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"Prevalence And Clinical Characteristics Of CAD In HF With Reduced Ejection Fraction (Hfref) With Echo"

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Abstract
Introduction: *In current clinical practice, obstructive coronary artery disease (CAD) remains the most common underlying cause of heart failure with reduced ejection fraction (HFrEF), with many of these patients having a history of myocardial infarction (MI) or revascularization. Despite advances in cardiovascular diseases, chronic heart failure (HF) is a category, which the prevalence, incidence, hospitalization rate, total burden of mortality, and costs have increased in the past 2-3 decades. Even though HF is a major global health problem, the data from developing countries are sparse.*
Objective: To *evaluated the prevalence and characteristics of CAD in HF with reduced ejection fraction (HFrEF) with Echo.*
Methods: *This was a hospital based, cross-sectional observational study was conducted at cardiology department, Sadar Hospital, Rajbari, Dhaka, Bangladesh from January to December 2021. 100 patients with Clinical diagnosis of HF, diagnosed by the Framingham Congestive Heart Failure criteria14, with EF ≤40% undergoing CAG were enrolled in the study*
Results: *Total 100 patients included in our study. The mean age of the patients was 62.7 ±10.1 years, with 66% males. Patients with age ≥ 65 years (42%) were more likely to have significant CAD (p = 0.025). After comparison of clinical and laboratory features in patients with and without CAD clinical factors such as age ≥ 65 years, smokers, dyslipidemia, obesity, angina and echocardiographic indicators iEDV, iLVIDs and RWMA were predictors of CAD. Obstructive CAD was present in 34(34%) with 50.0%, 37.5% and 12.5% having triple (TVD), single (SVD) and double vessel disease (DVD) respectively. Age ≥ 65 years, smokers, dyslipidemia, obesity, angina, indexed left ventricular end diastolic volume (iEDV), indexed LV systolic diameter (iLVIDs) and regional wall motion abnormality (RWMA) on echocardiography were predictors of CAD, among only which, smoking was the independent predictor of CAD.*
Conclusion: *Our results suggest a lower prevalence of CAD in HFrEF than previously reported from developed countries, which may be due to a systematic Echo approach and exclusion of previous coronary events. However, there are data showing that patients with left ventricular systolic dysfunction without chest pain or previous MI are unlikely to present extensive coronary disease that could explain left ventricular dysfunction or to have coronary anatomy suitable for bypass grafting. Demonstration of underlying etiology is cornerstone of HF diagnosis and virtually all patients with unexplained HF should be evaluated for the presence of CAD. Most patients with HF due to ischemic cardiomyopathy have known coronary heart disease. We encourage clinicians to aggressively identify this co-morbidity as it has important treatment and prognostic implementations.*
Keywords*: Coronary Artery Disease, Heart Failure, Ejection Fraction.*

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I. Introduction

In current clinical practice, obstructive coronary artery disease (CAD) remains the most common underlying cause of heart failure with reduced ejection fraction (HFrEF), with many of these patients having a history of myocardial infarction (MI) or revascularization.[1] It is important to distinguish between CAD- and non-CAD-related HFrEF in the initial assessment of patients presenting with new-onset HFrEF of unknown etiology, since CAD-related HFrEF usually requires revascularization in order to improve symptoms and long-term prognosis.[2,3] Despite advances in cardiovascular diseases, chronic heart failure (HF) is a category, which the prevalence, incidence, hospitalization rate, total burden of mortality, and costs have increased in the past 2-3 decades[4]. Even though HF is a major global health problem, the data from developing countries are sparse[5]. The

effect of the epidemiologic transition varies not only among countries but also among regions, communities or ethnicities in the same country, making it difficult to generalize evidence obtained not only from Western countries but also from Asian countries[6]. Myocardial ischemia due to epicardial coronary artery disease (CAD), coronary microvascular dysfunction (CMD), or both, may represent a disease mechanism and therapeutic target in some patients with heart failure with preserved ejection fraction (HFpEF)[7,8,9]**.** Myocardial ischemia can cause left-ventricular (LV) diastolic and systolic dysfunction, both of which are common in HFpEF[10,11]. Inflammation-associated CMD may also play a role in the pathophysiologic characteristics of HFpEF[12], which is a possibility supported by noninvasive studies, an autopsy series, and small invasive studies[9,13,14,15]. As such, it has been common practice to exclude CAD by invasive Echo independently of risk factors or medical history as a first-line approach. However, there are data showing that patients with left ventricular systolic dysfunction without chest pain or previous MI are unlikely to present extensive coronary disease that could explain left ventricular dysfunction or to have coronary anatomy suitable for bypass grafting[16] . Demonstration of underlying etiology is cornerstone of HF diagnosis and virtually all patients with unexplained HF should be evaluated for the presence of CAD. Most patients with HF due to ischemic cardiomyopathy have known coronary heart disease[17]. Occult disease is a not uncommon cause of dilated cardiomyopathy, accounting for approximately 7% of initially unexplained cases. Up to one-third of patients with non-ischemic cardiomyopathy have chest pain that may resemble angina or be atypical. Revascularization may be of benefit in the appreciable number of patients in whom hibernating myocardium or silent ischemia is in part responsible for the decline in myocardial function. Although ICA remains the gold-standard technique for the assessment of obstructive CAD, it is known that outside the setting of an acute coronary syndrome (ACS), the prevalence of clinically meaningful CAD on ICA is low, even in patients with chest pain and previous positive noninvasive tests, as previously demonstrated by our group[18]. Clinical guidelines have struggled to make clear recommendations regarding the management of patients presenting with new-onset HFrEF of unknown etiology[19]. In both studies, the commonest cause of HF was CAD. Therefore, we planned to conduct this study to evaluate the prevalence of significant CAD using Echo approach in patients with HFrEF without coronary events or significant valvular heart disease.

II. Materials & Methods

This was a hospital based, cross-sectional observational study was conducted at cardiology department, Sadar Hospital, Rajbari, Dhaka, Bangladesh from January to December 2022. 100 patients with Clinical diagnosis of HF, diagnosed by the Framingham Congestive Heart Failure criteria[20], with EF ≤40% undergoing CAG were enrolled in the study (figure-1) after excluding:

- Moderate to severe valvular heart disease
- Documented MI or Previous coronary revascularization
- Myocarditis
- Diagnosed Non-ischemic cardiomyopathy
- Echoally proven CAD

The clinical data recorded included the risk factors for CAD and the symptomatology of the patients. Echocardiographic assessment and chamber quantification was done with a Philips ultrasound system as per American Society of Echocardiography (ASE) recommendations[21]. Measurements of LV volumes and ejection fraction were done by manual tracing of an endocardial border from apical 4- and 2-chamber views using the disk summation method. Arteriograms of the right and left coronary arteries were performed and the best projection, representing stenosis of the lesion with progression, were selected and examined for percentage diameter stenosis by quantitative coronary Echo analysis by use of a cardiovascular measurement system (Philips Medical Imaging Systems) in accordance with standard guidelines[22]. Coronary arteriograms were reviewed by the principal investigator and one independent observer experienced in Echo interpretation and blinded to the clinical data. The degrees of coronary artery obstruction were expressed as the % diameter stenosis, by comparing the diameter of the site of greatest narrowing (minimal lumen diameter) to an adjacent segment assumed to be free of disease. Lesion in an epicardial coronary artery was considered significant in ≥ 70% stenosis of the examined vessel or ≥ 50% of Left Main Coronary Artery (LMCA). Lesion severity was also classified as:

- Minimal / minor CAD: <50% stenosis
- Moderate: 50-70% stenosis
- Significant: ≥ 70% stenosis

Statistical Analysis: Categorical variables were presented as proportions or percentages while continuous data were presented as mean ± SD or median (IQR) depending on the normality of the data. In data analysis, 95% confidence interval (CI), P-value, odds ratio (OR) was computed to conclude the result obtained. Continuous variables between the patients diagnosed with significant obstructive CAD and those who did not have significant obstructive CAD were analyzed using an independent samples t-test after assessing the normality of data. Categorical variables were analyzed using the $\chi 2$ test. Multivariate logistic regression analysis was utilized

to evaluate the independent variables and the presence or absence of significant obstructive CAD. A backward-selection technique was used to generate a multivariable logistic regression model to determine the independent predictors of CAD. The Hosmer and Lemeshow test were used to assess the fitness of the model (p = 0.824 and Nagelkerke R Square 0.42). Logistic regression analysis was used to evaluate the independent predictors of CAD. Statistical significance in all tests was assumed at p-value of <0.05. All statistical analysis was done using the SPSS version 20.

III. Results

Total 100 patients included in our study. The mean age of the patients was 62.7 ±10.1 years, with 66% males. Patients with age ≥ 65 years (42%) were more likely to have significant CAD (p = 0.025). After comparison of clinical and laboratory features in patients with and without CAD clinical factors such as age ≥ 65 years, smokers, dyslipidemia, obesity, angina and echocardiographic indicators iEDV, iLVIDs and RWMA were predictors of CAD. However, on multivariate analysis, only smoking was the independent predictor of significant CAD (Table-1 & 2). Only 23% among the current cohort were smokers, 45% were obese (BMI ≥ 25 kgm-2), while 51% were hypertensive, 22% had diabetes and 19% had dyslipidemia. Dyspnea was the most common clinical manifestation (88%), while 50% had angina. Broad QRS complex with QRS duration ≥ 150ms was noted in 60% of the patients and three patients had sustained ventricular tachycardia. On echocardiographic evaluation, only four (5%) had left ventricular hypertrophy, while the mean indexed LV systolic diameter diastole (iLVIDd) and indexed LV systolic diameter systole (iLVIDs) were 3.45 ± 0.42 and 2.76 ± 0.55 mm/m2, respectively. The median indexed end diastolic volume (EDV) and end systole volume (ESV) were 94.8 (86.2 – 102.9) and 60.8 (54.3 –74.3) ml/m2, respectively. Mitral regurgitation was observed in 68%. The mean LVEF 32.1 ± 7.8% with 59% having global LV wall hypokinesia and 26% had regional wall motion abnormality (RWMA). Among the 26 patients having RWMA, LAD territory was involved in 19(95%) while one pLAD territory was patient had wall motion in RCA territory. Obstructive CAD (≥ 70 coronary stenosis) was present in 32(32%) while 28(28%) had minor CAD with < 50% coronary stenosis and only six (6%) had moderate stenosis of ≥50 to < 70% stenosis [Table-4]. Most common pattern of CAD was TVD (50%), followed closely by SVD (37.5%) [Table-5]. Among the coronary arteries LAD (39.7%) was the most commonly diseased vessel [Table - 6].

Table-1: Sex distribution of **Obstructive CAD (N=100)**

Sex	**Total (n=100) %**	**Obstructive CAD**		**P value**
		Present (n=32) %	**Absent(n=68)%**	
Male	66(66.0%)	23(71.9%)	43(63.2%)	0.227
Female	34(34.0%)	9(28.1%)	25(36.8%)	

Table-2: Age distribution of **Obstructive CAD (N=100)**

Age	**Total (n=100) %**	**Obstructive CAD**		**P value**
		Present (n=32) %	**Absent(n=68)%**	
<65years	58(58.0%)	14(43.8%)	44(64.7%)	0.025
≥65years	42(42.0%)	18(56.3%)	24(35.3%)	

Table-3: Clinical profile of **Obstructive CAD (N=100)**

	Total (n=100) %	**Obstructive CAD**		**P value**
		Present (n=32) %	**Absent(n=68)%**	
Smokers	23(23.0%)	16(50.0%)	7(10.3%)	<0.001
Hypertension	51(51.0%)	19(59.4%)	32(47.1%)	0.211
Diabetes	22(22.0%)	11(31.3%)	11(16.2%)	0.154
Dyslipidemia	19(19.0%)	11(31.3%)	8(11.8%)	0.014
Obesity	45(45.0%)	23(71.9%)	22(32.4%)	<0.001
Angina ≥ FC 2	50(50.0%)	28(87.5%)	22(33.8%)	<0.001
Dyspnea ≥ FC2	88(88.0%)	30(93.8%)	58(85.3%)	0.429
QRSD ≥ 50ms	59(59.0%)	23(71.9%)	36(52.9%)	0.097
LVH	5(5.0%)	0	5(7.4%)	0.200
iLVIDd (mm/m2)	100	3.33=0.49	3.51=0.45	0.090
iLVIDs (mm/m2)	100	2.85=0.54	2.55=0.58	0.016
iEDV (ml/m2)	100	91=16	99=14	0.010
iEDS (ml/m2)	100	63=17	67=16	0.186

Mitral regurgitation	68(68.0%)	20(62.5%)	48(70.6%)	0.166
LVEF %				
>30-≤40%	56(56.0%)	17(53.1%)	39(57.4%)	0.362
≤30%	44(44.0%)	15(46.9%)	29(42.6%)	
Wall Motion:				
RWMA	26(26.0%)	15(46.9%)	11(16.2%)	0.009
Global LV hypokinesia	59(59.0%)	17(53.1%)	42(61.8%)	0.174

Table-4: Results of Echo approach.

	N	**%**
Normal	34	34.0
Minor	28	28.0
Moderate	6	6.0
Obstructive	32	32.0

Table-5: Number of Coronary Arteries Involved in Significant CAD with HFrEF.

	N	**%**
TVD	16	50.0
SVD	12	37.5
DVD	4	12.5

Table-6: Involvement of individual coronaries among significant CAD.

	N	**%**
RCA	20	29.4
LAD	27	39.7
LSX	20	29.4
RI	1	1.5

Table 7: Independent predictors of CAD in HFrEF – logistic regression analysis with 95% CI.

Variable	**B**	**Wald $\chi 2$**	**P-value**	**95% CI**		**Odds Ratio (OR)**
				Lower	**Upper**	
Age ≥ 65 y	1.012	3.052	0.081	0.884	8.569	2.752
Smoker	1.716	5.997	0.014	1.408	21.946	5.560
Obesity	0.860	1.848	0.174	0.684	8.168	2.363
Dyslipidemia	0.978	1.707	0.191	0.613	11.522	2.658
Angina	1.397	1.953	0.162	0.570	28.700	4.044
RWMA	0.745	1.154	0.283	0.541	8.208	2.107
iLVIDs	0.303	0.160	0.689	0.307	5.964	1.354
iEDV	-0.048	3.407	0.065	0.953	1.003	0.953
> 3 risk factors	-0.414	0.179	0.672	0.097	4.500	0.661

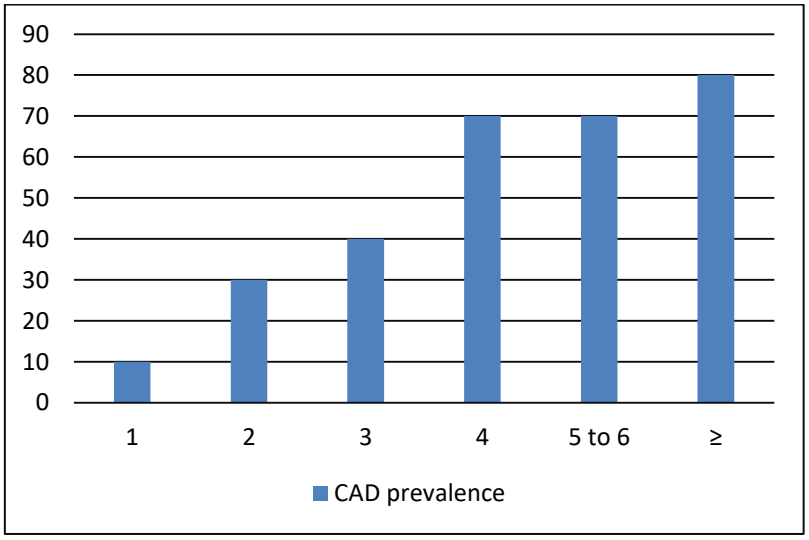

Fig -2: Effect of no of Risk Factors on CAD Prevalence.

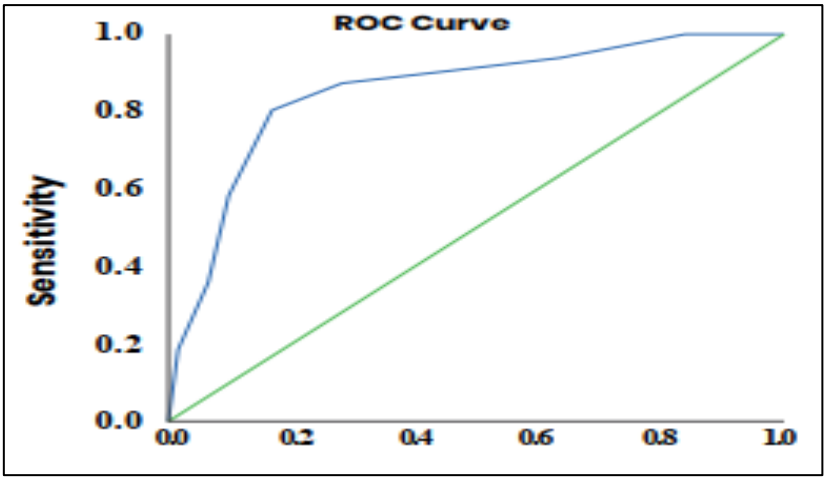

Fig -3: ROC Curve for Risk Factors >3 for Predicting CAD.

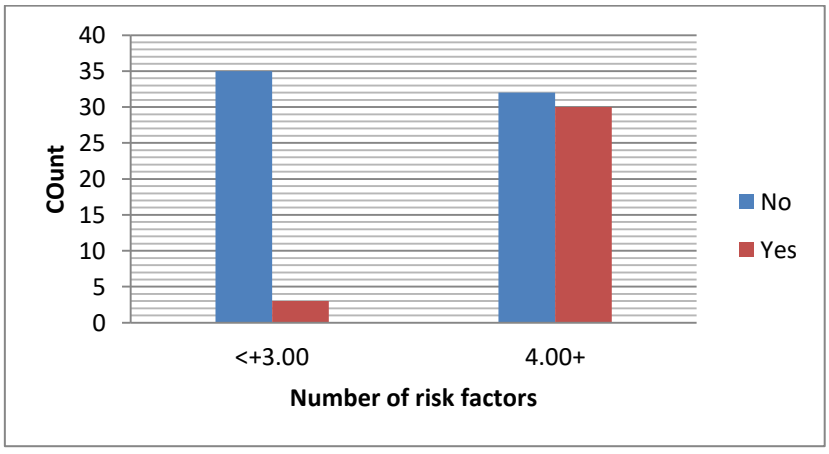

Figure – 4: Presence / absence of significant CAD in those with ≤ 3 vs > 3 risk fctors.

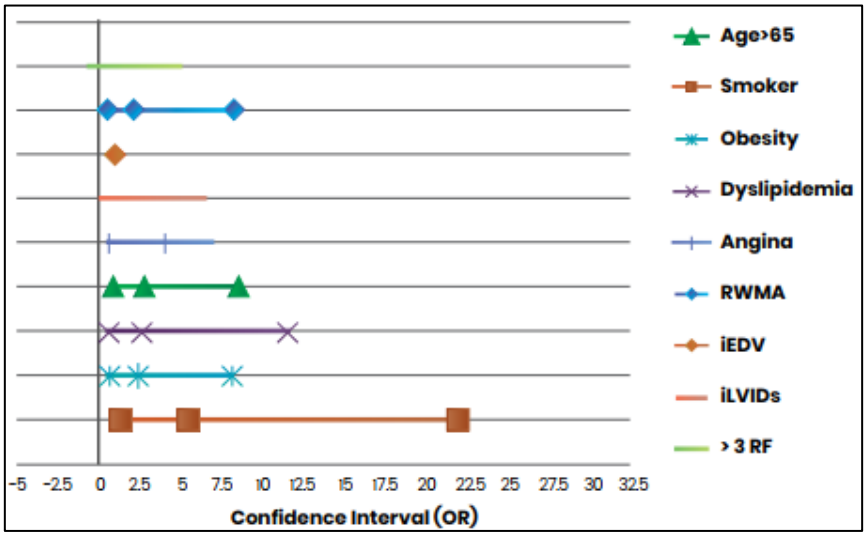

Figure - 5: Predictors of CAD in HFrEF.

IV. Discussion

In our non-selected population of patients admitted to cardiology departments due to HFrEF, we have found that, after adjusting for comorbidities, patients with CAD etiology had a prognosis similar to idiopathic DCM with comparable adjusted mortality and readmissions. Previous studies have found that the prevalence of non-ischemic DCM ranges from 30 to 50% HF patients. [23–25] Total 100 patients included in our study. The mean age of the patients was 62.7 ±10.1 years, with 66% males. Patients with age ≥ 65 years (42%) were more likely to have significant CAD (p = 0.025). After comparison of clinical and laboratory features in patients with and without CAD clinical factors such as age ≥ 65 years, smokers, dyslipidemia, obesity, angina and echocardiographic indicators iEDV, iLVIDs and RWMA were predictors of CAD. Patients with idiopathic DCM were younger, and had less cardiovascular risk factors and comorbidities than those with CAD. This is in agreement with preceding studies[26,27–29,30]. We performed a study analyzing the prevalence of CAD in patients with HFrEF undergoing CAG at our institute. Despite excluding patients with history or evidence of previous coronary events, the prevalence of CAD was 32%. This is in contrast to the overall CAD prevalence in about two-thirds of cases of HFrEF. But this higher prevalence reports are from series, which included patients with past coronary events like MI, Q waves on ECG and previous revascularization. Upon comparison with studies of CAD prevalence including cohorts with unexplained heart failure, our prevalence figures are similar16. However, a better outcome in patients with idiopathic DCM compared to CAD etiology was not found in some previous studies[31–34]. A possible explanation is that previous reports have been obtained from clinical trials performed in the 1980s [31,32,35], and in patients with a recent myocardial infarction[21,36]. Moreover, the substantial differences in age and clinical characteristics between the two groups may explain, at least in part, this prognostic difference. In the Revascularization for Ischemic Ventricular Dysfunction (REVIVED) trial, myocardial revascularization in patients with ischemic left ventricular dysfunction was not associated with a reduction in mortality or hospitalizations [37]; therefore, other factors, beyond ischemia per se, would have a greater weight in the evolution of HF patients. Some publications also used a coronary stenosis of ≥ 50% to define significant CAD, which would explain a higher prevalence of CAD. Our prevalence also closely matches the descriptive studies from Bangladesh[38, 39] suggesting one third of HFrEF are likely ischemic in our population. In clinical practice, systematic Echo is not always possible in all patients admitted for heart failure, but the potential survival benefit of revascularization[7, 40, 41], justifies that aggressive management of heart failure even in the elderly patients may be similar to the current approach for the treatment of aortic stenosis[42]. As previously demonstrated the use of Echo during the index hospitalization after admission for heart failure would allow CAD identification in a higher proportion of patients than after discharge[43]. In clinical practice it is challenging for all patients with systolic HF of unclear etiology to undergo Echo, hence we sought to derive clinical or echocardiographic predictors to suggest CAD as a cause of systolic HF. In our study CAD was significantly more common in patients with age ≥ 65 years, smokers, dyslipidemia, obesity and had angina. The echocardiographic predictors were iEDV, iLVIDs and regional wall motion abnormality (RWMA). With these predictors, we sought to derive and validate a clinical prediction rule to rule in CAD which showed that having > 3 risk factors is associated with ischemic cause for HF (figures - 3, 4, 5) with a sensitivity of 93% and specificity of 63%. However, when multivariate analysis was done only smoking was the independent risk predictor of CAD (figure – 5). This may be due to a small sample size in our study and hence, a larger study is likely to deliver us a better prediction model. Genetic testing was not addressed, and it could have had an

important impact on idiopathic DCM prognosis. Moderate–severe mitral regurgitation is a prognostic factor in HF with reduced ejection fraction, but we have no information regarding the surgical or invasive treatment performed after the index hospital admission. Information regarding active ischemia in the CAD group was not available as a study variable, so we cannot assess its impact on the outcome of this group of patients. Information regarding medical treatment during follow-up was not available. Data regarding the number of hospital readmissions during follow-up according to etiology was not recorded. Despite the high number of patients enrolled, the specific subgroups may have included a relatively low number of patients to assess the natural history of HFrEF. Finally, follow-up duration was 12 months, and a longer follow-up period may have shown significant differences in outcomes according to HF etiology. This study is based on a large-scale national registry, and patient follow-up data are only available 12 months after inclusion in the study. Future studies are desirable in order to address the potential differences according to etiology at subclinical and earlier stages of the disease. Relative to other previous large studies, our sample size was small and patients were enrolled from a single center, hence also subjected to referral bias. However, the current prospective design with Echo is a merit. We enrolled only on patients with HFrEF and excluded patients with HFmEF/ HFpEF. Finally, our study was limited by the fact that moderate lesions were not further analyzed with functional flow reserve (FFR) or intravascular coronary imaging. This may have led to underestimation of the prevalence of CAD. However, the identification of CAD led to the initiation of suitable medical treatment (antiplatelet therapy, statins) that has previously demonstrated its beneficial effect on outcomes.[44, 45]

V. Conclusions

We determined the prevalence and characteristics of CAD in patients with HFrEF in a prospective study and the use, for the first time, of a systematic Echo approach. In our study, otherwise unexplained HFrEF showed 33% significant CAD, which was higher than rates reported previously. Further studies are needed to evaluate systematic Echo in HFmEF/HFpEF, and whether this approach is cost- effective and revascularization improves morbidity or mortality. However, there are data showing that patients with left ventricular systolic dysfunction without chest pain or previous MI are unlikely to present extensive coronary disease that could explain left ventricular dysfunction or to have coronary anatomy suitable for bypass grafting. Demonstration of underlying etiology is cornerstone of HF diagnosis and virtually all patients with unexplained HF should be evaluated for the presence of CAD. Most patients with HF due to ischemic cardiomyopathy have known coronary heart disease. We encourage clinicians to aggressively identify this co-morbidity as it has important treatment and prognostic implementations.

Conflict of Interest: None

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