Supplementary Material

Prognostic Impact of Coronary Flow Reserve in Patients with Chronic Kidney Disease

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Table of Contents

Supplementary Tables

Table S1. Candidate Variables for Multivariable Analyses

Age
Female
Body mass index
Hypertension
Diabetes mellitus
Hyperlipidemia
Current smoking
Family history of cardiovascular disease
Chronic kidney disease
Ejection fraction
LA volume index
LVMI
E/e'
RV systolic pressure
Angiographic disease extent
Diameter stenosis
SYNTAX score
CFR
IMR

Abbreviations: CFR, coronary flow reserve; IMR, index of microcirculatory resistance; LA, left atrium; LVMI, left ventricular mass index; RV, right ventricle; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

Table S2. Baseline Characteristics According to the Presence of Chronic Kidney Disease and CFR

Variables	Total	CFR >2.0 No CKD	CFR >2.0 CKD	CFR ≤2.0 No CKD	CFR ≤2.0 CKD	P value
	N=351	N=226	N=27	N=83	N=15	
Age, years	59.8 ± 13.7	58.8 ± 13.5	61.0 ± 9.6	62.1 ± 15.34	59.6 ± 13.7	0.343
Female	103 (29.3%)	64 (28.3%)	3 (11.1%)	32 (38.6%)	4 (26.7%)	0.039
Body mass index, kg/m^2	23.5 ± 3.7	23.8 ± 3.7	22.1 ± 3.5	23.0 ± 3.7	23.3 ± 3.7	0.081
Hypertension	209 (59.5%)	128 (56.6%)	21 (77.8%)	48 (57.8%)	12 (80.0%)	0.065
Diabetes mellitus	163 (46.4%)	102 (45.1%)	21 (77.8%)	34 (41.0%)	6 (40.0%)	0.007
Hyperlipidemia	197 (56.1%)	132 (58.4%)	20 (74.1%)	37 (44.6%)	8 (53.3%)	0.036
Current smoking	165 (47.0%)	113 (50.0%)	14 (51.9%)	28 (33.7%)	10 (66.7%)	0.026
Family history of cardiovascular disease	89 (25.4%)	64 (28.3%)	8 (29.6%)	12 (14.5%)	5 (33.3%)	0.048
Laboratory Findings						
High sensitivity CRP, mg/dL	0.5 ± 1.5	0.5 ± 1.7	0.5 ± 0.8	0.5 ± 1.2	0.5 ± 1.0	0.996
Serum creatinine, mg/dL	1.0 ± 0.4	0.9 ± 0.3	1.3 ± 0.7	0.9 ± 0.3	1.8 ± 1.0	0.002
Estimated GFR, mL/min/1.73m^2	84.6 ± 25.9	89.0 ± 23.7	69.0 ± 23.1	83.9 ± 26.4	50.1 ± 25.4	<0.001
NT-proBNP, pg/mL	646.1 (118.3, 2978.8)	241.6 (77.9, 1534.0)	3504.0 (1289.5, 7885.3)	1822.0 (303.4, 4405.0)	2665.0 (2030.5, 4222.0)	<0.001
Echocardiographic Findings						
Ejection fraction, %	61.9 ± 7.9	62.4 ± 7.6	59.7 ± 6.4	61.4 ± 9.0	61.5 ± 9.5	0.234
LVEDD, mm	47.7 ± 5.2	48.3 ± 5.08	45.8 ± 3.8	46.4 ± 5.8	49.2 ± 4.5	0.004
LVESD, mm	29.3 ± 4.7	29.4 ± 4.84	28.8 ± 2.1	28.9 ± 5.1	30.0 ± 4.5	0.527
Septal wall thickness, mm	9.7 (8.5, 11.0)	9.2 (8.5, 10.4)	10.3 (9.5, 11.2)	10.0 (8.8, 12.9)	11.0 (8.8, 11.9)	0.001
Posterior wall thickness, mm	9.4 (8.2, 10.3)	9.00 (8.1, 10.0)	10.0 (9.6, 10.9)	10.0 (8.3, 11.7)	10.9 (10.0, 11.8)	<0.001
LA volume index, ml/m^2	40.8 (31.1, 54.4)	37.7 (29.6, 48.0)	61.2 (49.9, 76.2)	43.4 (34.4, 59.0)	45.0 (41.6, 50.6)	<0.001
Left atrial enlargement*	238 (70.4%)	139 (63.5%)	25 (96.2%)	60 (76.9%)	14 (93.3%)	<0.001
LVMI, g/m2	110.7 ± 35.5	106.06 ± 31.32	104.80 ± 25.63	121.75 ± 42.90	130.55 ± 46.45	0.01
Relative wall thickness	0.41 ± 0.10	0.38 ± 0.07	0.44 ± 0.08	0.45 ± 0.14	0.46 ± 0.13	<0.001
Left ventricular hypertrophy†	69 (19.8%)	20 (8.9%)	8 (29.6%)	35 (42.7%)	6 (40.0%)	<0.001
E velocity, cm/s	72.3 ± 22.4	69.2 ± 19.3	78.4 ± 24.1	76.8 ± 27.6	88.6 ± 25.7	0.017
A velocity, cm/s	61.3 ± 28.0	62.6 ± 25.3	37.1 ± 18.7	63.3 ± 33.1	71.6 ± 39.7	<0.001
e' velocity, cm/s	6.4 ± 2.4	6.8 ± 2.2	6.9 ± 2.8	5.5 ± 2.5	5.5 ± 1.7	0.001
E/e'	11.0 (8.8, 14.2)	10.4 (8.3, 12.6)	12.6 (8.9, 15.6)	13.8 (9.1, 19.8)	14.2 (13.0, 19.7)	<0.001
Peak TR velocity, m/s	2.4 ± 0.4	2.3 ± 0.3	2.5 ± 0.3	2.5 ± 0.5	2.5 ± 0.4	0.001
RV systolic pressure, mmHg	29.2 ± 8.5	26.8 ± 5.4	33.0 ± 8.5	33.5 ± 11.7	33.7 ± 11.2	<0.001

Interrogated Vessels						0.024
Left anterior descending artery	263 (74.9%)	157 (69.5%)	25 (92.6%)	69 (83.1%)	12 (80.0%)	
Left circumflex artery	42 (12.0%)	32 (14.2%)	0 (0.0%)	9 (10.8%)	1 (6.7%)	
Right coronary artery	46 (13.1%)	37 (16.4%)	2 (7.4%)	5 (6.0%)	2 (13.3%)	
Coronary Angiographic Parameters						
Angiographic disease extent						0.003
Insignificant stenosis	173 (49.3%)	98 (43.4%)	24 (88.9%)	42 (50.6%)	9 (60.0%)	
1-vessel disease	64 (18.2%)	45 (19.9%)	1 (3.7%)	17 (20.5%)	1 (6.7%)	
2-vessel disease	69 (19.7%)	52 (23.0%)	1 (3.7%)	13 (15.7%)	3 (20.0%)	
3-vessel disease	43 (12.3%)	31 (13.7%)	1 (3.7%)	9 (10.8%)	2 (13.3%)	
Reference vessel diameter, mm	3.0 ± 0.6	3.1 ± 0.6	2.9 ± 0.5	2.9 ± 0.5	3.0 ± 0.7	0.103
Diameter stenosis, %	37.2 ± 22.1	38.6 ± 21.7	20.8 ± 18.1	39.7 ± 22.5	33.2 ± 24.3	0.004
Lesion length, mm	13.3 ± 9.8	13.5 ± 10.1	9.6 ± 7.5	14.5 ± 10.1	14.2 ± 5.6	0.203
SYNTAX score	5.5 ± 7.1	6.1 ± 7.3	1.2 ± 3.6	5.3 ± 6.9	4.6 ± 6.6	<0.001
Coronary Physiologic Parameters						
Interrogated Vessels						0.024
- Left anterior descending artery	263 (74.9%)	157 (69.5%)	25 (92.6%)	69 (83.1%)	12 (80.0%)	
- Left circumflex artery	42 (12.0%)	32 (14.2%)	0 (0.0%)	9 (10.8%)	1 (6.7%)	
- Right coronary artery	46 (13.1%)	37 (16.4%)	2 (7.4%)	5 (6.0%)	2 (13.3%)	
Resting Pd/Pa	0.95 ± 0.04	0.96 ± 0.04	0.95 ± 0.03	0.93 ± 0.04	0.94 ± 0.04	<0.001
FFR	0.89 ± 0.05	0.89 ± 0.05	0.91 ± 0.04	0.89 ± 0.05	0.89 ± 0.05	0.092
Resting mean transit time, s	0.90 ± 0.49	1.02 ± 0.50	0.73 ± 0.31	0.66 ± 0.40	0.61 ± 0.37	<0.001
Hyperemic mean transit time, s	0.33 ± 0.23	0.28 ± 0.18	0.24 ± 0.14	0.47 ± 0.31	0.42 ± 0.27	<0.001
CFR	3.20 ± 1.72	3.97 ± 1.57	3.22 ± 0.84	1.42 ± 0.41	1.49 ± 0.29	<0.001
IMR, Unit	23.36 ± 15.29	20.53 ± 12.15	18.51 ± 11.19	31.65 ± 20.27	28.88 ± 14.73	<0.001

Data are presented as mean ± standard deviation and median with interquartile range or n (%).

* Defined as LA volume index >34 ml/m^2.

† Defined as LVMI ≥115/95 g/m^2 (male/female) and relative wall thickness >0.42.

Abbreviations: CFR, coronary flow reserve; CKD, chronic kidney disease; CRP, C-reactive protein; FFR, fractional flow reserve; GFR, glomerular filtration rate; IMR, index of microcirculatory resistance; LA, left atrium; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Pa, aortic pressure; Pd, distal pressure; RV, right ventricle; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; TR, tricuspid regurgitation.

Table S3. Multivariable Linear Regression Model of Predictors of CFR or IMR

Variable	Univariable analysis		Multivariable analysis*	
	β (95% CI)	P value	β (95% CI)	P value
Coronary Flow Reserve				
Glomerular filtration rate	0.016 (0.003 - 0.028)	0.017	0.016 (0.000 - 0.031)	0.045
Age	-0.017 (-0.047 - 0.014)	0.287	-0.008 (-0.039 - 0.024)	0.622
Diabetes mellitus	0.446 (-0.257 - 1.149)	0.207	0.418 (-0.270 - 1.105)	0.226
Body mass index	-0.027 (-0.123 - 0.069)	0.568	0.020 (-0.083 - 0.123)	0.695
Index of Microcirculatory Resistance				
Glomerular filtration rate	-0.184 (-0.342 - -0.026)	0.023	-0.142 (-0.330 - 0.047)	0.137
Age	0.291 (-0.083 - 0.666)	0.124	-0.199 (-0.189 - 0.588)	0.305
Diabetes mellitus	-4.381 (-13.080 - 4.318)	0.315	-4.653 (-13.150 - 3.841)	0.274
Body mass index	0.657 (-0.510 - 1.824)	0.262	0.188 (-1.088 - 1.464)	0.767

***** Adjusted covariables were age, diabetes mellitus and body mass index.

Abbreviations: CFR, coronary flow reserve; CI, confidence interval; HR, hazard ratio; IMR, index of microcirculatory resistance.

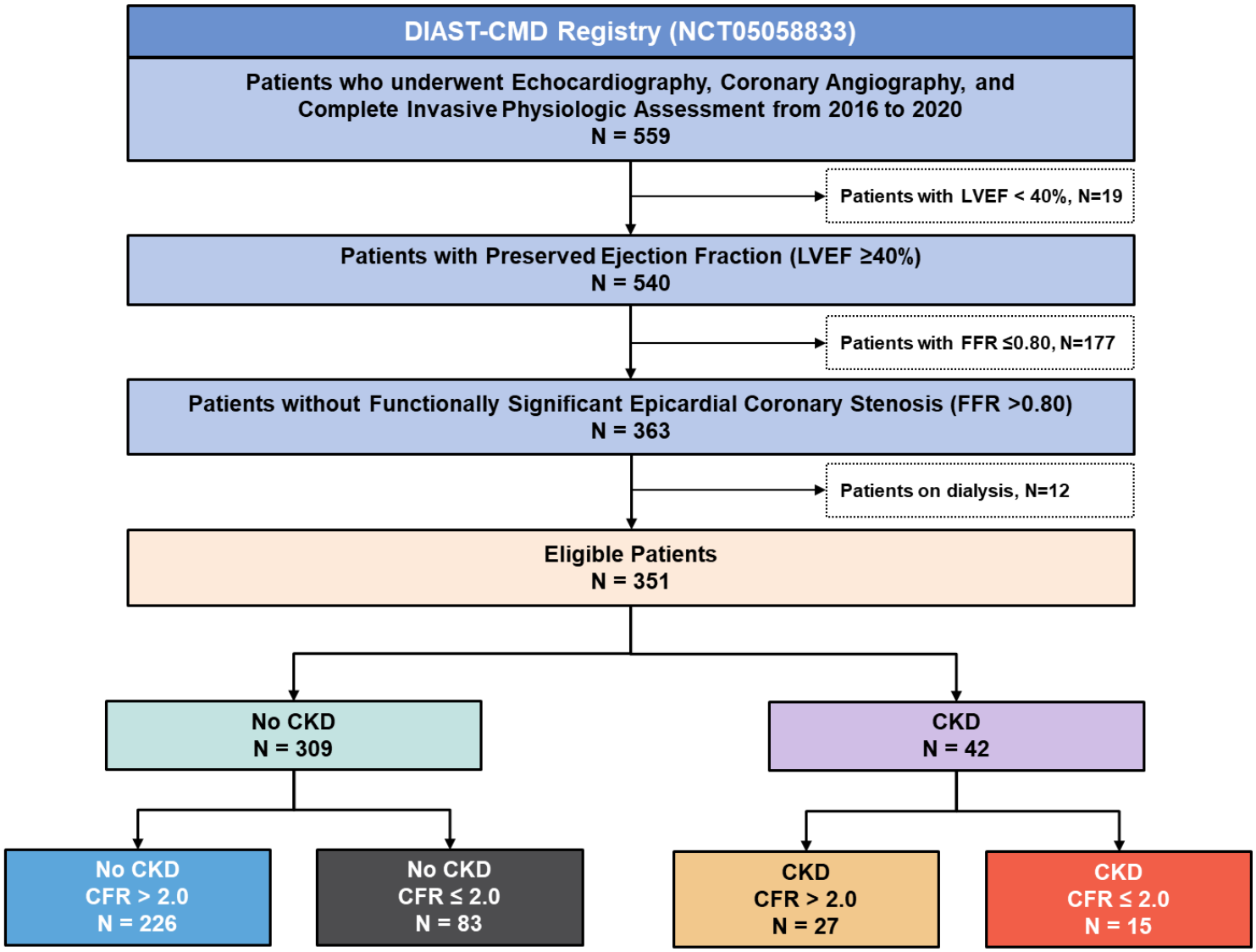
Supplementary Figures

Supplementary Figure 1. Study Flow

Study flow is shown. Among the registered population, patients with LVEF <40%, functionally significant epicardial coronary artery stenosis (FFR ≤0.80), or dialysis were excluded from the current analysis. A total of 351 patients were finally selected for the current analysis and grouped according to the presence of CKD and depressed CFR (≤2.0).

Abbreviations: CFR, coronary flow reserve; CKD, chronic kidney disease, DIAST-CMD, Prognostic Impact of Cardiac Diastolic Function and Coronary Microvascular Function; FFR, fractional flow reserve; LVEF, left ventricular ejection fraction.

Supplementary Figure 1. Study Flow



Modified STROBE Statement—checklist of items that should be included in reports of observational studies (Cohort/Cross-sectional and case-control studies)

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-9

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	*7-9*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at (if applicable)	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7-10
		(*e*) Describe any sensitivity analyses	10
Results			
Participants		(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for	11

	13*	eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	
		(c) **Use of a flow diagram**	S-Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results		Summarise key results with reference to study	13

	18	objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.