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EDITORIAL

Leveraging QFR and SYNTAX score II 2020 to guide PCI versus CABG decisions in multivessel CAD – broadening QFR's utility

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There is a greater need than ever to tailor revascularisation appropriately, taking into consideration a patient's comorbidities, coronary anatomy, personal preferences, and individual perception of risk. The multidisciplinary Heart Team (HT) approach has been espoused and deployed for multiple conditions relevant to cardiovascular medicine: valvular heart disease, peripheral vascular disease, pulmonary embolism, and cardiogenic shock. The landmark randomised SYNTAX trial introduced the concept of the HT in decision-making between coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) in complex coronary artery disease (CAD). This was done to overcome the historical practice of the cardiologist acting as a gatekeeper to revascularisation, with the consequence of patients potentially being denied guideline-directed revascularisation therapy (CABG or PCI) through inappropriate use or underuse[1,2]. It is notable that since the publication of the SYNTAX trial both European and US guidelines on myocardial revascularisation have given a Class IC recommendation for HT decision-making between CABG and PCI[3,4].

The anatomical SYNTAX score (aSS) was developed prior to the design of the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial as a tool to force the interventional cardiologist and cardiac surgeon to systematically analyse the coronary angiogram in order to specify the number of coronary lesions that require treatment and assess their angiographic location and anatomical complexity. Numerous validation studies have confirmed the clinical validity of the aSS to identify higher-risk subjects and aid in decision-making between CABG and PCI in a broad range of patient types. Eighteen years after its design, the aSS is still advocated in both the European and US revascularisation guidelines as part of the SYNTAX-pioneered HT approach[3,4]. The functional SYNTAX score (FSS) uses the principle of the functional assessment of coronary lesions to determine the functionality of the aSS, rather than the sole angiographic determination of the SYNTAX score (SS) on the basis of visual assessment. In the FAME 3 trial, the FSS reclassified more than one-quarter of patients from an SS >22 to an FSS ≤22. In the 50% of PCI patients who had an FSS ≤22, the primary endpoint, which was the occurrence within 1 year of a major adverse cardiac or cerebrovascular event (MACCE; defined as death from any cause, myocardial infarction, stroke, or repeat revascularisation), occurred at a similar rate to patients treated with CABG (p=0.77). The primary endpoint in patients without functionally significant 3-vessel CAD was similar in patients in the CABG group (p=0.97). The rate of myocardial infarction and revascularisation among all deferred lesions was 0.5% and 3.2%, respectively[5].

In this issue of EuroIntervention, Asano et al present the results of the randomised DECISION QFR trial, which was conducted at 10 centres in Japan[6]. The study explored the feasibility of using the quantitative flow ratio (QFR) during HT discussions to determine the optimal revascularisation strategy for patients with multivessel CAD. The study seems to be inspired by the design of SYNTAX III REVOLUTION Trial, which we designed to determine the agreement between two separate HTs on treatment recommendation and planning based either on coronary computed tomography angiography (CCTA; with and without fractional flow reserve derived from computed tomography [FFRCT]) or conventional angiography in patients with left main or 3-vessel CAD. The primary endpoint was the agreement on the revascularisation strategy between separate HTs[7]. An HT treatment decision based on CCTA showed high agreement with the decision derived from conventional coronary angiography[7].

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The DECISION QFR trial was designed to determine the level of agreement between two separate Heart Teams on their treatment recommendation based either on QFR- or FFR-based data of the included patients. The primary endpoint of the DECISION QFR trial was an agreement on the revascularisation strategy between the separate HTs. The QFR/FFR was used to calculate the non-invasive FSS by subtracting non-flow-limiting stenosis (QFR/FFR >0.80) from the angiography-derived aSS. Finally, the non-invasive FSS was used to calculate the SYNTAX score II 2020, which is conceptually a combination of coronary anatomical complexity, with its physiological repercussions, and the patient's clinical features and comorbidities. The trial included 248 patients with multivessel CAD. Cohen's kappa in the recommended revascularisation modes between the QFR and FFR approaches was 0.73 (95% confidence interval [CI]: 0.62-0.83). As for revascularisation planning, agreements in the target vessels for PCI and CABG were substantial for both revascularisation modes (Cohen's kappa=0.72 [95% CI: 0.66-0.78] and 0.72 [95% CI: 0.66-0.78], respectively). The team assigned to the QFR approach provided consistent recommended revascularisation modes even after being aware of the FFR data (Cohen's kappa=0.95 [95% CI: 0.90-1.00]). It was concluded that QFR provided feasible physiological data for Heart Team discussions to determine the optimal revascularisation strategy for multivessel CAD and that the QFR and FFR approaches agreed substantially in terms of treatment recommendations. The present work is probably the first to explore the feasibility of vessel-level QFR to inform HT discussions.

Previously, in the *post hoc* analyses of the SYNTAX II trial, we had shown that the FSS based on QFR appropriately reclassified 26.1% of the patients in the high-to-intermediate-risk group into the low-risk group[8]. The area under the curve for QFR-based FSS to predict the 2-year patient-oriented composite endpoint was higher than that of the classic aSS (0.68 vs 0.56; p=0.002)[8]. At 2- and 5-year follow-up, the SYNTAX II PCI strategy led to substantially improved clinical outcomes compared with the PCI strategy in SYNTAX I. Also, the SYNTAX II PCI strategy demonstrated equipoise to CABG at 2- and 5-year follow-up for MACCE[8].

The present work contributes an additional asset to the already extensive arsenal of QFR, elucidated as follows: (a) QFR has undergone extensive validation against wire-based FFR in patients presenting with intermediate stenosis (40-90% diameter stenosis), exhibiting good diagnostic accuracy; (b) QFR serves as a non-invasive alternative, mitigating the inherent complications associated with wire-based FFR procedures (as evidenced by a 1.5% incidence of wire-related complications in the FFR arm of the DECISION QFR trial); (c) remarkably, precise QFR values can now be derived from a single projection; (d) moreover, robust clinical evidence supports the utilisation of QFR in guiding revascularisation decisions, particularly PCI, in cases of intermediate stenosis; (e) furthermore, the application of post-procedure QFR enables the prediction of outcomes, facilitating informed discussions with patients regarding expected prognoses[9]; (f) the QFR pullback curve (pullback pressure gradient index [PPGi]) can be utilised to objectively define focal and diffuse disease; (g) QFR can be used as a modality to adjudicate ischaemia-driven target vessel revascularisation according to Academic Research Consortium-2 consensus.

The authors have to be commended for using QFR/FFR in the trial, enabling the calculation of FSS and subsequent derivation of the SYNTAX score II 2020. Employing the functional SYNTAX score rather than solely relying on the anatomical SYNTAX score to compute the SYNTAX score II 2020 represents a sensible approach used by the authors of the trial. Long-term follow-up outcomes from the SYNTAXES (SYNTAX Extended Survival) trial were used to redevelop the SYNTAX score II (SSII), producing the SSII 2020, which can predict the 5-year risk for MACCE and 10-year risk for all-cause mortality, depending on whether the treating physician intends to refer the patient for PCI or CABG. The SSII 2020 was validated using patient-level data from the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease), BEST, PRECOMBAT and EXCEL trials as well as the CREDO-Kyoto registry, all of which enrolled patients with multivessel CAD or left main CAD undergoing PCI or CABG[10,11]. In the DECISION QFR trial, the mean predicted 10-year mortality risks after PCI, derived from the QFR-based SSII ($SSII_{QFR}$) and FFR-based SSII ($SSII_{FFR}$), were 35.0±20.8% and 35.2±20.9%, respectively. The interclass correlation coefficient for the absolute risk difference in 10-year mortality between the $SSII_{FFR}$ and $SSII_{QFR}$ was calculated to be 0.97 (95% CI: 0.96-0.97), indicating a high level of agreement. This suggests that $SSII_{QFR}$ demonstrates comparable performance to $SSII_{FFR}$ in assessing 10-year mortality risk. Moving forward, it is imperative to investigate in a randomised controlled manner whether the utilisation of either purely aSS or FSS, such as QFR-based FSS or FFR-based FSS, in the computation of SYNTAX score II 2020 yields discernible differences in long-term clinical outcomes. Interventionalists, especially those who are not familiar with intravascular imaging, increasingly favour non-invasive modalities such as QFR – the analysis of which is achievable within minutes in cath labs. This preference is driven by QFR's efficiency in aiding decision-making, outcome prediction, post-PCI physiology optimisation, and objectively defining focal and diffuse disease, marking a transition from invasive techniques towards procedural simplification. We have recently shown that machine learning can be used to decide between PCI and CABG in patients with complex CAD[12]. The parameters derived from QFR (preprocedural QFR, PPGi, QFR gradient per unit length [dQFR/ds], post-PCI QFR, etc.) can ultimately be incorporated in machine learning risk models to predict clinical outcomes.

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Conflict of interest statement

P.W. Serruys has no conflicts of interest to declare related to this editorial and is not rewarded financially for participation on advisory boards. P.C. Revaiah has no conflicts of interest to declare relevant to the contents of this paper.

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