RESEARCH LETTER

Impact of chronic kidney disease on fractional flow reserve accuracy in severe aortic stenosis

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Introduction Severe aortic stenosis (AS) is a major valvular heart condition, particularly in the elderly. With a growing elderly population, the prevalence of AS is expected to rise, making its effective diagnosis and management imperative.[1] With the aging population also comes an increased likelihood of concomitant diseases, among which coronary artery disease (CAD) stands prominent due to shared risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus.[2,3] Notably, CAD is associated with worse outcomes of transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) among these patients,[1-3] highlighting the critical need to assess CAD in this population.

Current guidelines favor angio-guided revascularization for the patients undergoing TAVI or SAVR.[4] However, there is a growing trend toward utilizing coronary physiology assessment, such as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) in severe AS. These methods are predominantly used for functional evaluation of borderline lesions.[5] However, their effectiveness in patients with severe AS is debatable. Some authors suggest their accuracy might be affected by the AS severity.[6-9] Moreover, standard threshold values for FFR/iFR might not apply to these patients, and comorbidities, such as chronic kidney disease (CKD) could alter the results.[6-8,10] Thus, we sought to evaluate the impact of CKD on FFR performance in the setting of severe AS.

Patients and methods Between 2018 and 2020, 221 patients with severe AS underwent FFR/iFR assessment for coronary artery lesions with 40%–90% diameter stenosis (%DS). Severe AS was defined as aortic valve area below 1 cm^2 and a mean aortic valve pressure gradient above 40 mm Hg. Data on serum creatinine levels were available for 209 patients, and their estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula. Then, based on their eGFR, the patients were categorized into 2 groups: eGFR below 60 ml/min/1.73 m^2 (designated as the CKD group) and eGFR equal to or above 60 ml/min/1.73 m^2 (designated as the non-CKD group). FFR/iFR assessment protocols are detailed elsewhere.[10-12] iFR was measured thrice, with an average value used for analysis. FFR measurements were conducted using an intravenous adenosine infusion at a rate of 140 μg/kg/min. Thresholds for significant ischemia were equal to or below 0.80 for FFR and equal to or below 0.89 for iFR. Instances where FFR yielded a negative outcome while iFR was positive (FFR– | iFR+), and vice versa, where FFR was positive and iFR turned out negative (FFR+ | iFR–), were identified as discordant results. Metrics from quantitative coronary angiography (QCA) were derived by 2 experienced analysts who were blinded to the outcomes of the physiological assessments. This analysis was conducted using the CAAS 5.7 QCA package (Pie Medical, Maastricht, The Netherlands).

The study received ethics approval (1072.6120.1.2019) from the institutional ethical board of the Jagiellonian University Medical College and complied with the 1975 Declaration of Helsinki. The participants provided their written informed consent.

Statistical analysis Categorical data are shown as numbers (percentages), with group differences analyzed using the χ^2 test or the Fisher exact test. Continuous data are presented as mean (SD) or median (interquartile range [IQR]). Differences between the groups were compared using the *t* test for normally distributed variables and the Mann–Whitney test for non-normally distributed continuous variables. The congruence

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Received: October 21, 2023.
Revision accepted: December 22, 2023.
Published online: December 22, 2023.
Pol Arch Intern Med. 2024; 134 (1): 16649
doi:10.20452/pamw.16649

TABLE 1 Results of fractional flow reserve and instantaneous wave-free ratio assessment in patients with and without chronic kidney disease (per vessel)

Variable	Chronic kidney disease		*P* value
	Absent	Present	
All vessels	146 (100)	245 (100)	–
FFR ≤0.80	38 (26)	65 (26.5)	0.91
FFR	0.87 (0.80–0.89)	0.88 (0.80–0.89)	0.2
iFR ≤0.89	46 (31.5)	82 (33.5)	0.69
iFR	0.92 (0.88–0.93)	0.92 (0.88–0.94)	0.50
LAD	74 (50.6)	137 (55.9)	–
FFR ≤0.80	27 (36.5)	44 (32.1)	0.52
FFR	0.84 (0.78–0.87)	0.86 (0.80–0.89)	0.046
iFR ≤0.89	34 (45.9)	53 (38.7)	0.31
iFR	0.90 (0.86–0.92)	0.91 (0.87–0.93)	0.15
Non-LAD	72 (49.4)	108 (44.1)	–
FFR ≤0.80	11 (15.3)	21 (19.4)	0.47
FFR	0.89 (0.85–0.9)	0.89 (0.81–0.9)	0.61
iFR ≤0.89	12 (16.7)	29 (26.9)	0.11
iFR	0.93 (0.91–0.94)	0.93 (0.89–0.95)	0.68
Concordance – general	146 (100)	245 (100)	–
Concordant	138 (94.5)	228 (93.1)	0.57
Discordant	8 (5.5)	17 (6.9)	
FFR– | iFR–	100 (68.5)	163 (66.5)	0.83
FFR– | iFR+	8 (5.5)	17 (6.9)	
FFR+ | iFR –	0	0	
FFR+ | iFR+	38 (26)	65 (26.5)	

Data are presented as number (percentage) or median (interquartile range).

Abbreviations: FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; LAD, left anterior descending artery

between the FFR and iFR measurements was quantified using the intraclass correlation coefficient (ICC). Receiver operating characteristic (ROC) curve analysis was used to assess the ability of FFR to predict iFR equal to or below 0.89 and iFR to predict FFR equal to or below 0.80. The results include unadjusted areas under the curves (AUCs) with 95% CIs. The optimal threshold values for predictions were ascertained by maximizing the Youden index. Univariable analyses based on the logistic regression for predictors of FFR and iFR discordant results were presented as odds ratios (ORs) with 95% CIs. All the applied tests were 2-sided, and results yielding a *P* value below 0.05 were deemed significant. The analyses were done using STATISTICA 13.3 package (TIBCO Software Inc., Palo Alto, California, United States).

Results In the whole group of 209 patients with severe AS, 136 (65.1%) had CKD. The baseline characteristics were similar in the CKD and non-CKD groups (Supplementary material, *Table S1*). A total of 245 lesions (62.7%) were assessed in the CKD group, and 146 (37.3%) in the non-CKD group. Both groups showed consistent distribution of the affected vessels, primarily the left anterior descending artery (LAD). CAD severity was similar in both groups (Supplementary material, *Table S2*).

Median (IQR) FFR was 0.87 (0.80–0.89), and FFR equal to or below 0.80 was identified in 26.3% of the examined vessels. Median (IQR) iFR was 0.92 (0.88–0.93), with iFR equal to or below 0.89 in 32.7% of the assessed vessels. As shown in TABLE 1, both CKD and non-CKD patients had similar distributions of FFR and iFR values. The rate of significant ischemia (FFR ≤0.80 and iFR ≤0.89) was nearly equal in both groups. Only in the LAD, we saw a noticeable difference in median FFR values ($P = 0.046$).

There was a strong agreement between iFR and FFR values, as shown by the ICC value of 0.83 (95% CI, 0.80–0.86). This consistency persisted when the vessels were stratified by the CKD status, that is, non-CKD vessels demonstrated the ICC of 0.82 (95% CI, 0.75–0.86), and in CKD vessels the ICC was 0.84 (95% CI, 0.8–0.87) (Supplementary material, *Figure S1*). When we determined the diagnostic accuracy of FFR for detecting iFR equal to or below 0.89, the AUC from the ROC analysis was 0.997 (95% CI, 0.986–1.000; $P < 0.001$). Similarly, iFR's diagnostic accuracy in identifying FFR equal to or below 0.80 reached 0.995 (95% CI, 0.983–0.999; $P < 0.001$). The optimal FFR threshold to discern iFR equal to or below 0.89 was 0.82, offering sensitivity of 97.1% and specificity of 98.9%. The best iFR threshold for detecting FFR equal to or below 0.80 was 0.88, with sensitivity and specificity pegged at 99.1% and 95.8%, respectively. When we further scrutinized the vessels solely from the non-CKD patients (n = 146), the AUC in the ROC analysis for FFR in detecting iFR equal to or below 0.89 was 1.000 (95% CI, 0.980–1.000; $P < 0.001$), and for iFR in detecting FFR equal to or below 0.80 it was 0.998 (95% CI, 0.972–1.000; $P < 0.001$). Here, the optimal FFR threshold for detecting iFR equal to or below 0.89 was 0.83 (sensitivity, 100%; specificity, 99%), and for iFR to pinpoint FFR equal to or below 0.80, the optimal cutoff remained 0.88, with its sensitivity and specificity peaking at 100% and 98.2%, respectively. In the subset of vessels in the CKD patients (n = 245), the diagnostic accuracy (AUC in the ROC analysis) of FFR in detecting iFR equal to or below 0.89 was 0.996 (95% CI, 0.977–1.000; $P < 0.001$), and of iFR in detecting FFR equal to or below 0.80 was 0.997 (95% CI, 0.979–1.000; $P < 0.001$). The optimal FFR threshold to detect iFR equal to or below 0.89 was 0.82, with sensitivity and specificity of 96.3% and 98.2%, respectively, and for iFR to detect FFR equal to or below 0.80, a threshold of 0.88 yielded sensitivity of 98.5% and specificity of 96.1%.

The overall agreement between FFR and iFR was notably high in both the CKD and non-CKD groups, with concordant results observed in over 93% of the cases (TABLE 1). The only observed discordance was a scenario where FFR was negative and iFR was positive. Neither CKD status nor eGFR predicted discordant outcomes.

The sole identified predictor of discordance was %DS in QCA, with OR of 1.04 (95% CI, 1.01–1.07; $P = 0.008$).

Discussion Our study reaffirms that for the patients with severe AS, the threshold for FFR identifying significant ischemia could exceed the standard of 0.80. This necessitates careful interpretation of borderline FFR results in such patients to prevent false-negative findings on ischemia assessment.

CAD and CKD often coexist in patients with severe AS, impacting their outcomes.[2,3] The current guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery[4] for the management of valvular heart disease suggest surgical revascularization for coronary artery %DS equal to or greater than 70% (≥50% for left main) in patients primarily indicated for aortic valve surgery. Furthermore, coronary artery bypass grafting should be considered for coronary arteries with a %DS equal to or above 50% to 70%. Conversely, for patients with severe AS scheduled for TAVI, percutaneous coronary intervention (PCI) should only be considered for lesions with over 70% stenosis in proximal segments. This guidance seems unexpected, especially with increasing evidence linking CAD burden and post-TAVI outcomes. Moreover, the guidelines recommend functional assessment for coronary stenoses below 90% without noninvasive ischemia tests. Yet, distinguishing the chest pain as a symptom of CAD or severe AS remains challenging.[5] Despite this, FFR or iFR remains a gold standard in patients with severe AS, highlighted by a recent study underscoring FFR-guided benefits over angio-guided PCI in TAVI patients.[13] Both FFR and iFR values can be affected by factors such as restricted aortic valve or diminished vasodilation capability, often seen in patients with severe AS. iFR seems more reliable in such scenarios, less influenced by impaired vasodilation.[9] Consequently, iFR was employed as a reference method for ischemia assessment in our study. This notion was validated by several recent studies,[9] where a significant immediate decrease in FFR values following severe AS treatment with TAVI was observed, while no variation in iFR values was noted.

Microvascular dysfunction, often seen in patients with severe AS, can compromise FFR and iFR measurements.[14] Factors such as sex, age, diabetes mellitus, and CKD could affect microvascular function.[6] In particular, poorly-controlled diabetes and insulin therapy might lead to discrepancies in FFR and iFR / the resting full-cycle ratio (RFR) results.[15,16] However, the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization) trial[17] showed comparable outcomes of iFR- and FFR-guided strategies in diabetic patients. Another study[18] identified diabetes mellitus and creatinine clearance equal to or below 45 ml/min as independent predictors of FFR measurements, with CKD patients showing less frequent FFR indications of significant myocardial ischemia. CKD patients also have more diffuse atherosclerosis and elevated calcification levels that might impact coronary blood flow and intensify the hyperemic response. Studies have linked CKD with discrepancies between FFR and nonhyperemic assessment with the RFR, especially pronounced in patients with eGFR below 30 ml/min/1.73 m^2.[19,20] Nevertheless, FFR-guided revascularization strategy has been validated for CKD patients, although risks increase in those requiring hemodialysis. This could be attributed to CAD progression or the presence of other death causes.

Contrary to findings from other studies, our cohort demonstrated largely consistent FFR and iFR assessment results in the patients with and without CKD, with a notable difference in median FFR values specifically in the LAD. The overall concordance between FFR and iFR was high in both groups. This deviation in results might be attributed to the inclusion of a specific subset of patients with severe AS, a condition that could significantly impact the functional measurements.[19,20] Additionally, the risk profile of our cohort, which had a high prevalence of elderly individuals, women, and CKD patients, deviates from typical cohorts of patients featured in studies evaluating FFR/iFR in CAD.[19,20] Additionally, lesion location, pattern of coronary disease, lesion length, vessel diameter, and stenosis severity can influence the discordance between FFR and iFR/RFR. In our study, only %DS was identified as a predictor of discordant results.

Our findings suggest careful FFR interpretation in patients with severe AS, especially those with diabetes and / or CKD.[6,7,10] Such patients often show greater microvascular dysfunction. The RECOPA study (Resting Full-Cycle Ratio Comparation versus Fractional Flow Reserve)[19] proposed incorporating the predictors of discordance, such as CKD and diabetes, to improve RFR's diagnostic accuracy within a specific "grey zone" of RFR values. While FFR retains significant positive predictive value for ischemia detection in diabetic / severe AS patients, its precision in excluding ischemia appears diminished as compared with nondiabetic / nonsevere AS patients.[6] Borderline FFR values (0.80–0.83) might require further scrutiny, with potential benefits from intracoronary imaging and / or microvascular function assessment. Also, post-TAVI ischemia reassessment could be beneficial in these patients, especially in individuals with persistent angina or a lack of left ventricular function recovery.[7] The definitive role of CAD physiological assessment in patients with severe AS will likely emerge from ongoing randomized controlled trials, such as FAITAVI (Functional Assessment in TAVI), NOTION-3 (The third Nordic Aortic Valve Intervention), and TAVI-PCI (Optimal Timing of Transcatheter Aortic Valve Implantation and Percutaneous Coronary Intervention).[9]

Study limitations Our study has a few limitations. First, the modest sample size may affect robustness and generalizability of the findings. Second, we did not conduct noninvasive evaluations of myocardial ischemia, making alternative reference methods unavailable. Also, coronary physiology assessments were not revisited following treatment of severe AS. Information on microcirculatory dysfunction, coronary flow reserve, and central venous pressure was not collected. Furthermore, coronary pressure pullbacks were not conducted, preventing pullback pressure gradient calculations essential for characterizing the diffuse disease seen in CKD patients.

Conclusions In the patients with severe AS, FFR aligns closely with iFR. Nonetheless, the ideal FFR threshold for identifying significant ischemia (iFR ≤0.89) may differ from the standard cutoff of FFR equal to or below 0.80. Importantly, the presence of CKD did not alter this threshold.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS None.

FUNDING This work was supported by the National Science Center (grant number 2018/02/X/NZ5/02648; to PK) and by the Jagiellonian University Medical College (grant number N41/DBS/001013; to AD).

CONFLICT OF INTEREST None declared.

HOW TO CITE Dziewierz A, Rzeszutko Ł, Dudek D, et al. Impact of chronic kidney disease on fractional flow reserve accuracy in severe aortic stenosis. Pol Arch Intern Med. 2024; 134: 16649. doi:10.20452/pamw.16649

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