11-1-2022

Coronary flow abnormalities in chronic kidney disease: A systematic review and meta-analysis

Vardhmaan Jain

Kartik Gupta
Henry Ford Health, kgupta4@hfhs.org

Kirtipal Bhatia

Indranee Rajapreyar

Amitoj Singh

See next page for additional authors

Recommended Citation

Jain V, Gupta K, Bhatia K, Rajapreyar I, Singh A, Zhou W, Klein A, Nanda NC, Prabhu SD, and Bajaj NS. Coronary flow abnormalities in chronic kidney disease: A systematic review and meta-analysis. Echocardiography 2022.

Authors

Vardhmaan Jain, Kartik Gupta, Kirtipal Bhatia, Indranee Rajapreyar, Amitoj Singh, Wunan Zhou, Allan Klein, Navin C. Nanda, Sumanth D. Prabhu, and Navkaranbir S. Bajaj

Received: 9 April 2022 | Revised: 10 July 2022 | Accepted: 15 August 2022

DOI: 10.1111/echo.15445

Echocardiography WILEY

ORIGINAL ARTICLE

Coronary flow abnormalities in chronic kidney disease: A systematic review and meta-analysis

Vardhmaan Jain MD[1] | Kartik Gupta MD[2] | Kirtipal Bhatia MD[3] | Indranee Rajapreyar MD[4] | Amitoj Singh MD[5] | Wunan Zhou MD, MPH[6] | Allan Klein MD[2] | Navin C. Nanda MD[7] | Sumanth D. Prabhu MD[8] | Navkaranbir S. Bajaj MD, MPH[7,9]

[1]Department of Medicine, Cleveland Clinic, Cleveland, Ohio, USA

[2]Department of Medicine, Henry Ford Hospital, Detroit, Michigan, USA

[3]Department of Cardiology, Icahn School of Medicine at Mount Sinai (Morningside), New York, USA

[4]Advanced Heart failure and Transplantation Center, Jefferson University Hospital, Philadelphia, Pennsylvania, USA

[5]Division of Cardiology, University of Arizona College of Medicine-Tucson, Arizona, USA

[6]National Institute of Health, Bethesda, Maryland, USA

[7]Division of Cardiovascular Diseases, University of Alabama at Birmingham, Birmingham, Alabama, USA

[8]Division of Cardiology, Washington University, St. Louis, Missouri, USA

[9]Asheville Cardiology Associates, Asheville, North Carolina, USA

Correspondence
Navkaranbir S. Bajaj, MD, MPH, Division of Cardiovascular Diseases, The University of Alabama at Birmingham, Birmingham, AL 35294-0007, USA.
Email: bajaj.navkaran@gmail.com

Vardhmaan Jain and Kartik Gupta are co-primary authors.

Abstract

Background: Coronary vasomotion abnormalities have been described in small studies but not studied systematically. We aimed to review the present literature and analyze it to improve our understanding of chronic kidney disease (CKD) related-coronary microvascular dysfunction.

Objective: Coronary flow reserve (CFR) is a well-known measure of coronary vasomotion. We aimed to assess the difference in CFR among participants with and without CKD.

Methods: PubMed, Embase, and Cochrane CENTRAL were systematically reviewed to identify studies that compared CFR in participants with and without CKD. We estimated standardized mean differences in mean CFR reported in these studies. We performed subgroup analyses according to imaging modality, and the presence of significant epicardial coronary artery disease.

Results: In 14 observational studies with 5966 and 1410 patients with and without CKD, the mean estimated glomerular filtration rate (eGFR) was 29 ± 04 and 87 ± 25 ml/min/1.73 m^2, respectively. Mean CFR was consistently lower in patients with CKD in all studies and the cumulative mean difference was statistically significant (2.1 ± .3 vs. 2.7 ± .5, standardized mean difference −.8, 95% CI −1.1, −.6, $p < .05$). The lower mean CFR was driven by both significantly higher mean resting flow velocity (.58 cm/s, 95% CI .17, .98) and lower mean stress flow velocity (−.94 cm/s, 95% CI −1.75, −.13) in studies with CKD. This difference remained significant across diagnostic modalities and even in absence of epicardial coronary artery disease. In meta-regression, there was a significant positive relationship between mean eGFR and mean CFR ($p < .05$).

Conclusion: Patients with CKD have a significantly lower CFR versus those without CKD, even in absence of epicardial coronary artery disease. There is a linear association

Abbreviations: CAD, coronary artery disease; CFR, coronary flow reserve; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SMD, standardized mean difference.

between eGFR and CFR. Future studies are required to understand the mechanisms and therapeutic implications of these findings.

KEYWORDS
chronic kidney disease, coronary flow reserve, coronary microvascular dysfunction

Key Points

1. In this meta-analysis of observational studies, there was a significant reduction in coronary flow reserve in studies with chronic kidney disease versus those without.
2. This difference was seen even in absence of epicardial coronary artery disease.
3. In meta-regression, a lower estimate glomerular filtration rate was a significant predictor of lower coronary flow reserve.
4. Coronary microvascular dysfunction, rather than atherosclerosis-related epicardial disease may underly increase cardiovascular risk in a patient with chronic kidney disease.

1 | INTRODUCTION

There is a high prevalence of chronic kidney disease (CKD) in the United States.[1] Cardiovascular (CV) disease is the most important cause of morbidity and mortality in these patients and the risk increases with a decrease in the estimated glomerular filtration rate (eGFR).[2,3] Most CV morbidity and mortality in these patients are due to sudden cardiac death and heart failure-related death, and not due to type 1 myocardial infarction.[3] Coronary microvascular dysfunction, assessed by coronary flow reserve (CFR, ratio of stress to resting flow), may underly this increased risk.[4,5] CFR integrates the hemodynamic effects of coronary atherosclerosis, epicardial stenosis, and microvascular dysfunction,[6] and the risk of CV mortality increase with a reduction in CFR.[7,8] In this study, we explore the association between CFR and eGFR through a systematic review and metanalysis.

2 | METHODS

This study was reported per the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement (Table S1).[9]

2.1 | Study characteristics

We included studies (observation or randomized control trials) that reported CFR and eGFR in patients with and without CKD. We also included studies where patients were on hemodialysis or had renal transplants. For meta-regression, we also included studies that reported CFR and eGFR among patients with CKD only. We excluded studies where CFR was reported as a categorical variable (impaired or preserved). In the case of multiple publications, we included data from studies with larger sample size. Two reviewers (V.J. and K.G.) screened the title and abstracts of the retrieved studies. Disagreements were resolved through a third reviewer (N.S.B.). Full texts of the included studies were then screened to extract data by two independent reviewers (V.J. and K.G.) on pre-specified forms.

2.2 | Search strategy

We queried PubMed, Embase, and Cochrane CENTRAL from inception to May 31, 2020, for studies with the terms "coronary flow reserve," "CFR," "myocardial blood flow," "MBF," "myocardial flow reserve," "MFR," "fractional flow reserve," "FFR," "microcirculation," "chronic kidney disease," "CKD," and "impaired renal function." The search strategy has been detailed in the supplement (**eSearch Strategy**).

We further queried the references of the included studies to look for any other studies that may have been missed in the initial search. The review was registered on PROSPERO (ID CRD42020192357). This was a review of already published literature, and institutional review board approval was not required.

2.3 | Study variables

The study provided definition of CKD was used. In the studies, CKD was defined using Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as an estimated eGFR < 60 ml/min/1.73 m2 or markers of kidney damage, including albuminuria for >3 months.[10] In studies where patients with CKD were divided into sub-groups based on CKD stage, the overall mean eGFR was calculated from each stage using formulas provided in Cochrane's handbook.[11] Significant epicardial coronary artery disease (CAD) was defined using individual study definition or ≥50% obstruction in an epicardial coronary artery. All

patients with end-stage renal disease (ESRD) or on dialysis were considered to have a mean eGFR of 15 ml/min/1.73 m2 unless the mean was specified. When not available, mean eGFR was estimated by the Modification of Diet in Renal Disease (MDRD) equation using mean serum creatinine.[12]

2.4 | Outcome measure

The primary outcome was the standardized mean difference (SMD) of mean CFR in studies with and without CKD. Secondary outcomes were SMD of mean resting and stress coronary flow velocities and independent predictors of mean CFR.

2.5 | Statistical analysis

Random effects modeling was utilized given the heterogeneity between observational study populations for the outcomes of interest.[13] Inverse variance weighting and DerSimonian-Laird estimator using random-effects models were used. We also performed a meta-regression and subgroup analysis to evaluate the effect of eGFR, age, sex, diabetes mellitus, hypertension, body mass index (BMI), and imaging modality used on CFR. These variables were used based on their known association with CFR.[14–16]

In cases where meta-regression models identified a significant association, we confirmed the finding using permutation analysis. Publication bias was assessed using the funnel plot method as well as Egger regression asymmetry testing.[17] If there was a significant publication bias, we adjusted the pooled effect estimate with the Duval and Tweedie nonparametric *trim and fill* method of incorporating the estimates theoretically from the missing studies.[18] All statistical analysis was performed using R statistical software V 3.6.0.

3 | RESULTS

There were 14 studies with 4560 and 1410 participants with and without CKD that met our inclusion criteria (Figure S1). The baseline characteristics and comorbidities in the included studies are given in Table 1. The sample size in the studies varied from 24 to 3946. The mean age in the two groups was comparable in almost all studies. The proportion of women ranged from 16% to 81%. Fourteen studies excluded patients with significant epicardial CAD (Table 1). The definition of CAD in these studies varied and is summarized in Table S2. CFR was measured using Doppler echocardiography in ten studies, positron emission tomography in eight studies, and invasive angiography in four studies (Table 2).

3.1 | CFR in studies with and without CKD

The mean eGFR in participants with and without CKD was 29 ± 04 and 87 ± 25 ml/min/1.73 m2, respectively. Mean CFR was 2.1 ± .3 and 2.7 ± .5, respectively (SMD −.8, 95% CI −1.1, −.6, Figure 1). There was directional consistency in the results but there was high heterogeneity (I^2 83.0%, $p < .05$). There was a significant bias towards the publication of studies showing a statistically significant difference in CFR ($p = .02$, Figure S2). The effect estimate remained statistically significant after correction for publication bias (mean difference −.7, 95% CI −.5, −1.0, I2 52%, $p < .03$).

3.2 | Mean resting and stress coronary flow in studies with and without CKD

The lower mean CFR in studies with CKD was driven by a both a significantly higher resting flow velocity (SMD .58 cm/s, 95% CI .17, .98, Figure S3A) and lower stress flow velocity (SMD −.94 cm/s, 95% CI −1.75, −.13 Figure S3B).

3.3 | Sub-group analysis

Mean CFR was significantly lower in patients with CKD irrespective of significant epicardial CAD (Figure 1 and Table 3). Mean CFR was significantly lower in patients with CKD irrespective of imaging modality (p for sub-group difference < .05, Table 3).

3.4 | Dose-response relationship between eGFR and CFR

In addition to the 14 studies reporting CFR among participants with and without CKD, eight more studies reported CFR among patients with CKD only. In these 22 studies (5966 and 1410 patients with and without CKD, respectively), mean CFR had a significant positive association with mean eGFR such that mean CFR was reduced with a decrease in mean eGFR, suggesting a possible dose-response relationship (Figure 2).

In the multivariate analysis, besides mean eGFR, the presence of diabetes mellitus, and significant epicardial CAD were also significant predictors of mean eGFR, with a negative association. Table S3 summarizes the association of co-variates with CFR in the multivariate analysis.

4 | DISCUSSION

In this meta-analysis of observational studies, we found that mean CFR was lower among patients with CKD as compared to those with normal renal function. The lower mean CFR was driven by a higher mean resting flow but a lower mean stress flow. This difference was significant even in the absence of CAD and irrespective of the diagnostic modality. There appears to be a positive dose-response relation between mean eGFR and mean CFR in the studies.

CFR is the ratio of absolute myocardial blood flow during hyperemia (stress/exercise/maximal vasodilation) to rest.[19] It provides an integrated assessment of coronary abnormalities in the epicardial

TABLE 1 Baseline laboratory, demographic, clinical and imaging characteristics in the included studies

Sr. no	Author	Year	Sample size		Mean age		Women (%)		Diabetes (%)		Hyper-tension (%)		Vessel	Modality	Epicardial CAD	Vasodilator
Studies enrolling patients with and without CKD																
			No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD				
1.	Ragosta[8]	2004	43	21	52	52	53	52	25	100	53	90	LAD	Wire	No	Adenosine
2.	Tok[29]	2005	14	10	56	57	43	40	0	0	100	100	LAD	Doppler	No	Dipyridamole
3.	Chade[30]	2006	481	124	47	59	57	81	7	6	32	45	LAD	Wire	No	Adenosine
4.	Niizuma[31]	2008	20	21	68	64	30	5	44	68	55	100	LAD	Doppler	Yes	Adenosine
5.	Caliskan[32]	2008	39	75	38	36	46	39	0	0	0	81	LAD	Doppler	Yes	Dipyridamole
6.	Bozbas[33]	2008	26	60	37	36	31	27	0	0	4	63	LAD	Doppler	No	Dipyridamole
7.	Koivuviita[34]	2009	10	22	59	54	30	41	0	0	0	100	NA	PET	No	Dipyridamole
8.	Bezante[35]	2009	64	12	45	55	20	58	0	0	100	100	LAD	Doppler	No	Adenosine
9.	Charytan[14]	2010	158	277	50	64	16	39	0	0	100	100	NA	PET	Yes	Adenosine
10.	Sakamoto[36]	2012	60	13	61	68	57	62	7	15	42	62	LAD	Wire	No	Nitroglycerine
11.	Charytan[22]	2017	198	3,748	49	70	66	47	28	29	69	70	NA	PET	Yes	Dipyridamole
12.	Tsuda[37]	2017	46	46	74	77	59	61	28	28	72	67	NA	PET	No	Adenosine
13.	Nelson[43]	2018	15	15	53	52	40	27	27	47	53	80	LAD/LCx	Wire	No	Acetylcholine
14.	Bajaj[4]	2020	236	116	62	73	64	61	31	39	72	90	NA	PET	No	Dipyridamole, Adenosine, Regadenoson
Studies enrolling patients with CKD alone																
15.	Gorgulu3[9]	2010	NA	83	NA	37	NA	39	NA	0	NA	19	LAD	Doppler	No	Dipyridamole
16.	Nakanishi[40]	2011	NA	139	NA	73	NA	39	NA	29	NA	78	LAD	Doppler	Yes	Adenosine
17.	Caliskan[41]	2012	NA	37	NA	48	NA	59	NA	NA	NA	NA	LAD	Doppler	Yes	Dipyridamole
18.	Murthy[42]	2012	NA	866	NA	71	NA	50	NA	45	NA	91	NA	PET	Yes	Dipyridamole
19.	Shah[5]	2017	NA	168	NA	61	NA	39	NA	61	NA	93	NA	PET	Yes	Dipyridamole, Adenosine, Regadenoson
20.	Wenning[44]	2020	NA	39	NA	49	NA	36	NA	23	NA	100	NA	PET	No	Adenosine
21.	Lakkas[45]	2020	NA	45	NA	50	NA	33	NA	16	NA	87	LAD	Doppler	No	Dipyridamole
22.	Papamichail[38]	2020	NA	29	NA	63	NA	38	NA	17	NA	86	LAD	Doppler	No	Dipyridamole

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; LAD, left anterior descending artery; LCX, left circumflex artery; NA, not available; PET, positron emission tomography.

TABLE 2 Renal function and coronary flow reserve in individual studies

Sr. no	Author	Year	Mean eGFR (ml/min/1.73 m^2)		Mean coronary flow reserve	
			No CKD	CKD	No CKD	CKD
1	Ragosta[8]	2004	NA	15	2.7 ± .7	1.6 ± .5
2	Tok[29]	2005	87	12	2.6 ± .6	2.0 ± .3
3	Chade[30]	2006	76	53	3.0 ± .8	2.6 ± .6
4	Niizuma[31]	2008	94	7	2.4 ± .5	2.0 ± .5
5	Caliskan[32]	2008	112	11	2.7 ± .7	1.7 ± .4
6	Bozbas[33]	2008	95	32	3.0 ± .6	2.3 ± .5
7	Koivuviita[34]	2009	76	22	2.9 ± 1.1	2.6 ± 1.1
8	Bezante[35]	2009	92	68[τ]	3.0 ± .7	2.5 ± .8
9	Gorgulu[39]	2010	NA	15	NA	1.7 ± .3
10	Charytan[14]	2010	71	60*	2.8 ± 1.3	2.4 ± .9
11	Nakanishi[40]	2011	NA	46	NA	2.5 ± .7
12	Sakamoto[36]	2012	79	49	4.0 ± 1.1	3.1 ± .6
13	Caliskan[41]	2012	NA	6	NA	1.8 ± .4
14	Murthy[42]	2012	NA	37	NA	1.5 ± .6
15	Charytan[22]	2017	119	42	2.0 ± .7	1.8 ± 6
16	Shah[5]	2017	NA	15	NA	1.5 ± .4
17	Tsuda[37]	2017	72	44	2.2 ± .4	1.9 ± .4
18	Nelson[43]	2018	NA	7	3.1 ± .3	2.3 ± .4
19	Papamichail[38]	2020	NA	5	NA	1.6 ± .4
20	Wenning[44]	2020	NA	15	NA	2.9 ± 2.5
21	Lakkas[45]	2020	NA	51	NA	2.7 ± .8
22	Bajaj[4]	2020	85	39	2.0 ± .7	1.6 ± .6

In studies where patients had eGFR > 60 ml/min/1.73 m^2, CKD was determined by increased albumin-creatinine ratio.

vessels and microvasculature.[19] CFR < 2.0 is prognostic for future cardiovascular events.[7,19] Its non-invasive assessment by transthoracic doppler, MRI, and PET is a class IIb (Level of Evidence: B) recommendation by the 2019 European Society of Cardiology guidelines for patients with chronic coronary syndromes suspected to have coronary microvascular dysfunction.[7] CFR measurements correlate across diagnostic modalities, but the actual cut-off with the highest diagnostic accuracy for future CV events might differ.[20,21] We could not find any study that has compared CFR across all available non-invasive modalities and reported modality-specific CFR cut-offs for future risk.

Increased risk of sudden cardiac death, rather than atherosclerosis-related myocardial infarction, in patients with CKD, led to the recognition that coronary microvascular dysfunction could be one of the underlying mechanisms.[4,14,22] This microvascular dysfunction is seen in other arterial beds such as retinal and renal.[23,24]

Our data suggest that lower mean CFR in studies among studies with CKD was due to a significantly higher rest flow and comparable (but statistically lower) stress flow. Low hemoglobin CKD can result in higher resting cardiac output and subsequently higher resting myocardial blood flow, with relatively less effect on peak stress flow. Data from individual studies suggest that in the early stages of CKD, rest flow is increased, and stress flow is comparable.[14]

Other pathophysiological mechanisms with a relatively larger impact on myocardial work at rest, such as hypertension and heart rate, may also explain higher rest flow in CKD. The impaired mean peak flow velocities could be due to both functional (smooth muscle dysfunction and inflammation) and structural (vascular calcification and capillary rarefaction) changes that constitute coronary microvascular dysfunction.[25,26]

Our meta-regression results suggest a possible dose-response relationship such that mean CFR declines proportionately with a decline in mean eGFR. Data from individual studies suggest a stepwise decrease in CFR with increasing stages of CKD, such that there is a marked decline during the initial stages (2.06 and 1.91 in stages 1 and 2, respectively), with a plateau in later stages (1.54 and 1.66 in stages 4 and 5, respectively).[22] Stepwise decrease in CFR seen with advancing CKD is likely multifactorial, with confounding from other known factors such as age, hypertension, and diabetes mellitus. Further studies should also explore the effect of renal replacement therapy and renal transplantation on CFR. Newer therapeutics, such as sodium-glucose transporter 2 inhibitors and non-steroidal mineralocorticoid receptor antagonists, are associated with improved CV and renal outcomes.[27,28] It would be interesting to know if this CV benefit is mediated by any improvement in coronary microvascular dysfunction. Currently, it is unknown

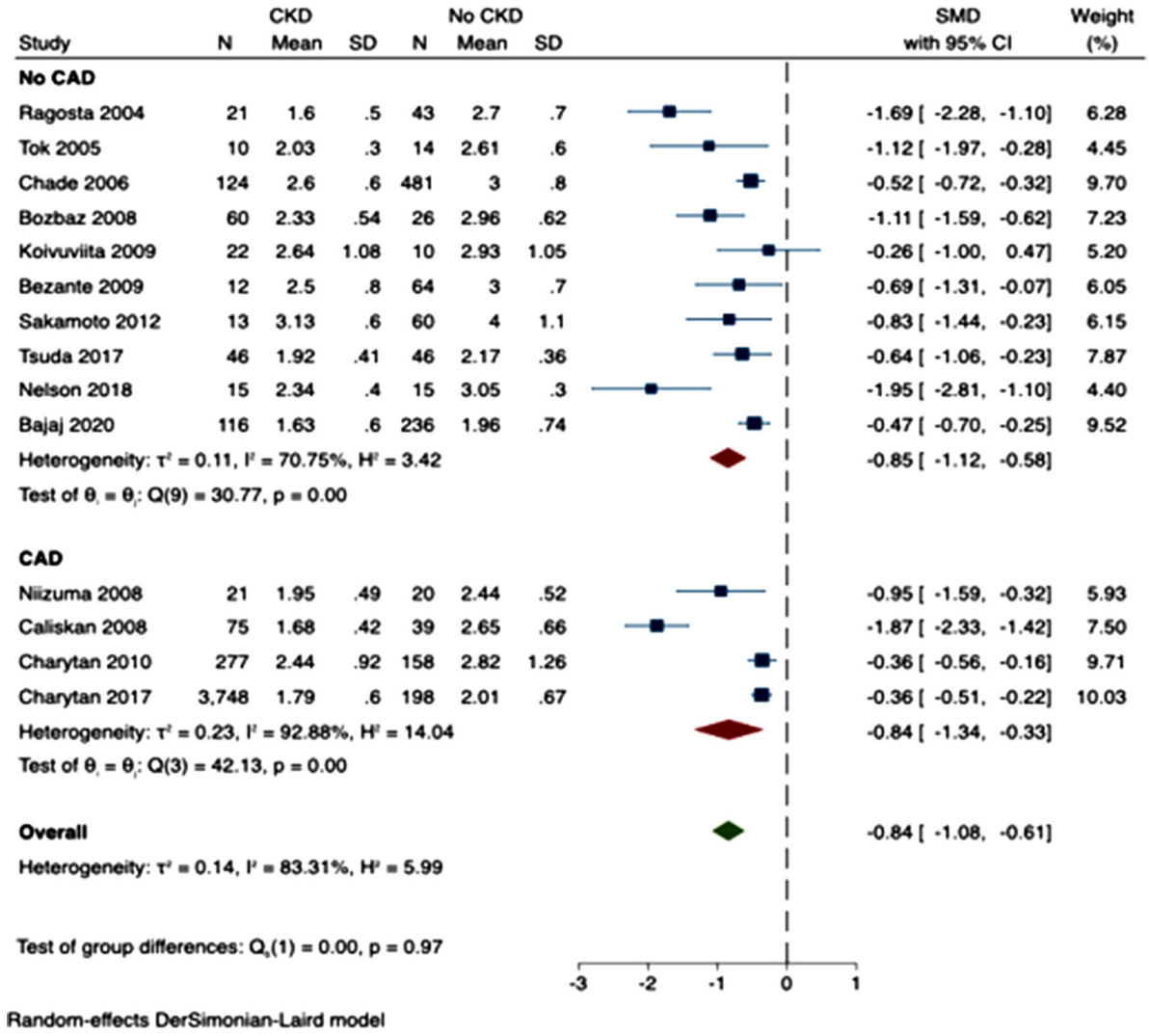

FIGURE 1 Forest plot showing the standardized mean difference for CFR between patients with and without CKD stratified by the presence or absence of epicardial coronary artery disease. The gray square boxes represent the mean difference reported in each study listed in the left column. Black solid diamond markers and associated solid lines represent the summary mean differences and 95% confidence interval (CI). The summary solid red diamond represents the effect estimate for the standardized mean difference using a random-effect meta-analysis. CKD denotes chronic kidney disease; CFR denotes coronary flow reserve; CAD denotes coronary artery disease.

TABLE 3 Summary of subgroup analysis based on imaging modality and epicardial CADR

	Mean eGFR (ml/min/1.73 m^2)		Mean CFR		
Subgroup	No CKD	CKD	No CKD	CKD	CFR mean difference
Imaging modality					
Invasive angiography	75 ± 5	30 ± 6	3.2 ± .4	2.4 ± .5	−.7 (−.9; −.5)
Doppler	96 ± 15	28 ± 4	2.7 ± .3	2.1 ± .4	−1.25 (−1.5; −1.0)
PET	85 ± 29	30 ± 4	2.3 ± .3	1.9 ± .3	−.40 (−.5; −.3)
Presence/absence of significant epicardial CAD					
Present	99 ± 29	20 ± 2.	2.5 ± .4	2.0 ± .3	−.83(−1.3, −. 3)
Absent	81 ± 7	35 ± 7	2.8 ± .6	2.3 ± .6	−.84 (−1.1, −.6)

Abbreviations: eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; CFR, coronary flow reserve; CKD, chronic kidney disease; PET, positron emission tomography.

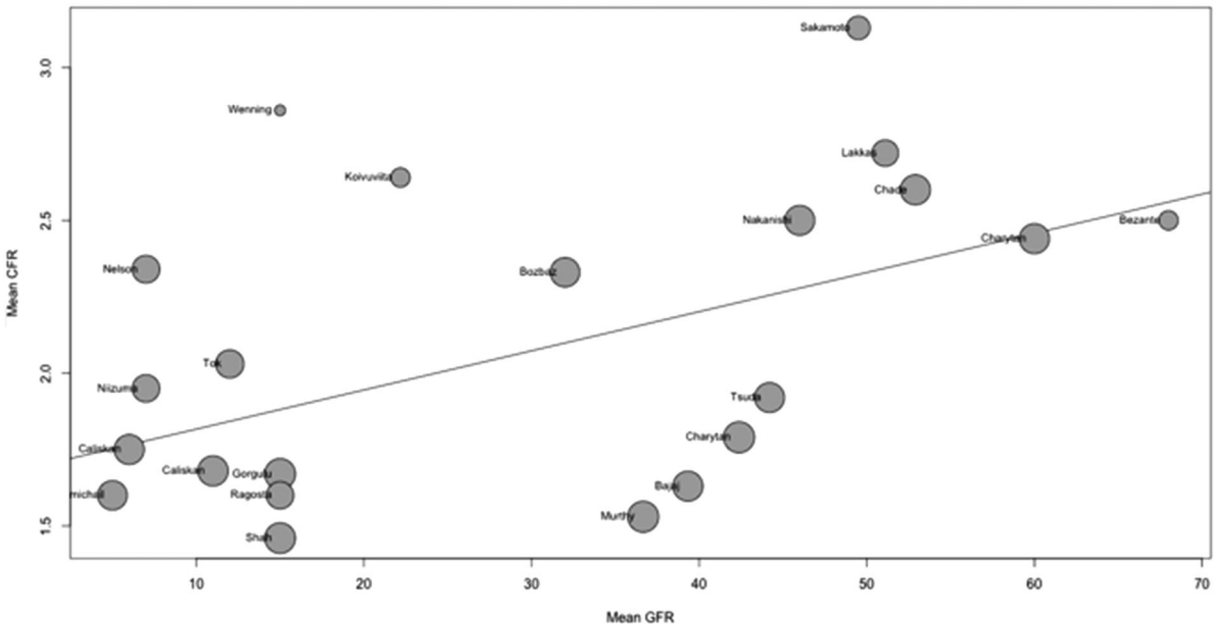

FIGURE 2 Bubble plot showing the meta-regression of the pooled mean eGFR as the independent variable and pooled mean CFR as the dependent variable in patients with CKD. Each bubble represents a study and the size of each bubble reflects the weight in the pooled effect. The slope of the regression line corresponds to the coefficient for eGFR (.01) and the y-intercept corresponds to the CFR when eGFR is zero (1.7). CFR denotes coronary flow reserve; GFR denotes glomerular filtration rate; CKD denotes chronic kidney disease.

if the assessment of coronary microvascular dysfunction improves prognostication in asymptomatic patients beyond already known risk factors.

To the best of our knowledge, this is the first quantitative synthesis of observational studies comparing CFR among patients with CKD and normal renal function. Despite directional consistency, there was significant heterogeneity in the reported results. This is likely due to varying baseline characteristics (such as age and comorbidities), etiology (such as diabetes and glomerulonephritis), and stage of CKD. Our study has important limitations. In studies where we computed mean eGFR from mean serum creatinine using the MDRD equation, patient-level factors such as race and BMI were not available for all studies. There was insufficient data on the etiology of CKD. Some etiologies, such as diabetes mellitus, may independently cause coronary microvascular dysfunction, and their prevalence is likely higher among patients with CKD. We used a random-effect meta-analysis; the results may be fundamentally skewed in a non-random fashion when comparing the two groups. Lastly, patients with renal transplants are a distinct group but were reported with patients without transplants if they had the same eGFR.

5 | CONCLUSION

In this meta-analysis of observational studies, we report that mean CFR is significantly lower in studies with CKD versus no CKD. The lower CFR is due to both higher resting flow and lower stress flow. This difference remains significant even in the absence of epicardial coronary artery disease.

CONFLICT OF INTEREST

The authors do not have conflicts of interest in relation to the content of this manuscript.

REFERENCES

1. Kidney Disease Statistics for the United States | NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed July 16, 2020. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease
2. United States Renal Data System: 2013 Atlas of CKD & ESRD. Accessed September 25, 2022. https://render.usrds.org/atlas.aspx
3. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol*. 1999;10(7): 1606-1615.
4. Bajaj NS, Singh A, Zhou W, et al. Coronary microvascular dysfunction, left ventricular remodeling, and clinical outcomes in patients with chronic kidney impairment. *Circulation*. 2020; 141(1): 21-33. https://doi.org/10.1161/CIRCULATIONAHA.119.043916
5. Shah NR, Charytan DM, Murthy VL, et al. Prognostic value of coronary flow reserve in patients with dialysis-dependent ESRD. *J Am Soc Nephrol JASN*. 2016; 27(6): 1823-1829. https://doi.org/10.1681/ASN.2015030301
6. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol*. 2013; 62(18): 1639-1653. https://doi.org/10.1016/j.jacc.2013.07.076

7. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020; 41(3): 407-477. https://doi.org/10.1093/eurheartj/ehz425
8. Ragosta M, Samady H, Isaacs RB, Gimple LW, Sarembock IJ, Powers ER. Coronary flow reserve abnormalities in patients with diabetes mellitus who have end-stage renal disease and normal epicardial coronary arteries. *Am Heart J*. 2004; 147(6): 1017-1023. https://doi.org/10.1016/j.ahj.2003.07.029
9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009; 62(10): 1006-1012. https://doi.org/10.1016/j.jclinepi.2009.06.005
10. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). *Kidney Int*. 2005; 67(6): 2089-2100. https://doi.org/10.1111/j.1523-1755.2005.00365.x
11. 7.7.3.8 Combining groups. Accessed August 15, 2020. https://handbook-5-1.cochrane.org/chapter_7/7_7_3_8_combining_groups.htm
12. GFR Calculator. National Kidney Foundation. Accessed August 15, 2020. https://www.kidney.org/professionals/kdoqi/gfr_calculator
13. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. (2009). Random-Effects Model. In Introduction to Meta-Analysis (eds M. Borenstein, L.V. Hedges, J.P.T. Higgins and H.R. Rothstein). Accessed August 9, 2020. https://www.wiley.com/en-us/Introduction+to+Meta+Analysis-p-9780470057247
14. Charytan DM, Shelbert HR, Di Carli MF. Coronary microvascular function in early chronic kidney disease. *Circ Cardiovasc Imaging*. 2010; 3(6): 663-671. https://doi.org/10.1161/CIRCIMAGING.110.957761
15. Nahser PJ, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. *Circulation*. 1995; 91(3): 635-640. https://doi.org/10.1161/01.CIR.91.3.635
16. Mathew RC, Bourque JM, Salerno M, Kramer CM. Cardiovascular imaging techniques to assess microvascular dysfunction. *JACC Cardiovasc Imaging*. 2020; 13(7): 1577-1590. https://doi.org/10.1016/j.jcmg.2019.09.006
17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315(7109): 629-634. https://doi.org/10.1136/bmj.315.7109.629
18. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000; 56(2): 455-463. https://doi.org/10.1111/j.0006-341x.2000.00455.x
19. Taqueti VR. Coronary flow reserve: a versatile tool for interrogating pathophysiology, and a reliable marker of cardiovascular outcomes and mortality. *Eur Heart J*. 2022; 43(16): 1594-1596. https://doi.org/10.1093/eurheartj/ehac001
20. Morton G, Chiribiri A, Ishida M, et al. Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography. *J Am Coll Cardiol*. 2012; 60(16): 1546-1555. https://doi.org/10.1016/j.jacc.2012.05.052
21. Pärkkä JP, Niemi P, Saraste A, et al. Comparison of MRI and positron emission tomography for measuring myocardial perfusion reserve in healthy humans. *Magn Reson Med*. 2006; 55(4): 772-779. https://doi.org/10.1002/mrm.20833
22. Charytan DM, Skali H, Shah NR, et al. Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage. *Kidney Int*. 2018; 93(2): 501-509. https://doi.org/10.1016/j.kint.2017.07.025
23. Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities related to atherosclerosis? the atherosclerosis risk in communities study. *Arterioscler Thromb Vasc Biol*. 2000; 20(6): 1644-1650. https://doi.org/10.1161/01.atv.20.6.1644
24. Ooi QL, Tow FKNFH, Deva R, et al. The microvasculature in chronic kidney disease. *Clin J Am Soc Nephrol CJASN*. 2011; 6(8): 1872-1878. https://doi.org/10.2215/CJN.10291110
25. Amann K, Neusüß R, Ritz E, Irzyniec T, Wiest G, Mall G. Changes of vascular architecture independent of blood pressure in experimental uremia. *Am J Hypertens*. 1995; 8(4_Pt_1): 409-417. https://doi.org/10.1016/0895-7061(94)00248-A
26. Amann K, Wiest G, Zimmer G, Gretz N, Ritz E, Mall G. Reduced capillary density in the myocardium of uremic rats—A stereological study. *Kidney Int*. 1992; 42(5): 1079-1085. https://doi.org/10.1038/ki.1992.390
27. Dapagliflozin in Patients with Chronic Kidney Disease | NEJM. Accessed January 27, 2022. https://www.nejm.org/doi/full/10.1056/NEJMoa2024816
28. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med*. 2021; 385(24): 2252-2263. https://doi.org/10.1056/NEJMoa2110956
29. Tok D, Gullu H, Erdogan D, et al. Impaired coronary flow reserve in hemodialysis patients: a transthoracic Doppler echocardiographic study. *Nephron Clin Pract*. 2005; 101(4): c200-206. https://doi.org/10.1159/000087579
30. Chade AR, Brosh D, Higano ST, Lennon RJ, Lerman LO, Lerman A. Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease. *Kidney Int*. 2006; 69(2): 266-271. https://doi.org/10.1038/sj.ki.5000031
31. Niizuma S, Takiuchi S, Okada S, et al. Decreased coronary flow reserve in haemodialysis patients. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2008; 23(7): 2324-2328. https://doi.org/10.1093/ndt/gfm954
32. Caliskan Y, Oflaz H, Demirturk M, et al. Coronary flow reserve dysfunction in hemodialysis and kidney transplant patients. *Clin Transplant*. 2008; 22(6): 785-793. https://doi.org/10.1111/j.1399-0012.2008.00879.x
33. Bozbas H, Pirat B, Demirtas S, et al. Evaluation of coronary microvascular function in patients with end-stage renal disease, and renal allograft recipients. *Atherosclerosis*. 2009; 202(2): 498-504. https://doi.org/10.1016/j.atherosclerosis.2008.04.043
34. Koivuviita N, Tertti R, Järvisalo M, et al. Increased basal myocardial perfusion in patients with chronic kidney disease without symptomatic coronary artery disease. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2009; 24(9): 2773-2779. https://doi.org/10.1093/ndt/gfp175
35. Bezante GP, Viazzi F, Leoncini G, et al. Coronary flow reserve is impaired in hypertensive patients with subclinical renal damage. *Am J Hypertens*. 2009; 22(2): 191-196. https://doi.org/10.1038/ajh.2008.351
36. Sakamoto N, Iwaya S, Owada T, et al. A reduction of coronary flow reserve is associated with chronic kidney disease and long-term cardio-cerebrovascular events in patients with non-obstructive coronary artery disease and vasospasm. *Fukushima J Med Sci*. 2012; 58(2): 136-143. https://doi.org/10.5387/fms.58.136
37. Tsuda E, Toyoshima Y, Yamada O, et al. Cellular fraction analysis of pericardial effusion helps the diagnosis of eosinophilic myocarditis. *Cardiol Young*. 2019; 29(2): 140-145. https://doi.org/10.1017/S1047951118001956
38. Papamichail N, Bechlioulis A, Lakkas L, et al. Impaired coronary microcirculation is associated with left ventricular diastolic dysfunction in end-stage chronic kidney disease patients. *Echocardiogr Mt Kisco N*. 2020;37(4):536-545. https://doi.org/10.1111/echo.14625
39. Gorgulu N, Yelken B, Caliskan Y, et al. Endothelial dysfunction in hemodialysis patients with failed renal transplants. *Clin Transplant*. 2010; 24(5): 678-684. https://doi.org/10.1111/j.1399-0012.2009.01160.x
40. Nakanishi K, Fukuda S, Shimada K, et al. Prognostic value of coronary flow reserve on long-term cardiovascular outcomes in patients with

chronic kidney disease. *Am J Cardiol*. 2013; 112(7): 928-932. https://doi.org/10.1016/j.amjcard.2013.05.025

41. Caliskan Y, Ozkok A, Akagun T, et al. Cardiac biomarkers and non-invasive predictors of atherosclerosis in chronic peritoneal dialysis patients. *Kidney Blood Press Res*. 2012; 35(5): 340-348. https://doi.org/10.1159/000332084
42. Murthy VL, Naya M, Foster CR, et al. Coronary vascular dysfunction and prognosis in patients with chronic kidney disease. *JACC Cardiovasc Imaging*. 2012; 5(10): 1025-1034. https://doi.org/10.1016/j.jcmg.2012.06.007
43. Nelson AJ, Dundon BK, Worthley SG, et al. End-stage renal failure is associated with impaired coronary microvascular function. *Coron Artery Dis*. 2019; 30(7): 520-527. https://doi.org/10.1097/MCA.0000000000000727
44. Wenning C, Vrachimis A, Pavenstädt HJ, Reuter S, Schäfers M, Coronary artery calcium burden, carotid atherosclerotic plaque burden, and myocardial blood flow in patients with end-stage renal disease: a non-invasive imaging study combining PET/CT and 3D ultrasound. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol*. 2021;28:2660-2670. https://doi.org/10.1007/s12350-020-02080-w
45. Lakkas L, Naka KK, Bechlioulis A, et al. The prognostic role of myocardial strain indices and dipyridamole stress test in renal transplantation patients. *Echocardiogr Mt Kisco N*. 2020;37(1):62-70. https://doi.org/10.1111/echo.14570

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Jain V, Gupta K, Bhatia K, et al. Coronary flow abnormalities in chronic kidney disease: A systematic review and meta-analysis. *Echocardiography*. 2022;39:1382–1390. https://doi.org/10.1111/echo.15445