

EDITORIAL COMMENT

Reclassification of Treatment Strategy by Routine Coronary Pressure Assessment—Episode 7 of the Saga



The More You Look, the More You Find It!*

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FROM DEFERRAL TO RECLASSIFICATION

A possible clinical use of trans-stenotic pressure-wire measurement to safely defer coronary angioplasty was first reported in the mid-1990s (1). The concept earned worldwide recognition with the publication in 2001 of the results of the DEFER (Deferral of Percutaneous Coronary Intervention) study (2). That study elegantly demonstrated that among 325 patients with angiographic stenosis referred for percutaneous coronary intervention (PCI), 181 (55%) had fractional flow reserve (FFR) values ≥ 0.75 , and those patients could be safely deferred without paying the price of an increased risk for cardiovascular events (2).

The concept of “pressure wire-based reclassification” was proposed some 15 years later in the paper “Outcome Impact of Coronary Revascularization Strategy Reclassification With Fractional Flow Reserve at Time of Diagnostic Angiography,” reporting on the results of the R3F study (episode 1 of the reclassification saga) (3). The 2 main findings of that study were that 1) among the 1,075 patients referred

for diagnostic angiography, the use of FFR reallocated (reclassified) the treatment decision compared with the angiography-based decision in 43% of patients; and 2) it was safe to pursue an FFR-guided treatment strategy divergent from the initial angiographic approach. Those results were confirmed by the reports of 2 studies investigating the same concept: the RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain) and POST-IT (Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease) studies (episodes 2 and 3) (4-7).

WHY “RECLASSIFICATION” CONVERTED PRESSURE-WIRE MEASUREMENT FROM AN INTERVENTIONAL TO A DIAGNOSTIC TOOL

At first, reclassification can be seen as a relatively simple and logical extension of the concept of deferral. In other words, deferral was a form of “reclassification,” but limited to PCI patients, while reclassification embeds also patients potentially considered for optimal medical therapy or coronary artery bypass grafting. Reclassification is more versatile than deferral, however, as any decision can be reallocated in any direction, as opposed to a single direction. Also, as opposed to “deferral,” which by definition is restricted to the PCI setting and to a PCI suite, “reclassification” repositions pressure-wire interrogations to a much earlier stage of the therapeutic decision and ultimately to the diagnostic workflow. In that regard, the recent development and validation of instantaneous wave-free ratio (iFR) as an alternative to FFR (8,9) is a perfect match for such a

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TABLE 1 Studies Evaluating Reclassification of the Treatment Strategy by Routine Coronary Pressure Assessment and Its Impact on Revascularization Rates

Study	Number of Patients	Target Population	Patients Considered for Revascularization Based on Angiography†	Reclassification Rate	Gain/Loss in Patients Undergoing Revascularization Following Pressure Wire	Number of Patients With 1-Year Clinical Outcome
Episode 1: R3F	1,075	Mostly stable	488 (45%)	43%	-32 (-6%)	1,075
Episode 2: RIPCORD	200	Stable	113 (56%)	27%	-3 (-1%)	0
Episode 3: POST-IT	918	Mostly stable	357 (39%)	44.2%	+123 (+34%)‡	918
Episode 4: FAMOUS-NSTEMI	176	ACS	158 (90%)	22%	-22 (-12%)	176
Episode 5: PRIME-FFR	533*	ACS	206 *(39%)	38%	+42* (+24%)	533*
Episode 6: DEFINE-REAL	484	MVD	346 (71%)	45%	-39 (-11%)	0
Episode 7: iFR-SWEDEHEART	2,013	Mostly stable Including 722 with MVD	1,282 (64%) 648 (89%)	40% 49%	-177 (-14%) -64 (-9%)	2,013
Total	4,866*		2,744 (56%)		-150 (-5%)	4,182*

*Because patients from PRIME-FFR were also part of R3F and POST-IT, they are not included in the total number of patients investigated. †Includes patients initially proposed for percutaneous coronary intervention and/or coronary artery bypass grafting. ‡Includes patients initially proposed to noninvasive ischemia testing, which had a final revascularization decision based on FFR evaluation.

ACS = acute coronary syndrome(s); DEFINE-REAL = Real-life information for the utilization of instantaneous wave-free ratio™ (iFR®) in assessing coronary stenosis relevance in the multi-vessel disease patient population; FAMOUS-NSTEMI = Fractional flow reserve versus angiography in guiding management to optimize outcomes in non-ST-elevation myocardial infarction; IFR SWEDEHEART = Instantaneous Wave-Free Ratio versus Fractional Flow Reserve A multicenter, prospective, randomized controlled clinical trial based on the Swedish angiography and angioplasty registry (SWEDEHEART) platform; MVD = multivessel disease; POST-IT = Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease; PRIME-FFR = Insights From the POST-IT (Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease) and R3F (French FFR Registry) Integrated Multicenter Registries-Implementation of FFR (Fractional Flow Reserve) in Routine Practice; RIPCORD = Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain; R3F = Registre Français de la FFR.

diagnostic-oriented approach, while keeping it simple.

Additional important pieces of data are supporting the use of pressure-wire measurement at the diagnostic stage. First, only 50% of “stable” patients currently referred for diagnostic coronary angiography underwent noninvasive testing before catheterization (5,7). Does this imply poor clinical judgment or bad practice? Not necessarily. In 2010, Patel et al. (10), reporting on nearly 400,000 patients referred for diagnostic angiography, suggested that the added value of “noninvasive tests” to predict the presence of significant coronary artery disease in patients undergoing an extensive clinical evaluation (including the collection of Framingham risk score, clinical risk factors, and symptoms) was limited. Furthermore, the R3F (Registre Français de la FFR) and DEFINE-REAL studies demonstrated that even among patients with positive noninvasive stress test results, the rate of reclassification remained well above 30% (3,11). Altogether, these observations suggest that a diagnostic workflow that allows patients to undergo one-stop coronary angiography combined with routine pressure-wire evaluation, while skipping noninvasive testing, can be a reasonable approach in some cases (providing, however, that clinical evaluation was extensive and thorough) and also that pressure-wire evaluation should not be denied to a patient solely on the basis of the result of any given stress test.

RECENT EXTENSIONS TO THE CONCEPT OF RECLASSIFICATION AND INSIGHTS FROM IFR-SWEDEHEART

Although reclassification was initially investigated in populations comprising mainly patients in stable condition, it has recently been extended to those with acute coronary syndromes (mainly non-ST-segment elevation myocardial infarction), as reported in the FAMOUS-NSTEMI and PRIME-FFR studies (episodes 4 and 5) (12,13). Both studies demonstrated that reclassification rates were considerable in this highly specific population (22% and 38%, respectively) (12,13). The PRIME-FFR (Insights From the POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French FFR Registry] Integrated Multicenter Registries-Implementation of FFR [Fractional Flow Reserve] in Routine Practice) study further demonstrated that the pattern of reclassification was different, with fewer patients with acute coronary syndromes reclassified from revascularization to medical treatment, compared with those without acute coronary syndrome. It also confirmed that a management strategy opposite to the one suggested by angiography remained safe in this population subset (13).

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A more recent addition to the reclassification concept relates to patients with multivessel disease

(MVD), who were investigated in DEFINE-REAL and in the substudy of iFR-SWEDEHEART (Instantaneous Wave-Free Ratio versus Fractional Flow Reserve A multicenter, prospective, randomized controlled clinical trial based on the Swedish angiography and angioplasty registry) published in this issue of *JACC: Cardiovascular Interventions* (episodes 7 and 8) (11,14). Both studies included altogether 1,206 patients with multivessel disease and demonstrated that reclassification was also very high in this population (45% in DEFINE-REAL and 58% in iFR-SWEDEHEART) (11,14). They further demonstrated that the chances of reclassification increased significantly with the number of vessels investigated: 37%, 47%, and 66% for patients investigated in 1, 2, and 3 vessels, respectively, in DEFINE-REAL and 36%, 52%, and 53%, respectively, in iFR-SWEDEHEART (11,14).

Another important addition of the study by Andell et al. (14) is to provide, all at once, 2,000 more patients in whom the impact of reclassification on 1-year clinical outcome was studied, thus bringing the total number of patients investigated to date to nearly 5,000 (Table 1).

As acknowledged by the investigators, although patients undergoing pressure-wire assessment with iFR or FFR were included in the study, “the treatment strategies of specific lesions pre and post-physiology were not recorded in the study protocol. Thus, in [the present] study [they] were unable to ascertain potential differences between iFR and FFR reclassifications on the lesion level. This should be addressed in future studies.”

WILL EXTENSIVE USE OF PRESSURE-WIRE ANALYSIS TRANSLATE INTO LESS REFERRAL OF PATIENTS FOR REVASCULARIZATION?

Most likely not. This issue has been in play since the first report of the DEFER study (2). One of the interpretations of the study was that extensive use of invasive physiology would translate into a massive decrease in the number of patients referred for revascularization (nearly 50%). As suggested by the DEFER trial findings, it is true that some proportion of patients referred for revascularization (namely, PCI) will end up with medical treatment as a result of pressure-wire interrogations; in fact, R3F, POST-IT, and iFR-SWEDEHEART are consistent with this initial observation, with decreases of 46%, 24%, and 28%, respectively (3,6,14). But the same studies also

demonstrated that for every 4 patients considered for medical treatment and undergoing pressure-wire evaluation, 1 will end up undergoing revascularization (33% in R3F, 27% in POST-IT, and 24% in iFR-SWEDEHEART) (3,6,14). Altogether, whether the use of invasive physiology decreases (or on the contrary increases) the number of patients referred for revascularization depends mainly on the evaluated population, more precisely on the proportion of patients considered for medical treatment or revascularization as the primary option (Table 1). When used in a population in which the majority of patients were not primarily considered for revascularization, as in POST-IT and PRIME-FFR, the net result is actually an increase (rather than a decrease) in the number of patients referred for revascularization.

These observations should also be interpreted in the light of the results of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and FAME-2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation-2) studies (15,16). Although the former study, which included mainly patients selected on the basis of positive noninvasive test results and abnormal angiographic findings, failed to show a clinical benefit of coronary revascularization over medical treatment, the latter, which included patients on the basis of the combination of both abnormal angiographic findings and abnormal pressure-wire results, demonstrated a sustained decrease of clinical events in those undergoing revascularization (15,16).

The accumulated evidence firmly demonstrates that physicians should not be afraid of extensive use of pressure-wire techniques during diagnostic coronary angiography. Definitely, its purpose is not to prevent patients from deriving the potential benefit of coronary revascularization but rather to define and deliver the most appropriate and refined treatment to each individual patient. The results from more than 5,000 patients (Table 1) are supportive of this approach, whereas the integration of the user-friendly iFR pressure-wire technique will help break down the last barriers.

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