	version
1. Cover Letter		
1.Submission letter.pdf	26/02/2019	
FFR-CT in NSTEMI_lettre de réponse CER-VD.docx	24/04/2019	
2019-00392-form-rep-190401.docx	24/04/2019	
cover-letter-26-08-2019.pdf	26/08/2019	
2019-00392-form-rep-190509.docx	20/05/2019	
2. Synopsis of the study plan		
see doc/cat: **4**, page/ref: **5**		
3. Participant information sheet and informed consent (ICF)		
3.FFR-CT in NSTEMI Informed Consent Form ORH_FINAL_2019.02.25.pdf	26/02/2019	1
FFR-CT in NSTEMI Informed Consent Form ORH_Version2_suivi des modifications.docx	24/04/2019	2
FFR-CT in NSTEMI Informed Consent Form ORH_Version2_modifications acceptées.docx	24/04/2019	2
ffr-ct-in-nstemi-informed-consent-form-orh-version4-track-change.docx	19/08/2019	4
FFR-CT in NSTEMI Informed Consent Form ORH_Version3_modifications acceptées.docx	20/05/2019	3
FFR-CT in NSTEMI Informed Consent Form ORH_Version3_suivi des modifications.docx	20/05/2019	3
ffr-ct-in-nstemi-informed-consent-form-orh-version4-clean.docx	19/08/2019	4
4. Study plan (protocol), signed and dated		
4.FFR-CT in NSTEMI_CE_FINAL_2019.02.25.pdf	26/02/2019	1.0
FFR-CT in NSTEMI_CE_Version2_suivi des modifications.docx	24/04/2019	2
FFR-CT in NSTEMI_CE_Version2_modifications acceptées.docx	24/04/2019	2
FFR-CT in NSTEMI_CE_Version3_modifications acceptées.docx	20/05/2019	3
FFR-CT in NSTEMI_CE_Version3_suivi des modifications.docx	20/05/2019	3
6. Investigator's CV, dated		
6.CV Fournier signé.pdf	28/01/2019	
8. Details on infrastructure suitability and availability at the location where the trial is executed		
8.Infrastructure.pdf	26/02/2019	
9. Agreement between sponsor/commissioned institution / grant provider or other third parties and the investigator		
cathworks-dta.pdf	26/08/2019	
heartflow-dta.pdf	26/08/2019	
10. Insurance		
10.attestation responsabilité et garantie 2019.pdf	07/01/2019	
11. Other documents handed over to study participants		

No other documents handed over to study participants

12. Details on nature and scope/value of compensation for participants

There is no compensation for the participation in this study

13. Other personnel

13.Site List.pdf 26/02/2019

14. Information on secure handling of biological material and personal data, and in particular on the storage thereof

see doc/cat: **3**, page/ref: **5**

34. Table with values of estimated effective radiation dose

see doc/cat: **4**, page/ref: **19**

12.4 Pocket Card Project Summary in French Language

Service de Cardiologie

Protocole:

Capacité du FFR-CT à détecter l'absence de lésion coronarienne significative parmi les patients avec un syndrome coronarien aigu à haut risque

Service de cardiologie

CHUV

TITRE

Capacité du FFR-CT à détecter l'absence de lésion coronarienne significative; parmi les patients avec un syndrome coronarien aigu à haut risque

OBJECTIF

Etudier l'intérêt du scanner coronaire avec mesure de la réserve de flux coronarien (FFR-CT) dans le syndrome coronarien aigu à haut risque.

CRITERES DE PRE-INCLUSION

- √ ≥18 ans
- √ Elévation ou baisse de la troponine T ultrasensible (hs-cTnT) mesuré au CHUV à au moins 2 reprises avec au moins une valeur supérieure au 99e percencentile et au moins un des critères suivants :
  - Symptômes d'ischémie
  - Changements ECG nouveaux ou présumés nouveaux au niveau des ondes T et/ou du segment ST (ST-T)
- √ Disponibilité présumée pour le suivi jusqu'à un an (c'est-à-dire que les patients uniquement en transit en Suisse sont exclus de facto)
- √ Admission dans le service de Cardiologie depuis les urgences via la filière institutionnelle dite « NSTEMI »

CRITERES D'EXCLUSION

- ⊗ Patients STEMI
- ⊗ eGFR <45 ml / min
- ⊗ Présence de critères de très haut risque :
  - Instabilité hémodynamique ou choc cardiogénique
  - Douleur thoracique récurrente ou persistante réfractaire au traitement médical
  - Arythmies mettant en jeu le pronostic vital ou arrêt cardiaque
  - Complications mécaniques de l'infarctus du myocarde
  - Insuffisance cardiaque aiguë
  - Changements dynamiques récurrents ST-T, en particulier sus-décalage ST intermittent
- ⊗ Femmes enceintes et allaitantes
- ⊗ Contre-indication au bêta-bloquant et / ou à la nitroglycérine
- ⊗ Patients transférés d'un autre hôpital où le diagnostic a été posé avec un dosage de la troponine autre que hs-TnT
- ⊗ Patients avec antécédent de pontage aortocoronarien (PAC)
- ⊗ Fraction d'éjection du ventricule gauche connue inférieure à 30%
- ⊗ Patients incapables de discernement ou sous tutelle
- ⊗ Patient en détresse émotionnelle ou autre condition psychique instable incompatible avec la signature du consentement éclairé

canton de vaud

Service de cardiologie

Patient remplissant critères de pré-inclusion et exclusion**:**

Timing : Dès que possible

Appeler l'équipe responsable du protocole

No Pronto : 45914

Timing : Entre T0 et T6

Admettre le patient dans le service de cardiologie

Timing: Par investigateurs

Présentation du protocole et du consentement

(Se trouve au bureau du 16ème étage)

Timing : Entre signature et T23[1,2,3,4]

Demande et réalisation du CT coronaire

En contactant le Dr. D. Rotzinger (62 538)

Timing : Entre CT et T24 [1]

Réalisation d'une coronarographie

Selon la procédure habituelle

[1] **Ce délai est applicable en semaine et peut être plus long les weekends et jours fériés**

[2] **En cas de survenue de critères de très haut risque nécessitant une coronarographie en urgence, le patient est exclu de l étude est le protocole et interrompu**

[3] **CAVE : Par design, les résultats du CT ne sont pas divulgués et le patient bénéficie donc d'une coronarographie de toute manière**

[4] **Le CT doit TOUJOURS être réalisé AVANT la coronarographie ou le patient sera exclu de l'étude**

Nous vous remercions d'avance pour votre collaboration

Vous pouvez à tout moment poser toutes vos questions et demander toutes les précisions nécessaires aux :

Numéro pronto de l'équipe responsable du protocole:

0213145914

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