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Prediction of mortality and heart failure hospitalisations in patients undergoing M-TEER: external validation of the COAPT risk score

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KEYWORDS

- chronic heart failure
- mitral regurgitation
- mitral valve repair

Abstract

Background: A risk score was recently derived from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) Trial. However, external validation of this score is still lacking.

Aims: We aimed to validate the COAPT risk score in a large multicentre population undergoing mitral transcatheter edge-to-edge repair (M-TEER) for secondary mitral regurgitation (SMR).

Methods: The Italian Society of Interventional Cardiology (GIse) Registry of Transcatheter Treatment of Mitral Valve RegurgitaTiOn (GIOTTO) population was stratified according to COAPT score quartiles. The performance of the COAPT score for 2-year all-cause death or heart failure (HF) hospitalisation was evaluated in the overall population and in patients with or without a COAPT-like profile.

Results: Among the 1,659 patients included in the GIOTTO registry, 934 had SMR and complete data for a COAPT risk score calculation. The incidence of 2-year all-cause death or HF hospitalisation progressively increased through the COAPT score quartiles in the overall population (26.4% vs 44.5% vs 49.4% vs 59.7%; log-rank p<0.001) and COAPT-like patients (24.7% vs 32.4% vs 52.3% vs. 53.4%; log-rank p=0.004), but not in those with a non-COAPT-like profile. The COAPT risk score had poor discrimination and good calibration in the overall population, moderate discrimination and good calibration in COAPT-like patients and very poor discrimination and poor calibration in non-COAPT-like patients.

Conclusions: The COAPT risk score has a poor performance in the prognostic stratification of real-world patients undergoing M-TEER. However, after application to patients with a COAPT-like profile, moderate discrimination and good calibration were observed.

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Abbreviations

COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
GDMT	guideline-directed medical therapy
GIOTTO	Italian Society of Interventional Cardiology (GIse) Registry Of Transcatheter Treatment of Mitral Valve regurgitaTiOn
HF	heart failure
MITRA-FR	Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation
M-TEER	mitral transcatheter edge-to-edge repair
PMR	primary mitral regurgitation
SMR	secondary mitral regurgitation

Introduction

Mitral transcatheter edge-to-edge repair (M-TEER) is a valuable therapeutic option for patients with secondary mitral regurgitation (SMR) who meet specific criteria derived from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) Trial[1,2]. COAPT was the first randomised controlled trial showing a prognostic benefit of M-TEER on top of guideline-directed medical therapy (GDMT) in patients with SMR and chronic heart failure (HF)[3]. On the other hand, the Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) trial reported similar outcomes in patients with SMR receiving M-TEER and GDMT or GDMT alone[4]. Notably, in a real-world setting, there is a fair degree of overlap between the COAPT and MITRA-FR profiles[5] so although selection for M-TEER is crucial for outcome purposes, identifying which patients will have a prognostic benefit from the procedure may be hard. Many efforts have been made to identify prognostic variables and to develop specific tools to predict clinical events after M-TEER[6-9].

A simple new risk model, derived from the COAPT population, was recently proposed to predict all-cause mortality or HF hospitalisation in patients with SMR and HF treated with either M-TEER and GDMT or GDMT alone[10]. The COAPT risk score has good performance in its derivation SMR cohort, but it has not yet been validated in external populations.

The Italian Society of Interventional Cardiology (GIse) Registry Of Transcatheter Treatment of Mitral Valve regurgitaTiOn (GIOTTO) is a large multicentre registry including patients undergoing M-TEER.

The aim of this study was to provide an external validation of the COAPT risk model in the SMR cohort of the GIOTTO registry.

Methods

STUDY POPULATION

The design and main results of the GIOTTO registry have been previously published[11,12]. Briefly, GIOTTO is a multicentre, prospective, observational registry that included all M-TEER procedures performed at 18 participating sites from 2016 to 2021. The registry reflects the real-world experience of M-TEER with the MitraClip (Abbott) device (including the latest generations of the MitraClip, the XTR and NTR, and excluding the MitraClip G4) in both primary mitral regurgitation (PMR) and SMR, without strict selection criteria. For the purposes of the present analysis, from the original cohort, we selected those with SMR and with complete data for COAPT risk score calculation.

The COAPT risk score was recently presented as a new tool for predicting 2-year all-cause death or HF hospitalisation in patients with SMR and HF after M-TEER and GDMT (device group) or GDMT alone (control group)[10]. The score includes 4 clinical variables: i) chronic kidney disease (CKD) stage III (+1 point) or stage IV or greater (+3 points); ii) New York Heart Association (NYHA) Functional Class III or IVa (+1 point); iii) chronic obstructive pulmonary disease (COPD; +1 point); and iv) history of atrial fibrillation or flutter (+1 point); as well as 4 echocardiographic parameters: i) right ventricular systolic pressure (RVSP) >45 mmHg (+3 points); ii) left ventricle ejection fraction (LVEF) 25-35% (+1 point), LVEF <25% (+2 points); iii) left ventricular end-systolic diameter (LVESD) >5.5 cm (+2 points); and iv) tricuspid regurgitation (TR) >1+ (+2 points), in addition to MitraClip therapy (–3 points). Thus, the score ranges between –3 (low risk) and +15 points (high risk). The COAPT risk score was calculated and assigned to each patient.

The population was stratified according to quartiles of COAPT risk score in the following groups: –3 to 1 points; 2 to 3 points; 4 to 5 points; and 6 to 12 points.

The impact of the COAPT risk score was evaluated in the overall SMR population, and after stratification, according to the presence of a COAPT-like profile as previously defined[13].

DATA COLLECTION AND STUDY OUTCOMES

A web-based electronic case report form, periodically cross-checked for accuracy, was used for data collection. Subsequent follow-up data were obtained by outpatient clinical visits and/or telephone calls scheduled at 30 days, 1 year, and yearly thereafter.

Clinical outcomes were defined according to the Mitral Valve Academic Research Consortium (MVARC) criteria[14]. Procedural outcomes included acute technical success (defined as successful access, delivery and retrieval of the device delivery system; successful deployment of the device without procedural mortality or urgent surgery), 30-day device success (defined as optimal residual mitral regurgitation [rMR 1+] or an acceptable [rMR 2+] reduction in MR at 30 days after M-TEER), and 30-day procedural success (defined as a composite of device success and absence of major cardiovascular adverse events).

Procedural complications, mortality and hospitalisation were also reported according to MVARC definitions. The cause of hospitalisation, including HF, was site-reported.

In order to faithfully validate the COAPT risk score in our population, we considered the primary outcome to be the composite of 2-year all-cause death and HF hospitalisation after M-TEER.

The study complied with the Declaration of Helsinki and was approved by all the local ethical committees. All patients included in the study signed a written informed consent, after receiving an oral and written explanation of the risks and benefits concerning the procedure.

STATISTICAL ANALYSIS

Categorical and dichotomous covariates are presented as counts and percentages and were compared by Pearson's chi-square or Fisher's exact tests with 2 degrees of freedom, as appropriate. Continuous covariates are presented as median and interquartile range (25th-75th IQR) and were compared using one-way analysis of variance (ANOVA) or a T-test, as appropriate.

A time-to-first-event analysis using the Kaplan-Meier method was performed to assess the 2-year cumulative incidence of all-cause death or HF hospitalisation in the population stratified by the COAPT risk score quartiles, and comparisons were made by means of the log-rank test.

A Cox regression analysis was performed to calculate the hazard ratio (HR) and corresponding 95% confidence interval (CI) of the primary outcome for the COAPT score as a dichotomic variable (4th, 3rd, 2nd quartiles vs 1st) and as a continuous variable for the COAPT risk score items.

The performance of the COAPT score was evaluated in terms of discrimination and calibration.

Discrimination was measured using the area under the curve (AUC) of the receiver operating characteristic (ROC), which ranged from 0.50 (no discrimination) to 1.0 (perfect discrimination). Model calibration was assessed using the Hosmer-Lemeshow (HL) goodness-of-fit test with a p-value of >0.05 indicating good calibration.

For all analyses, the primary outcome was evaluated in the overall SMR population and in patients both fulfilling and not fulfilling the COAPT-like profile. A two-sided $p<0.05$ was considered significant. Data were analysed by using the SPSS statistics software (version 21, IBM).

Results

BASELINE CHARACTERISTICS

Among the 1,659 patients included in the GIOTTO registry, 934 had SMR and complete data for the COAPT risk score calculation and were included in this analysis **(Figure 1)**. Baseline characteristics of the overall population, stratified by COAPT-like profile are reported in **Supplementary Table 1**. The COAPT risk score has a Gaussian distribution **(Supplementary Figure 1)**. The median COAPT score was 4 (IQR 2-6) in the overall population, 1 (IQR 3-6) in patients fulfilling a COAPT-like profile and 3 (IQR 5-7) in those not fulfilling a COAPT-like profile. Distribution of the COAPT score items in the population stratified by COAPT-like profile is reported in **Figure 2**. A history of atrial fibrillation, LVEF <25%, RVSP >45 mmHg and TR >1+ were more frequently observed in patients with a non-COAPT-like profile as compared to those with a COAPT-like profile.

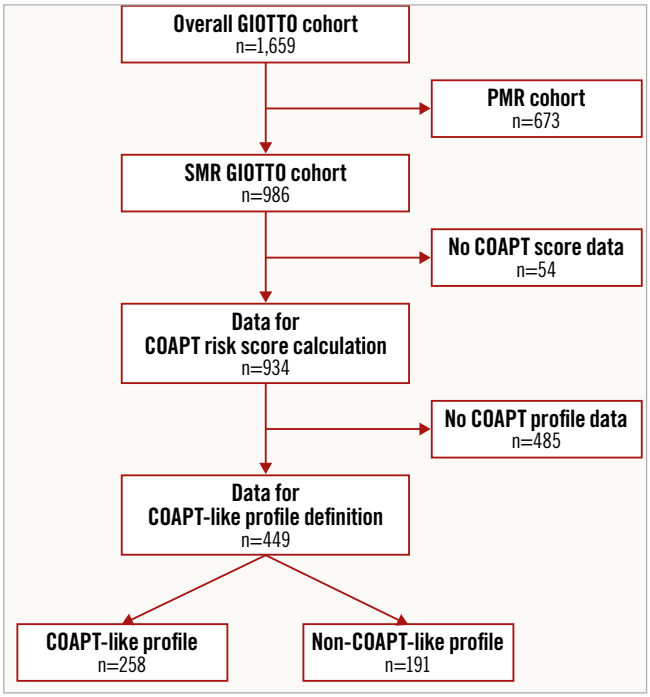

Figure 1. *Study flowchart. Patients excluded and included in the present analysis are reported. COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; GIOTTO: Italian Society of Interventional Cardiology (GIse) Registry of Transcatheter Treatment of Mitral Valve RegurgitaTiOn; PMR: primary mitral regurgitation; SMR: secondary mitral regurgitation*

Baseline demographic and clinical characteristics of the overall population stratified by quartiles of the COAPT risk score are reported in **Table 1**. As expected, the prevalence of variables included in the COAPT risk model increased with the increasing COAPT score quartiles. A similar trend was observed for age, the European System for Cardiac Operative Risk Evaluation (EuroSCORE II), the Society of Thoracic Surgeons (STS) score, levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), prevalence of hypertension, peripheral artery disease (PAD) and severity of MR. Moreover, body mass index (BMI) and haemoglobin were lower in the 4th quartile of the COAPT score compared with the others **(Table 1)**.

Similar differences were observed in the COAPT-like and non-COAPT-like populations stratified by quartiles of COAPT risk score **(Supplementary Table 2, Supplementary Table 3)**.

ACUTE OUTCOMES

Acute outcomes are reported in **Table 2**. Residual MR 1+ was more frequent in the lowest COAPT score quartiles, whereas residual MR 2+ and 3/4+ were more frequent in the highest COAPT score quartiles. The rate of in-hospital acute kidney injury, the need for an intra-aortic balloon pump and length of the ward stay were higher in the 4th COAPT score quartile compared with the others.

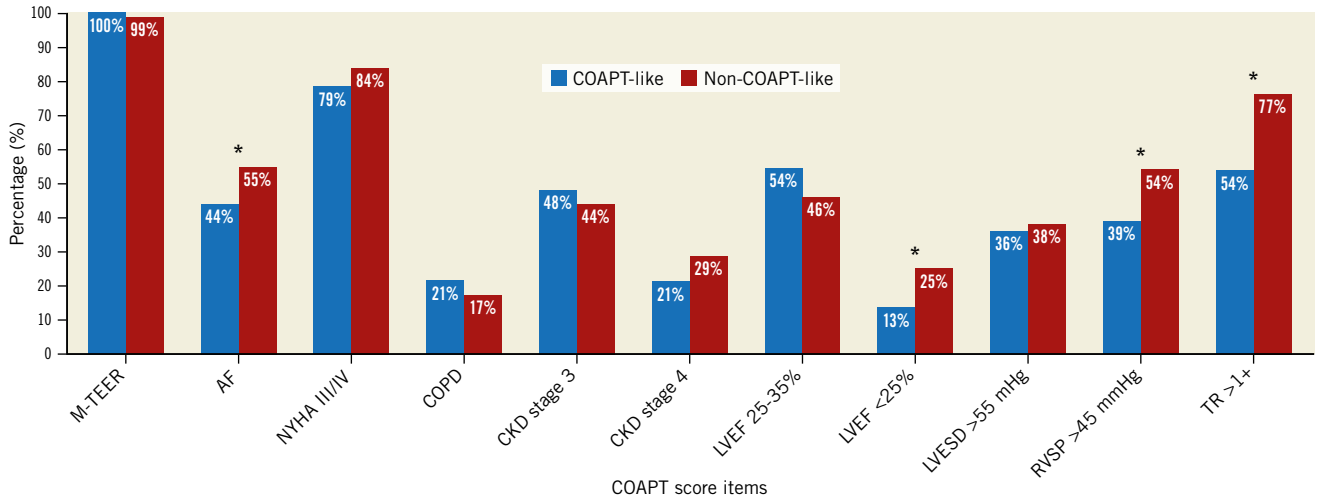

Figure 2. *Proportion of patients with and without a COAPT-like profile presenting different items included in the COAPT risk score. *indicates p<0.05 in the comparison between groups. AF: atrial fibrillation; CKD: chronic kidney disease; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; M-TEER: mitral transcatheter edge-to-edge repair; NYHA: New York Heart Association; RVSP: right ventricular systolic pressure; TR: tricuspid regurgitation*

TWO-YEAR OUTCOMES

Clinical follow-up data were available for 833 out of 934 patients (182/191 COAPT-like and 231/258 non-COAPT-like). The median follow-up was 370 (184-734) days with 538 patients (65%) reaching 2-year follow-up. The primary outcome occurred in 253 patients within the 2-year follow-up. The cumulative incidence of 2-year all-cause death or HF hospitalisation progressively increased through the COAPT score quartiles (26.4% vs 44.5% vs 49.4% vs 59.7%; log-rank p<0.001) **(Figure 3)**. Similar results were observed in patients fulfilling a COAPT-like profile (24.7% vs 32.4% vs 52.3% vs 53.4%; log-rank p=0.004), whereas different trends were noted in patients who did not fulfil a COAPT-like profile (25.4% vs 59.3% vs 57.6% vs 49.1%; log-rank p=0.048) **(Figure 3)**. The relative risk of the primary outcome increased with the increasing of the COAPT score in the overall population **(Supplementary Figure 1, Table 3)** and in the COAPT-like subgroup but not in the non-COAPT-like subgroup, even after adjustment for possible confounders **(Table 3)**.

The association between single COAPT risk score items and the primary outcome was reported in **Supplementary Table 4**. Device success did not affect the impact of the COAPT risk score on the primary endpoint (p for interaction=0.858), but there was a trend towards a decreased risk of clinical events in patients with device success (HR 0.75, 95% CI: 0.55-1.01; p=0.061) regardless of the COAPT score.

PERFORMANCE OF THE COAPT SCORE

The COAPT risk score had poor discrimination power and good calibration in predicting 2-year all-cause death or HF hospitalisation in the overall population (AUC 0.62; HL p=0.658). Moderate discrimination and good calibration were noted in the COAPT-like subgroup (AUC 0.67; HL p=0.952). On the other hand, a very poor performance was observed in the non-COAPT-like subgroup (AUC 0.48; HL p=0.012) **(Central illustration)**.

Discussion

The key finding of this study is that the recently proposed COAPT risk score has a poor performance in the prognostic stratification of real-world patients undergoing M-TEER. However, in patients with a COAPT-like profile, the COAPT score had moderate discrimination and good calibration in predicting 2-year all-cause death or HF hospitalisation.

Patient selection for M-TEER remains challenging in spite of many efforts to identify predictors of outcomes[8,9,15,16]. Since surgical risk scores overpredict mortality in these patients[17], some specific models have been developed to predict the risk of adverse events after M-TEER[6,7,10,18]. Shah et al recently proposed a risk score derived from the COAPT population, including 614 patients with SMR treated with optimised HF therapies, enrolled at 78 centres in the United States and Canada and randomised to receive M-TEER or not. The endpoint used to build the model was the 2-year rate of death or HF hospitalisation. M-TEER was strongly associated with a reduced risk of events. Moreover, 4 clinical variables, 4 echocardiographic parameters, and the MitraClip treatment, were identified as independently associated with the endpoint of interest in the multivariate analysis. Thus, 9 variables were included in the risk score with a final score ranging from –3 to 12[10].

All the included variables have already been reported as associated with outcome in M-TEER populations[5,8,13,15,19-28]. However, the COAPT risk model may represent a user-friendly tool to easily perform a comprehensive patient evaluation and selection in clinical practice[29].

We validated the COAPT score in a large multicentre real-world population included in the GIOTTO registry. Overall, the

Table 1. Baseline characteristics according to COAPT score quartiles.

	COAPT score –3 to 1 (n=229)	COAPT score 2 to 3 (n=207)	COAPT score 4 to 5 (n=243)	COAPT score 6 to 12 (n=255)	*p*-value
Age, years	71 [70-72]	74 [73-75]	73 [72-74]	74 [73-75]	0.001
Male sex	151 (66)	143 (69)	177 (73)	189 (74)	0.192
BMI, kg/m²	25.8 [25.2-26.3]	25.6 [25.1-26.2]	25.5 [24.9-25.9]	24.9 [24.4-25.4]	0.070
EuroSCORE II, %	5.9 [5.3-6.5]	7.3 [6.4-8.2]	7.1 [6.4-7.8]	10.5 [9.5-11.6]	0.001
STS risk score, %	3.6 [2.8-4.3]	4.5 [3.6-5.4]	5.1 [4.1-6.0]	6.5 [5.4-7.6]	0.001
NYHA Class III/IV	157 (69)	173 (84)	216 (89)	233 (91)	0.001
Comorbidities, laboratory data and medical therapies					
Hypertension	162 (71)	154 (74)	193 (79)	175 (69)	0.039
Diabetes mellitus	84 (37)	70 (34)	80 (33)	85 (33)	0.825
Prior HF	145 (63)	143 (69)	164 (67)	190 (74)	0.064
COPD	19 (8)	27 (13)	42 (17)	49 (19)	0.004
Prior cerebrovascular disease	13 (6)	21 (10)	20 (8)	23 (9)	0.364
AF	72 (31)	102 (49)	138 (57)	153 (60)	0.001
CAD	129 (56)	109 (53)	119 (49)	153 (60)	0.082
Prior cardiac surgery	73 (32)	61 (29)	51 (21)	66 (26)	0.087
PAD	22 (10)	15 (7)	20 (8)	28 (11)	0.006
GFR <30 mL/min	12 (5)	34 (16)	48 (20)	115 (45)	0.001
30 mL/min ≤ GFR ≤ 60mL/min	113 (49)	118 (57)	126 (52)	112 (44)	0.001
GFR >60 mL/min	104 (45)	55 (27)	69 (28)	28 (11)	0.001
Haemoglobin, g/dL	12.6 [12.3-12.8]	12.4 [12.2-12.7]	12.3 [12.0-12.6]	12.0 [11.8-12.3]	0.017
Creatinine, mg/dL	1.25 [1.18-1.31]	1.49 [1.38-1.60]	1.57 [1.45-1.68]	1.97 [1.84-2.11]	0.001
NT-proBNP, ng/L	1,258 [808-1,707]	1,463 [933-1,993]	2,520 [1,785-3,254]	3,496 [2,714-4,278]	0.001
CRT	66 (29)	94 (45)	99 (41)	141 (55)	0.001
Beta blocker	190 (83)	172 (83.1)	207 (85.2)	212 (83.1)	0.899
ACEi/ARB/ARNI	89 (38.9)	71 (34.3)	87 (35.8)	83 (32.5)	0.525
MRA	125 (54.6)	116 (56)	139 (57.2)	138 (54.1)	0.900
Furosemide	207 (90.4)	194 (93.7)	232 (95.5)	239 (93.7)	0.164
Echocardiographic data					
LAD, mm	56 [46-65]	53 [46-59]	54 [48-60]	54 [48-60]	0.945
LVEDD, mm	60 [58-61]	62 [61-64]	63 [61-64]	66 [65-67]	0.001
LVESD, mm	46 [45-48]	50 [48-51]	48 [47-50]	55 [53-56]	0.001
LVEDV, mL	156 [149-164]	175 [165-185]	176 [167-184]	193 [185-201]	0.001
LVEDVi, mL/m²	86 [82-90]	97 [91-102]	96 [91-100]	108 [103-112]	0.001
LVESV, mL	98 [92-104]	116 [108-125]	114 [107-121]	137 [130-144]	0.001
LVESVi, mL/m²	54 [51-57]	64 [60-69]	62 [58-66]	77 [73-80]	0.001
LVEF, %	39 [37-40]	34 [32-35]	34 [33-36]	29 [28-30]	0.001
MR 2+	5 (2.2)	2 (1)	3 (1.2)	1 (0.4)	0.330
MR 3+	74 (32)	61 (29)	39 (16)	42 (16)	0.001
MR 4+	150 (50)	144 (69)	201 (83)	212 (83)	0.001
MVA planimetry, cm²	4.9 [4.7-5.1]	4.9 [4.8-5.2]	5.2 [4.9-5.4]	5.2 [4.9-5.4]	0.286
Severe TR	12 (5)	18 (9)	34 (14)	52 (20)	0.001
TAPSE, mm	19 [19-20]	19 [18-19]	18 [17-19]	18 [16-19]	0.041
sPAP, mmHg	37 [36-38]	42 [41-44]	52 [50-53]	57 [55-58]	0.001

Values are expressed as n (%), or median [interquartile range]. ACEi/ARB/ARNI: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or angiotensin receptor/neprilysin inhibitors; AF: atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; EuroSCORE II: European System for Cardiac Operative Risk Evaluation; GFR: glomerular filtration rate; HF: heart failure; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEDVi: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESVi: left ventricular end-systolic volume index; MR: mitral regurgitation; MRA: mineralocorticoid receptor antagonist; MVA: mitral valve area; NT-proBNP: N-terminal pro-B-type natriuretic peptide NYHA: New York Heart Association; OMT: optimal medical therapy; PAD: peripheral artery disease; sPAP: systolic pulmonary artery pressure; STS: Society of Thoracic Surgeons; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation

Table 2. Procedural and in-hospital outcomes.

		COAPT score −3 to 1 (n=229)	COAPT score 2 to 3 (n=207)	COAPT score 4 to 5 (n=243)	COAPT score 6 to 12 (n=255)	*p*-value
Device time, min		60 [35-90]	50 [30-90]	58 [35-85]	60 [35-90]	0.537
Procedural time, min		100 [140-190]	90 [120-170]	135 [90-180]	145 [95-190]	0.373
Clip(s) implanted	1	93 (40.6)	76 (36.7)	84 (34.6)	92 (36)	0.573
	2	117 (51.1)	115 (55.6)	133 (54.7)	130 (51)	0.662
	3	16 (7)	16 (7.7)	23 (9.5)	27 (10.6)	0.469
	4	1 (0.4)	0 (0)	1 (0.4)	4 (1.6)	0.163
Failed implantation		2 (0.9)	0 (0)	2 (0.8)	2 (0.8)	0.629
Procedural outcomes						
Technical success		223 (97.4)	201 (97.1)	235 (96.7)	249 (97.6)	0.932
Device success		206 (90)	180 (87)	212 (87.2)	213 (83.5)	0.219
Procedural success		200 (87.3)	177 (85.5)	205 (84.4)	207 (81.2)	0.294
Intraprocedural death		0 (0)	0 (0)	1 (0.4)	1 (0.4)	0.472
Clip detachment		1 (0.4)	2 (1)	3 (1.2)	2 (0.8)	0.818
Residual MR 1+		171 (74.7)	130 (62.8)	148 (60.9)	156 (61.2)	0.001
Residual MR 2+		55 (24)	70 (33.8)	82 (33.7)	90 (35.3)	
Residual MR 3+/4+		3 (1.3)	7 (3.4)	13 (13.6)	9 (3.5)	
Mean gradient		3 [2-4]	3 [2.8-4.5]	3 [2-4]	3 [2-4]	0.117
In-hospital outcomes						
Vascular complications		10 (4.4)	9 (4.3)	6 (2.5)	6 (2.4)	0.431
Major bleeding		4 (1.7)	4 (1.9)	6 (2.5)	9 (3.5)	0.585
Cardiac tamponade		0 (0)	0 (0)	1 (0.4)	1 (0.4)	0.624
Myocardial infarction		0 (0)	1 (0.5)	0 (0)	0 (0)	0.319
AKI		7 (3.1)	6 (2.9)	2 (0.8)	17 (6.7)	0.004
Malignant arrhythmia		1 (0.4)	1 (0.5)	0 (0)	1 (0.4)	0.780
Stroke		0 (0)	2 (1)	1 (0.4)	1 (0.4)	0.494
LVAD implantation		0 (0)	0 (0)	0 (0)	1 (0.4)	0.446
IABP		0 (0)	0 (0)	0 (0)	4 (1.6)	0.013
Need for urgent surgery		1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	0.834
ICCU length of stay, hours		24 [0-43]	24 [2-48]	24 [0-48]	24 [0-48]	0.095
Ward length of stay, days		3 [5-7]	4 [3-7]	5 [4-8]	6 [4-10]	0.001

Values are expressed as n (%), or median [interquartile range]. AKI: acute kidney injury; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; IABP: intra-aortic balloon pump; ICCU: intensive coronary care unit; LVAD: left ventricular assistant device; MR: mitral regurgitation

COAPT and GIOTTO populations are extremely different, as the former included only SMR patients undergoing M-TEER or conservative care, whereas the latter included both SMR and PMR patients undergoing M-TEER. To partially overcome this issue, we included only SMR patients in this analysis, but several differences between the device arm of COAPT and the SMR group of GIOTTO had already been reported[11]. Briefly, GIOTTO patients had more advanced symptoms, severe SMR and were less likely to receive angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or angiotensin receptor/neprilysin inhibitors compared to COAPT patients. Moreover, in COAPT but not in GIOTTO, patients with a non-ambulatory NYHA Class IV were excluded. and optimisation of HF medical therapies was centrally evaluated by a dedicated committee. In addition, while patients

Table 3. Association between COAPT risk score and relative risk of 2-year all-cause death or HF hospitalisation.

	HR	95% CI	*p*-value	Adj HR*	95% CI	*p*-value
Overall population	1.21	1.08-1.67	<0.001	1.09	1.05-1.13	<0.001
COAPT-like profile	1.15	1.06-1.27	<0.001	1.14	1.06-1.23	<0.001
Non-COAPT-like profile	0.99	0.93-1.06	0.769	0.97	0.90-1.04	0.425

*Variables included in the model: age, gender, EuroSCORE II, mitral regurgitation grade. CI: confidence interval; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; EuroSCORE II: European System for Cardiac Operative Risk Evaluation; HF: heart failure; Adj HR: adjusted hazard ratio

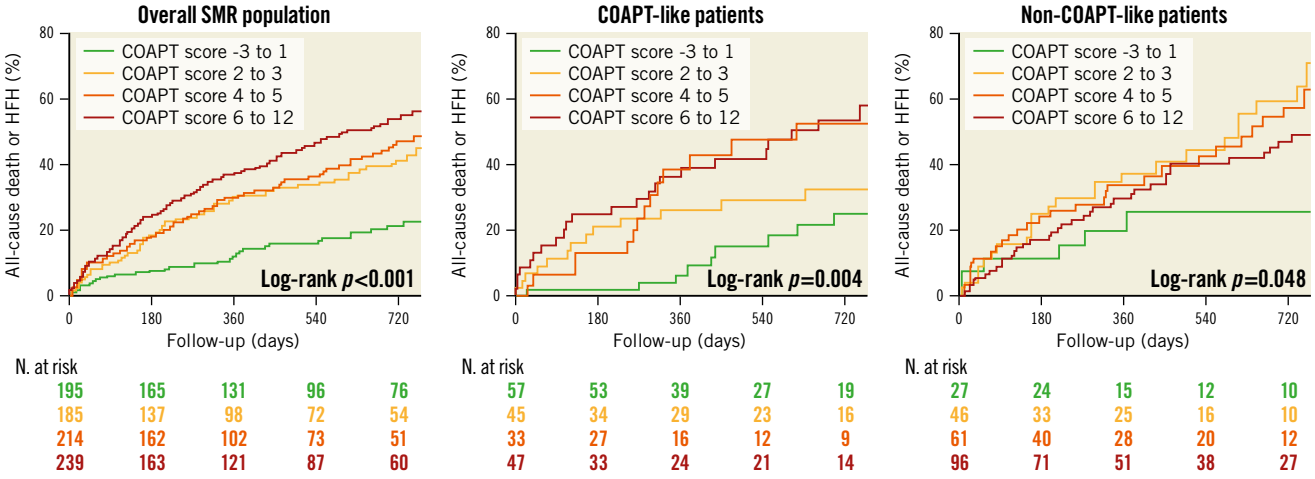

Figure 3. *Cumulative incidence of 2-year all-cause mortality or HF hospitalisation in the overall population, in COAPT-like patients and in non-COAPT-like patients. COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; HFH: heart failure hospitalisation; SMR: secondary mitral regurgitation*

with severe TR were excluded from COAPT, 15% of SMR patients in GIOTTO had severe TR. Importantly, in our analysis, NYHA Class III-IV and TR >1+ were the most frequent items observed among clinical and echocardiographic items, respectively.

Aware of these disparities between the COAPT population and our validation cohort, we evaluated the COAPT score in patients with and without a COAPT-like profile. As expected, the performance of the score was significantly better in the former as compared to the latter group. However, the performance of the COAPT score observed in the derivation cohort (AUC 0.74; HL p=0.97) was still better than that observed in our COAPT-like population (AUC 0.67; HL p=0.95). This could be explained by the fact that clinical events in GIOTTO are not centrally adjudicated and HF hospitalisations are probably underestimated because of underreporting. Indeed, while the mortality rate was similar between the COAPT and SMR GIOTTO populations, the HF hospitalisation rate was lower in SMR GIOTTO versus COAPT, and the cumulative incidence of the composite endpoint was lower through the COAPT risk score quartiles in GIOTTO versus COAPT. Moreover, the follow-up length was shorter in our population as compared to COAPT, with only 65% reaching 2-year follow-up. Finally, only half of the patients with SMR and data for a COAPT risk score calculation also had data for a COAPT-like profile definition **(Figure 1)**, mainly because of a high rate of missing values for right ventricular function. Therefore, the low number of patients included in the analysis as well as the lower number of events in GIOTTO versus COAPT, due to the underreported HF hospitalisations and the shorter follow-up, may have

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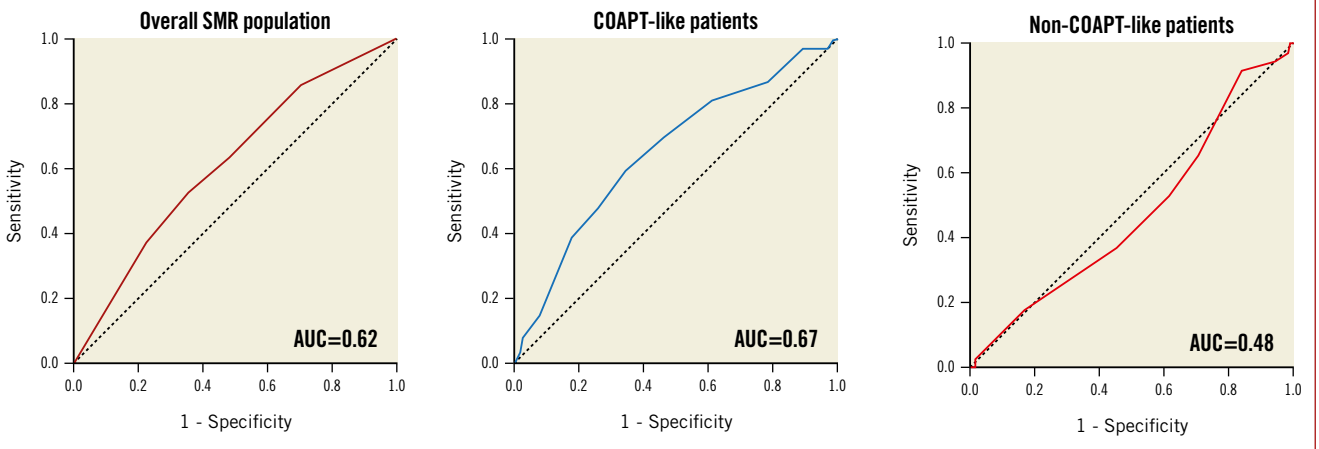
CENTRAL **ILLUSTRATION** **Receiver operating characteristic curves for the association between COAPT risk score and primary outcome in the overall population, in COAPT-like patients and in non-COAPT-like patients**



AUC: area under the curve; SMR: secondary mitral regurgitation

affected the poorer performance of the COAPT score in predicting clinical events in our COAPT-like population compared with the derivation cohort.

Nevertheless, we can conclude that the COAPT risk score might reasonably be used for prognostic stratification of COAPT-like patients with SMR undergoing M-TEER. On the other hand, in SMR patients not fulfilling COAPT criteria, other recently proposed tools[30] should be used, since the performance of the COAPT risk score in this subgroup of patients is very poor.

Limitations

Several limitations of this study must be acknowledged. This is an observational registry whose variables were site-reported, and both clinical outcomes and echocardiographic data were not adjudicated by a central committee and a core laboratory, respectively. However, the echocardiographers involved in GIOTTO were all accredited by the Italian Society of Echocardiography (SIECVI), and all examinations were performed in accordance with its required standards. Moreover, guideline-directed optimal medical therapy was not established in all patients before M-TEER as in COAPT. In addition, complete 2-year follow-up data were not available for the overall population as in COAPT. Indeed, among patients with clinical follow-up data available (89%), only 65% reached 2-year follow-up. Finally, being site-reported and not centrally evaluated, HF hospitalisations may be underreported since the incidence is lower compared to the COAPT study. These limitations may explain the lower performance of the COAPT risk score in the GIOTTO population as compared to the derivation cohort.

Conclusions

In a large real-world SMR population undergoing M-TEER, the recently proposed COAPT risk score had a poor performance for the prediction of 2-year all-cause mortality or HF hospitalisation. However, moderate discrimination and good calibration were observed in the subgroup of patients fulfilling a COAPT-like profile, whereas a very poor performance was observed in non-COAPT-like patients.

Impact on daily practice

The COAPT risk score may be useful for the prognostic stratification of patients with a COAPT-like profile undergoing mitral transcatheter edge-to-edge repair. On the other hand, its performance is poor when applied to non-COAPT like patients.

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Conflict of interest statement

M. Adamo received consultation and/or speaker fees from Abbott Vascular, outside the submitted work. F. Bedogni received consultation and/or speaker fees from Abbott Vascular, outside the submitted work. P. Denti received consultation and/or speaker fees from Abbott Vascular, outside the submitted work. C. Grasso received consultation and/or speaker fees from Abbott Vascular, outside the submitted work. A. Giordano received consultation and/or speaker fees from Abbott Vascular, outside the submitted work. F. De Marco, A.S. Petronio and G. Tarantini received consultation and/or speaker fees from Abbott Vascular outside the submitted work. M. Metra received consultation and/or speaker fees from Abbott Vascular, outside the submitted work. C. Tamburino received consultation and/or speaker fees from Abbott Vascular, outside the submitted work. The other authors have no conflicts of interest to declare.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-726.

2. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *EuroIntervention.* 2022;17:e1126-e1196.

3. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ; COAPT Investigators. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med.* 2018;379:2307-18.

4. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefèvre T, Piot C, Rouleau F, Carrié D, Nejjari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu J-N, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N; MITRA-FR Ivestigators. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Engl J Med.* 2018;379:2297-306.

5. Koell B, Orban M, Weimann J, Kassar M, Karam N, Neuss M, Petrescu A, Iliadis C, Unterhuber M, Adamo M, Giannini C, Melica B, Ludwig S, Massberg S, Praz F, Pfister R, Thiele H, Stephan von Bardeleben R, Baldus S, Butter C, Lurz P, Windecker S, Metra M, Petronio AS, Hausleiter J, Lubos E, Kalbacher D; EuroSMR Investigators. Outcomes Stratified by Adapted Inclusion Criteria After Mitral Edge-to-Edge Repair. *J Am Coll Cardiol.* 2021;78:2408-21.

6. Raposeiras-Roubin S, Adamo M, Freixa X, Arzamendi D, Benito-González T, Montefusco A, Pascual I, Nombela-Franco L, Rodes-Cabau J, Shuvy M, Portolés-Hernández A, Godino C, Caneiro-Queija B, Lupi L, Regueiro A, Li CH, Fernández-Vázquez F, Frea S, Avanzas P, Tirado-Conte G, Paradis JM, Peretz A, Moñivas V, Baz JA, Galasso M, Branca L, Sanchis L, Asmarats L, Garrote-Coloma C, Angelini F, León V, Pozo E, Alperi A, Beeri R, Cani D, Sabaté M, Fernández-Peregrina E, Gualis J, Bocchino PP, Curello S, Abu-Assi E, Íñiguez-Romo A, Bedogni F, Rubbio AP, Testa L, Grasso C, Estévez-Loureiro R. A Score to Assess Mortality After Percutaneous Mitral Valve Repair. *J Am Coll Cardiol.* 2022;79:562-73.

7. Zweck E, Spieker M, Horn P, Iliadis C, Metze C, Kavsur R, Tiyerili V, Nickenig G, Baldus S, Kelm M, Becher MU, Pfister R, Westenfeld R. Machine Learning Identifies Clinical Parameters to Predict Mortality in Patients Undergoing Transcatheter Mitral Valve Repair. *JACC Cardiovasc Interv.* 2021;14:2027-36.

8. Godino C, Scotti A, Taramasso M, Adamo M, Russo M, Chiarito M, Melillo F, Beneduce A, Pivato CA, Arrigoni L, Toscano E, Salerno A, Cappelletti A, Magni V, Stella S, Fragasso G, Montorfano M, Agricola E, Ettori F, Margonato A, Maisano F, Colombo A. Two-year cardiac mortality after MitraClip treatment of functional mitral regurgitation in ischemic and non-ischemic dilated cardiomyopathy. *Int J Cardiol.* 2018;269:33-9.

9. Adamo M, Cani DS, Gavazzoni M, Taramasso M, Lupi L, Fiorelli F, Giannini C, Branca L, Zuber M, Curello S, Petronio AS, Maisano F, Metra M. Impact of disproportionate secondary mitral regurgitation in patients undergoing edge-to-edge percutaneous mitral valve repair. *EuroIntervention.* 2020;16:413-20.

10. Shah N, Madhavan MV, Gray WA, Brener SJ, Ahmad Y, Lindenfeld J, Abraham WT, Grayburn PA, Kar S, Lim DS, Mishell JM, Whisenant BK, Zhang Z, Redfors B, Mack MJ, Stone GW. Prediction of Death or HF Hospitalization in Patients With Severe FMR: The COAPT Risk Score. *JACC Cardiovasc Interv.* 2022;15:1893-905.

11. Bedogni F, Popolo Rubbio A, Grasso C, Adamo M, Denti P, Giordano A, Tusa M, Bianchi G, De Marco F, Bartorelli AL, Montorfano M, Godino C, Citro R, De Felice F, Mongiardo A, Monteforte I, Villa E, Giannini C, Crimi G, Tarantini G, Testa L, Tamburino C. Italian Society of Interventional Cardiology (GIse) registry Of Transcatheter treatment of mitral valve regurgitaTiOn (GIOTTO): impact of valve disease aetiology and residual mitral regurgitation after MitraClip implantation. *Eur J Heart Fail.* 2021;23:1364-76.

12. Bedogni F, Testa L, Rubbio AP, Bianchi G, Grasso C, Scandura S, De Marco F, Tusa M, Denti P, Alfieri O, Giordano A, Ferraro P, Bartorelli AL, Mongiardo A, Petronio AS, Giannini C, De Felice F, Baldi C, Castriota F, Adamo M, Masiero G, Godino C, Montorfano M, Tarantini G, Tamburino C. Real-World Safety and Efficacy of Transcatheter Mitral Valve Repair With MitraClip: Thirty-Day Results From the Italian Society of Interventional Cardiology (GIse) Registry Of Transcatheter Treatment of Mitral Valve RegurgitaTiOn (GIOTTO). *Cardiovasc Revasc Med.* 2020;21:1057-62.

13. Adamo M, Fiorelli F, Melica B, D'Ortona R, Lupi L, Giannini C, Silva G, Fiorina C, Branca L, Chiari E, Chizzola G, Spontoni P, Espada Guerreiro C, Curello S, Petronio AS, Metra M. COAPT-Like Profile Predicts Long-Term Outcomes in Patients With Secondary Mitral Regurgitation Undergoing MitraClip Implantation. *JACC Cardiovasc Interv.* 2021;14:15-25.

14. Stone GW, Adams DH, Abraham WT, Kappetein AP, Généreux P, Vranckx P, Mehran R, Kuck KH, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS; Mitral Valve Academic Research Consortium (MVARC). Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document From the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol.* 2015;66:308-21.

15. Ben-Shoshan J, Overtchook P, Buithieu J, Mousavi N, Martucci G, Spaziano M, de Varennes B, Lachapelle K, Brophy J, Modine T, Baumbach A, Maisano F, Prendergast B, Tamburino C, Windecker S, Piazza N. Predictors of Outcomes Following Transcatheter Edge-to-Edge Mitral Valve Repair. *JACC Cardiovasc Interv.* 2020;13:1733-48.

16. Caneiro-Queija B, Raposeiras-Roubin S, Adamo M, Freixa X, Arzamendi D, Benito-Gonzalez T, Montefusco A, Pascual I, Nombela-Franco L, Rodes-Cabau J, Shuvy M, Portolés-Hernández A, Godino C, Haberman D, Lupi L, Regueiro A, Li CH, Fernández-Vázquez F, Frea S, Avanzas P, Tirado-Conte G, Paradis JM, Peretz A, Moñivas V, Baz JA, Galasso M, Branca L, Sanchís L, Asmarats L, Garrote-Coloma C, Angelini F, León V, de Agustín JA, Alperi A, Beeri R, Maccagni G, Sabaté M, Fernández-Peregrina E, Gualis J, Bocchino PP, Curello S, Íñiguez-Romo A, Estévez-Loureiro R. Prognostic Impact of Nutritional Status After Transcatheter Edge-to-Edge Mitral Valve Repair: The MIVNUT Registry. *J Am Heart Assoc.* 2022;11:e023121.

17. Adamo M, Capodanno D, Cannata S, Giannini C, Laudisa ML, Barbanti M, Curello S, Immè S, Maffeo D, Grasso C, Bedogni F, Petronio AS, Ettori F, Tamburino C; GRASP-IT Investigators. Comparison of three contemporary surgical scores for predicting all-cause mortality of patients undergoing percutaneous mitral valve repair with the MitraClip system (from the multicenter GRASP-IT registry). *Am J Cardiol.* 2015;115:107-12.

18. Buccheri S, Capodanno D, Barbanti M, Popolo Rubbio A, Di Salvo ME, Scandura S, Mangiafico S, Ronsivalle G, Chiarandà M, Capranzano P, Grasso C, Tamburino C. A Risk Model for Prediction of 1-Year Mortality in Patients Undergoing MitraClip Implantation. *Am J Cardiol.* 2017;119:1443-9.

19. Sisinni A, Munafò A, Pivato CA, Adamo M, Taramasso M, Scotti A, Parlati ALM, Italia L, Voci D, Buzzatti N, Denti P, Ancona F, Marengo A, Sala A, Bodega F, Ruffo MM, Curello S, Castiglioni A, Montorfano M, de Bonis M, Alfieri O, Agricola E, Colombo A, Maisano F, Metra M, Margonato A, Godino C; MiZüBr registry. Effect of Chronic Kidney Disease on 5-Year Outcome in Patients With Heart Failure and Secondary Mitral Regurgitation Undergoing Percutaneous MitraClip Insertion. *Am J Cardiol.* 2022;171:105-14.

20. Godino C, Sisinni A, Pivato CA, Adamo M, Taramasso M, Parlati A, Italia L, Voci D, Scotti A, Munafo A, Buzzatti N, Denti P, Ancona F, Fiore G, Sala A, Vergara P, Bodega F, Ruffo MM, Curello S, Castiglioni A, De Bonis M, Alfieri O, Agricola E, Maisano F, Metra M, Colombo A, Margonato A; MiZüBr registry. Prognostic Value of Pre-operative Atrial Fibrillation in Patients With Secondary Mitral Regurgitation Undergoing MitraClip Implantation. *Am J Cardiol.* 2021;143:51-9.

21. Adamo M, Grasso C, Capodanno D, Rubbio AP, Scandura S, Giannini C, Fiorelli F, Fiorina C, Branca L, Brambilla N, Bedogni F, Petronio AS, Curello S, Tamburino C. Five-year clinical outcomes after percutaneous edge-to-edge mitral valve repair: Insights from the multicenter GRASP-IT registry. *Am Heart J.* 2019;217:32-41.

22. Adamo M, Godino C, Giannini C, Scotti A, Liga R, Curello S, Fiorina C, Chiari E, Chizzola G, Abbenante A, Visco E, Branca L, Fiorelli F, Agricola E, Stella S, Lombardi C, Colombo A, Petronio AS, Metra M, Ettori F. Left ventricular reverse remodelling predicts long-term outcomes in patients with functional mitral regurgitation undergoing MitraClip therapy: results from a multicentre registry. *Eur J Heart Fail.* 2019;21:196-204.

23. Caiffa T, De Luca A, Biagini E, Lupi L, Bedogni F, Castrichini M, Compagnone M, Tusa M, Berardini A, Merlo M, Fabris E, Popolo Rubbio A, Tomasoni D, Di Pasquale M, Arosio R, Perkan A, Barbati G, Saia F, Adamo M, Stolfo D, Sinagra G. Impact on clinical outcomes of right ventricular response to percutaneous correction of secondary mitral regurgitation. *Eur J Heart Fail.* 2021;23:1765-74.

24. Saxon JT, Cohen DJ, Chhatriwalla AK, Kotinkaduwa LN, Kar S, Lim DS, Abraham WT, Lindenfeld J, Mack MJ, Arnold SV, Stone GW. Impact of COPD on Outcomes After MitraClip for Secondary Mitral Regurgitation: The COAPT Trial. *JACC Cardiovasc Interv.* 2020;13:2795-803.

25. Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, Zuern CS, Bekeredjian R, Sievert H, Nickenig G, Eggebrecht H, Senges J, Schillinger W. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. *Eur Heart J.* 2016;37:703-12.

26. Senni M, Adamo M, Metra M, Alfieri O, Vahanian A. Treatment of functional mitral regurgitation in chronic heart failure: can we get a 'proof of concept' from the MITRA-FR and COAPT trials? *Eur J Heart Fail.* 2019;21:852-61.

27. Kavsur R, Iliadis C, Spieker M, Brachtendorf BM, Tiyerili V, Metze C, Horn P, Baldus S, Kelm M, Nickenig G, Pfister R, Westenfeld R, Becher MU. Predictors and prognostic relevance of tricuspid alterations in patients undergoing transcatheter edge-to-edge mitral valve repair. *EuroIntervention.* 2021;17:827-34.

28. Lerakis S, Kini AS, Asch FM, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Weissman NJ, Rinaldi MJ, Sharma SK, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Tang GHL, Li D, Crowley A, Lindenfeld J, Abraham WT, Mack MJ, Stone GW. Outcomes of transcatheter mitral valve repair for secondary mitral regurgitation by severity of left ventricular dysfunction. *EuroIntervention.* 2021;17:e335-42.

29. Pighi M, Adamo M. A Step Forward in Risk Stratification and Patient Selection for Mitral TEER in SMR. *JACC Cardiovasc Interv.* 2022;15:1906-9.

30. Scotti A, Latib A, Rubbio AP, Testa L, Adamo M, Denti P, Melillo F, Taramasso M, Sisinni A, De Marco F, Grasso C, Giordano A, Bartorelli AL, Buzzatti N, Citro R, De

Felice F, Indolfi C, Monteforte I, Villa E, Giannini C, Petronio AS, Crimi G, Tarantini G, Colombo A, Agricola E, Metra M, Zangrillo A, Margonato A, Tamburino C, Maisano F, Bedogni F, Godino C; MiZüBr and GIOTTO Investigators. Derivation and Validation of a Clinical Risk Score for COAPT-Ineligible Patients Who Underwent Transcatheter Edge-to-Edge Repair. *Am J Cardiol.* 2023;186:100-8.

Supplementary data

Supplementary Table 1. Baseline characteristics according to COAPT-like profile.

Supplementary Table 2. Baseline characteristics according to COAPT score quartiles in COAPT-like patients.

Supplementary Table 3. Baseline characteristics according to COAPT score quartiles in non-COAPT-like patients.

Supplementary Table 4. Association between COAPT risk score items and 2-year all-cause death or HF hospitalisation.

Supplementary Figure 1. Distribution of COAPT score points and association between COAPT score quartiles and primary outcome.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00992

Supplementary data

Supplementary Table 1. Baseline characteristics according to COAPT-like profile.				
	Overall	**COAPT-like**	**Non-COAPT-like**	**P value**
Age, years	75 [68-79]	75 [68-81]	74 [68-79]	0.504
Male sex	285 (63)	123 (29)	162 (36)	0.727
BMI, kg/m2	24.9 [22.6-27.7]	24.9 [22.2-27.7]	24.6 [22.0-24.6]	0.115
EuroSCORE II, %	5.7 [3.3-9.4]	4.8 [3.1-9.0]	7.0 [4.2-11.9]	0.001
STS Risk Score, %	3.4 [1.8-5.9]	3.4 [1.6-5.5]	3.5 [2.0-7.5]	0.120
NYHA class III/IV	369 (82)	151 (34)	218 (49)	0.137
Comorbidities, laboratory data and medical therapies				
Hypertension	318 (71)	138 (31)	180 (40)	0.567
Diabetes mellitus	146 (33)	63 (14)	83 (18)	0.856
Prior HF	328 (73)	128 (28)	200 (45)	0.013
COPD	85 (19)	41 (9)	44 (10)	0.238
Prior cerebrovascular disease	41 (9)	14 (3)	27 (6)	0.254
AF	226 (51)	84 (19)	142 (32)	0.020
CAD	245 (55)	95 (21)	150 (33)	0.077
Prior cardiac surgery	125 (28)	42 (9)	83 (18)	0.038
PAD	39 (9)	18 (4)	21 (5)	0.083
GFR < 30 mL/min	114 (25)	40 (9)	74 (16)	0.173
30 mL/min ≤ GFR ≤ 60mL/min	206 (46)	92 (20)	114 (25)	0.173
GFR > 60 mL/min	129 (29)	59 (13)	70 (16)	0.173

Haemoglobin, g/dL	12.3 [11.0-13.7]	12.2 [11.0-13.5]	12.6 [10.9-13.9]	0.452
Creatinine, mg/dL	1.3 [1.1-1.8]	1.2 [1.0-1.7]	1.4 [1.0-2.0]	0.115
NT-proBNP, ng/L	876 [342-3076]	383 [196-799]	1129 [356-3189]	0.003
CRT	240 (53)	93 (21)	147 (33)	0.082
Beta-blocker	374 (83)	166 (37)	208 (46)	0.167
ACEi/ARB/ARNI	153 (34)	61 (14)	92 (20)	0.216
MRA	274 (61)	114 (25)	160 (36)	0.617
Furosemide	420 (94)	175 (39)	245 (55)	0.155
Echocardiographic data				
LAD, mm	50 [45-55]	48 [44-53]	50 [45-55]	0.055
LVEDD, mm	63 [57-69]	62 [57-68]	63 [56-70]	0.102
LVESD, mm	50 [43-58]	51 [42-58]	50 [44-61]	0.058
LVEDV, mL	172 [130-211]	171 [130-211]	172 [124-214]	0.468
LVEDVi, mL/m2	95 [73-115]	96 [75-118]	96 [70-121]	0.497
LVESV, mL	112 [76-148]	115 [79-148]	119 [81-164]	0.072
LVESVi, mL/m2	63 [43-81]	65 [45-83]	69 [45-92]	0.084
LVEF, %	32 [26-40]	32 [28-40]	30 [24-38]	0.003
MR 2+	5 (1)	2 (0.4)	3 (0.7)	0.908
MR 3+	102 (23)	51 (11)	51 (11)	0.083
MR 4+	342 (76)	138 (31)	204 (45)	0.094
MVA planimetry, cm2	4.8 [4.0-6.0]	4.8 [4.3-5.6]	4.8 [4.0-6.2]	0.653
Severe TR	116 (26)	0 (0)	116 (26)	0.001

TAPSE, mm	18 [15-21]	18 [17-21]	14 [12-14]	0.001
sPAP, mmHg	45 [39-55]	45 [35-55]	50 [40-62]	0.001

Values are expressed as n (%), or median [interquartile range].
Abbreviations. AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; GFR, glomerular filtration rate; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESVi, left ventricular end-systolic volume index; MR, mitral regurgitation, MVA, mitral valve area; OMT, optimal medical therapy; NYHA, New York Heart Association; PAD, peripheral artery disease; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Supplementary Table 2. Baseline characteristics according to COAPT score quartiles in COAPT-like patients.					
	COAPT score -3 to 1	**COAPT score 2 to 3**	**COAPT score 4 to 5**	**COAPT score 6 to 12**	**P value**
Age, years	70 [68-73]	74 [72-77]	74 [70-77]	75 [73-77]	0.046
Male sex	42 (22)	23 (12)	23 (12)	35 (18)	0.129
BMI, kg/m2	25.9 [24.9-27.0]	24.7 [23.5-26.0]	25.3 [23.9-26.6]	25.2 [24.1-26.3]	0.472
EuroSCORE II, %	5.3 [4.4-6.3]	6.1 [4.5-7.7]	6.2 [4.5-7.8]	10.0 [7.9-12.2]	0.001
STS Risk Score, %	3.3 [2.5-4.1]	4.4 [2.9-6.0]	5.3 [3.2-7.4]	5.9 [4.2-7.5]	0.045
NYHA class III/IV	44 (23)	34 (18)	26 (14)	47 (25)	0.008
Comorbidities, laboratory data and medical therapies					
Hypertension	41 (21)	34 (18)	26 (14)	37 (19)	0.618
Diabetes mellitus	22 (11)	13 (7)	11 (6)	17 (9)	0.871
Prior HF	36 (19)	32 (17)	23 (12)	37 (19)	0.263
COPD	7 (4)	11 (6)	11 (6)	12 (6)	0.085
Prior cerebrovascular disease	5 (3)	3 (2)	3 (2)	3 (2)	0.958
AF	17 (9)	21 (11)	21 (11)	25 (13)	0.006
CAD	28 (15)	19 (10)	14 (7)	34 (18)	0.016
Prior cardiac surgery	15 (8)	8 (4)	4 (2)	15 (8)	0.176
PAD	5 (3)	2 (1)	2 (1)	18 (9)	0.178
GFR < 30 mL/min	5 (3)	10 (5)	14 (7)	30 (16)	0.001

30 mL/min ≤ GFR ≤ 60mL/min	27 (14)	17 (9)	19 (10)	29 (15)	0.001
GFR > 60 mL/min	17 (9)	7 (4)	13 (7)	3 (2)	0.001
Haemoglobin, g/dL	12.6 [12.2-13.1]	12.3 [11.8-12.9]	12.1 [11.3-12.8]	11.7 [11.2-12.2]	0.084
Creatinine, mg/dL	1.23 [1.09-1.36]	1.53 [1.26-1.80]	1.79 [1.26-2.32]	1.77 [1.51-2.03]	0.010
NT-proBNP, ng/L	569 [54-1084]	442 [310-574]	1199 [66-2331]	3072 [1675-4468]	0.001
CRT	31 (16)	24 (13)	12 (6)	26 (14)	0.379
Beta-blocker	54 (28)	41 (21)	32 (17)	39 (20)	0.255
ACEi/ARB/ARNI	26 (14)	13 (7)	7 (4)	15 (8)	0.158
MRA	36 (19)	28 (15)	20 (10)	30 (16)	0.985
Furosemide	56 (29)	42 (22)	31 (16)	46 (24)	0.924
Echocardiographic data					
LAD, mm	49 [46-51]	49 [47-51]	49 [45-53]	49 [47-51]	0.978
LVEDD, mm	59 [57-61]	60 [57-64]	62 [59-65]	66 [64-68]	0.001
LVESD, mm	46 [44-49]	48 [44-51]	49 [46-53]	56 [54-58]	0.001
LVEDV, mL	156 [143-168]	169 [148-189]	177 [158-196]	205 [185-224]	0.001
LVEDVi, mL/m2	88 [81-95]	96 [85-107]	96 [87-105]	114 [103-125]	0.001
LVESV, mL	98 [89-107]	111 [94-128]	117 [100-134]	147 [130-164]	0.001
LVESVi, mL/m2	55 [50-60]	63 [54-72]	64 [55-72]	82 [72-91]	0.001
LVEF, %	37 [34-39]	36 [32-39]	34 [31-37]	30 [27-32]	0.002
MR 2+	2 (1)	0 (0)	0 (0)	0 (0)	0.240
MR 3+	20 (10)	17 (9)	6 (3)	8 (4)	0.056

MR 4+	40 (21)	29 (15)	28 (15)	41 (21)	0.033
MVA planimetry, cm2	5.0 [4.6-5.6]	5.3 [4.7-5.9]	5.1 [4.3-5.8]	5.1 [4.5-5.8]	0.963
Severe TR	0 (0)	0 (0)	(0)	0 (0)	.
TAPSE, mm	20 [19-20]	20 [19-21]	20 [18-21]	18 [17-19]	0.041
sPAP, mmHg	36 [35-38]	42 [39-46]	48 [44-52]	57 [55-59]	0.001

Values are expressed as n (%), or median [interquartile range].
Abbreviations. AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; GFR, glomerular filtration rate; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESVi, left ventricular end-systolic volume index; MR, mitral regurgitation, MVA, mitral valve area; OMT, optimal medical therapy; NYHA, New York Heart Association; PAD, peripheral artery disease; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Supplementary Table 3. Baseline characteristics according to COAPT score quartiles in non-COAPT-like patients.					
	COAPT score -3 to 1	**COAPT score 2 to 3**	**COAPT score 4 to 5**	**COAPT score 6 to 12**	**P value**
Age, years	69 [65-72]	74 [73-76]	73 [71-75]	72 [71-74]	0.037
Male sex	26 (10)	27 (10)	36 (14)	73 (28)	0.015
BMI, kg/m2	24.6 [23.3-25.9]	26.3 [25.2-27.3]	24.4 [23.4-25.3]	24.4 [23.7-25.1]	0.021
EuroSCORE II, %	5.8 [4.6-7.1]	9.1 [6.7-11.5]	8.4 [7.0-9.8]	11.9 [10.0-13.8]	0.001
STS Risk Score, %	3.9 [1.9-6.1]	4.7 [3.2-6.1]	5.3 [3.8-6.9]	6.5 [4.9-8.1]	0.176
NYHA class III/IV	18 (7)	42 (20)	64 (25)	94 (36)	0.001
Comorbidities, laboratory data and medical therapies					
Hypertension	21 (8)	32 (12)	55 (21)	72 (28)	0.315
Diabetes mellitus	10 (4)	17 (7)	22 (9)	34 (13)	0.963
Prior HF	23 (9)	34 (13)	57 (22)	86 (33)	0.439
COPD	2 (0.8)	7 (3)	13 (5)	22 (9)	0.284
Prior cerebrovascular disease	1 (0.4)	8 (3)	9 (3)	9 (3)	0.190
AF	11 (4)	23 (9)	40 (15)	68 (26)	0.025
CAD	17 (7)	25 (10)	41 (16)	67 (26)	0.630
Prior cardiac surgery	13 (5)	18 (7)	22 (8)	30 (12)	0.502
PAD	2 (1)	2 (1)	7 (3)	10 (4)	0.395
GFR < 30 mL/min	1 (0.4)	5 (2)	16 (6)	52 (20)	0.001
30 mL/min ≤ GFR ≤ 60mL/min	13 (5)	30 (12)	32 (12)	39 (15)	0.001

GFR > 60 mL/min	18 (7)	13 (5)	22 (8)	17 (7)	0.001
Haemoglobin, g/dL	12.9 [12.2-13.6]	12.6 [11.9-13.2]	12.3 [11.8-12.8]	12.2 [11.8-12.5]	0.017
Creatinine, mg/dL	1.08 [0.95-1.21]	1.43 [1.26-1.60]	1.51 [1.31-1.71]	2.10 [1.87-2.33]	0.001
NT-proBNP, ng/L	1219 [359-2079]	1001 [496-1506]	2551 [1299-3802]	3283 [2178-4389]	0.001
CRT	11 (4)	26 (10)	36 (14)	74 (29)	0.004
Beta-blocker	19 (7)	41 (16)	56 (22)	92 (36)	0.036
ACEi/ARB/ARNI	9 (3)	14 (5)	31 (12)	38 (15)	0.452
MRA	16 (6)	28 (11)	49 (19)	67 (26)	0.258
Furosemide	30 (12)	46 (18)	69 (27)	100 (39)	0.341
Echocardiographic data					
LAD, mm	49 [46-53]	49 [46-53]	50 [49-52]	51 [50-53]	0.448
LVEDD, mm	58 [54-61]	62 [59-66]	61 [58-64]	66 [64-68]	0.001
LVESD, mm	45 [40-49]	50 [46-55]	50 [47-54]	55 [53-58]	0.001
LVEDV, mL	140 [115-165]	186 [158-214]	165 [147-182]	197 [184-210]	0.001
LVEDVi, mL/m2	78 [65-91]	102 [87-116]	92 [83-102]	110 [103-117]	0.001
LVESV, mL	90 [69-112]	130 [107-154]	113 [98-129]	145 [134-156]	0.001
LVESVi, mL/m2	50 [39-61]	71 [59-83]	64 [55-72]	81 [75-87]	0.001
LVEF, %	39 [34-43]	31 [28-34]	34 [31-36]	28 [26-29]	0.001
MR 2+	2 (1)	0 (0)	0 (0)	1 (0.4)	0.340
MR 3+	6 (2)	13 (5)	10 (4)	22 (8)	0.393
MR 4+	24 (9)	35 (14)	60 (23)	85 (33)	0.348

MVA planimetry, cm2	5.3 [4.3-6.3]	4.8 [4.1-5.5]	5.2 [4.7-5.8]	5.3 [4.9-5.7]	0.618
Severe TR	12 (5)	18 (7)	34 (13)	52 (20)	0.455
TAPSE, mm	15 [13-17]	15 [13-17]	16 [14-17]	16 [14-17]	0.936
sPAP, mmHg	37 [34-40]	41 [38-45]	56 [52-60]	59 [56-62]	0.001

Values are expressed as n (%), or median [interquartile range].
Abbreviations. AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; GFR, glomerular filtration rate; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESVi, left ventricular end-systolic volume index; MR, mitral regurgitation, MVA, mitral valve area; OMT, optimal medical therapy; NYHA, New York Heart Association; PAD, peripheral artery disease; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Supplementary Table 4. Association between COAPT risk score items and 2-year all-cause death or HF hospitalisation.

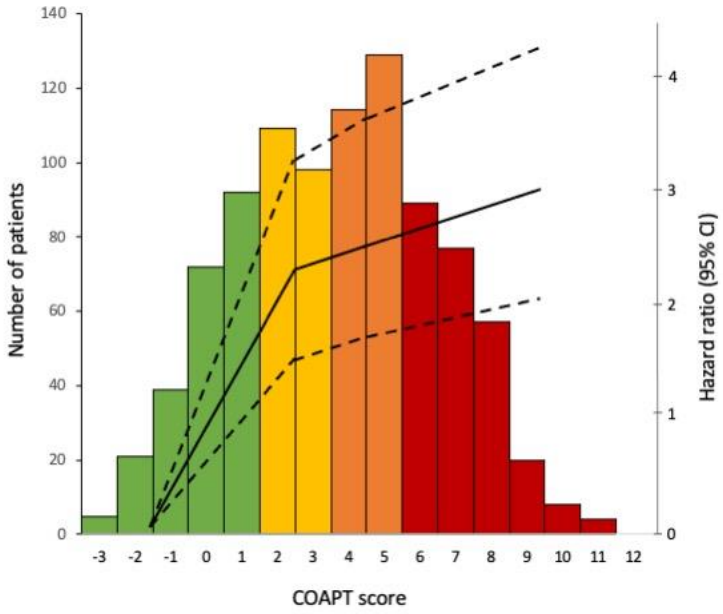
Overall population

	Univariate			Multivariable		
COAPT score items	HR	95% CI	p-value	HR	95% CI	p-value
History of Atrial Fibrillation	1.15	0.93-1.42	0.186	1.31	0.98-1.75	0.073
CKD stage 3	1.22	1.11-1.34	<0.001	1.07	0.94-1.23	0.304
COPD	1.37	1.04-1.79	0.023	1.15	0.81-1.64	0.430
NYHA class III or IV	2.08	1.32-3.28	0.002	2.02	1.28-3.19	0.002

LVEF<25%	1.34	1.09-1.65	0.006	1.34	1.09-1.65	0.006
LVESD>55 mm	1.01	0.87-1.18	0.860	0.89	0.75-1.05	0.170
RVSP>45 mmHg	1.06	0.96-1.17	0.247	1.05	0.95-1.16	0.310
TR>1+	0.98	0.84-1.14	0.757	0.90	0.76-1.06	0.193
COAPT-like profile						
	Univariate			Multivariable		
COAPT score items	HR	95% CI	p-value	HR	95% CI	p-value
History of Atrial Fibrillation	1.59	0.98-2.55	0.059	1.67	1.02-2.76	0.044
CKD stage 3	1.38	1.11-1.70	0.003	1.39	1.11-1.73	0.004
COPD	1.42	0.83-2.41	0.198	1.38	0.80-2.37	0.248
NYHA class III or IV	2.15	1.07-4.34	0.032	1.82	0.89-3.71	0.101
LVEF<25%	1.36	0.94-1.98	0.106	1.48	1.01-2.16	0.044
LVESD>55 mm	1.00	0.79-1.28	0.985	0.92	0.69-1.22	0.566
RVSP>45 mmHg	1.19	1.02-1.40	0.030	1.09	0.92-1.29	0.302
TR>1+	1.17	0.92-1.50	0.197	1.02	0.78-1.34	0.893
Non-COAPT like profile						
	Univariate			Multivariable		
COAPT score items	HR	95% CI	p-value	HR	95% CI	p-value
History of Atrial Fibrillation	1.05	0.73-1.52	0.789	1.23	0.83-1.81	0.301

CKD stage 3	0.97	0.83-1.14	0.718	0.92	0.78-1.09	0.328
COPD	1.18	0.75-1.87	0.475	1.12	0.70-1.77	0.644
NYHA class III or IV	1.94	1.06-3.53	0.031	1.92	1.05-3.49	0.033
LVEF<25%	1.28	0.99-1.64	0.057	1.23	0.95-1.58	0.122
LVESD>55 mm	1.01	0.84-1.21	0.936	0.85	0.69-1.05	0.129
RVSP>45 mmHg	0.96	0.85-1.09	0.516	1.01	0.88-1.16	0.878
TR>1+	0.77	0.64-0.94	0.010	0.78	0.64-0.95	0.011

Abbreviations. AF, atrial fibrillation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HF, heart failure, HR, hazard ratio; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.



Supplementary Figure 1. Distribution of COAPT score points and association between COAPT score quartiles and primary outcome.