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Renal Function and Peak Exercise Oxygen Consumption in Chronic Heart Failure With Reduced Left Ventricular Ejection Fraction

Domenico Scrutinio, MD; Piergiuseppe Agostoni, MD, PhD; Loreto Gesualdo, MD; Ugo Corrà, MD; Alessandro Mezzani, MD; Massimo Piepoli, MD; Andrea Di Lenarda, MD; Annamaria Iorio, MD; Claudio Passino, MD; Damiano Magrì, MD, PhD; Daniele Masarone, MD; Elisa Battaia, MD; Davide Girola, MD; Federica Re, MD; Gaia Cattadori, MD; Gianfranco Parati, MD; Gianfranco Sinagra, MD; Giovanni Quinto Villani, MD; Giuseppe Limongelli, MD; Giuseppe Pacileo, MD; Marco Guazzi, MD; Marco Metra, MD; Maria Frigerio, MD; Mariantonietta Cicoira, MD; Chiara Minà, MD; Gabriella Malfatto, MD, PhD; Sergio Caravita, MD; Maurizio Bussotti, MD; Elisabetta Salvioni, PhD; Fabrizio Veglia, PhD; Michele Correale, MD; Angela B. Scardovi, MD; Michele Emdin, MD; Pantaleo Giannuzzi, MD; Paola Gargiulo, MD; Marta Giovannardi, BSc; Pasquale Perrone-Filardi, MD; Rosa Raimondo, MD; Roberto Ricci, MD; Stefania Paolillo, MD; Stefania Farina, MD; Romualdo Belardinelli, MD; Andrea Passantino, MD; Rocco La Gioia, MD on behalf of the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) Score Research Group

Background: Chronic kidney disease is associated with sympathetic activation and muscle abnormalities, which may contribute to decreased exercise capacity. We investigated the correlation of renal function with peak exercise oxygen consumption ($\dot{V}O_2$) in heart failure (HF) patients.

Methods and Results: We recruited 2,938 systolic HF patients who underwent clinical, laboratory, echocardiographic and cardiopulmonary exercise testing. The patients were stratified according to estimated glomerular filtration rate (eGFR). Mean follow-up was 3.7 years. The primary outcome was a composite of cardiovascular death and urgent heart transplantation at 3 years. On multivariable regression, eGFR was predictor of peak$\dot{V}O_2$ (P<0.0001). Other predictors were age, sex, body mass index, HF etiology, NYHA class, atrial fibrillation, resting heart rate, B-type natriuretic peptide, hemoglobin, and treatment. After adjusting for significant covariates, the hazard ratio for primary outcome associated with peak$\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1} was 1.75 (95% confidence interval (CI): 1.06–2.91; P=0.0292) in patients with eGFR ≥60, 1.77 (0.87–3.61; P=0.1141) in those with eGFR of 45–59, and 2.72 (1.01–7.37; P=0.0489) in those with eGFR <45 ml·min^{-1}·1.73 m^{-2}. The area under the receiver-operating characteristic curve for peak$\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1} was 0.63 (95% CI: 0.54–0.71), 0.67 (0.56–0.78), and 0.57 (0.47–0.69), respectively. Testing for interaction was not significant.

Conclusions: Renal dysfunction is correlated with peak$\dot{V}O_2$. A peak$\dot{V}O_2$ cutoff of 12 ml·kg^{-1}·min^{-1} offers limited prognostic information in HF patients with more severely impaired renal function. (*Circ J* 2015; **79:** 583–591)

Key Words: Heart failure; Peak exercise oxygen consumption; Prognosis; Renal function

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Division of Cardiology, "S. Maugeri" Foundation, IRCCS, Institute of Cassano Murge, Bari (D.S., A.P., R.L.G.); Centro Cardiologico Monzino, IRCCS, Milano (P.A., G.C., E.S., F.V., M. Giovannardi, S.F.); Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milano, Milano (P.A.); Renal, Dialysis and Transplant Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari (L.G.); Division of Cardiology Rehabilitation, "S. Maugeri" Foundation, IRCCS, Scientific Institute of Veruno, Veruno (U.C., A.M., P. Giannuzzi); UOC Cardiologia, G da Saliceto Hospital, Piacenza (M.P., G.Q.V.); Cardiovascular Center, Health Authority no.°1 and University of Trieste, Trieste (A.D.L.); Cardiovascular Department, Ospedali Riuniti and University of Trieste, Trieste (A.I., G.S.); Gabriele Monasterio Foundation, CNR-Regione Toscana, Pisa (C.P., M.E.); Scuola Superiore S. Anna, Pisa (C.P.); Department of Clinical and Molecular Medicine, Azienda Ospedaliera Sant'Andrea, "Sapienza" University of Roma, Roma (D. Magrì); Cardiology SUN, Monaldi Hospital (Azienda dei Colli), Second University of Napoli, Napoli (D. Masarone, G.L., G. Pacileo); Section of Cardiology, Department of Medicine, University of Verona, Verona (E.B., M. Cicoira); Cardiologic Department "A. De Gasperis", Cà Granda-A.O. Hospital Niguarda, Milano (D.G., M.F.); Cardiology Division, Cardiac Arrhythmia Center and Cardiomyopathies Unit,
(Footnote continued the next page.)

Chronic kidney disease (CKD) is highly prevalent in patients with chronic heart failure (HF), affecting nearly half of them.[1] In addition, a 13% rate of incident renal dysfunction over 6 months has been observed in systolic CHF patients,[2] even though progression to end-stage renal disease is rare.[3] Renal dysfunction strongly affects morbidity and mortality risk, and estimated glomerular filtration rate (eGFR) is a well-known predictor of mortality.[4] Furthermore, CKD may complicate the management of HF.[5]

Cardiopulmonary exercise testing (CPET) has several clinical applications in HF, including investigation of the pathophysiology of exercise intolerance and symptoms, evaluation of functional capacity and response to therapeutic interventions, prognostic evaluation, and prescription of exercise training. Risk stratification is a major clinical application of CPET. Peak exercise oxygen consumption ($\dot{V}O_2$) is regarded as an important prognostic variable; although not formally tested, a cutoff value of 12 $ml \cdot kg^{-1} \cdot min^{-1}$ is currently used as a criterion to guide heart transplant listing in ambulatory patients with advanced HF receiving optimized medical treatment including β-blockers.[6,7] Peak $\dot{V}O_2$ is, however, affected by age, sex, and anthropometric characteristics; thus, equations to adjust peak $\dot{V}O_2$ for such variables have been developed.[8] Because CKD is associated with sympathetic activation and skeletal muscle abnormalities,[9–11] which may contribute to reduced exercise capacity in HF patients, defining whether renal dysfunction influences peak $\dot{V}O_2$ does appear to be a relevant issue.

In the present study, we sought to investigate the correlation of residual renal function with peak $\dot{V}O_2$ and assess the effect of renal dysfunction on the prognostic value of peak $\dot{V}O_2$ in HF patients with reduced left ventricular ejection fraction (LVEF).

Methods

The study population consisted of 2,938 ambulatory patients with HF and reduced LVEF included in the MECKI score database.[12] Selection criteria and methods are described in detail elsewhere.[12,13] Briefly, the patients were recruited and prospectively followed up in 14 Italian HF centers. The clinical, laboratory, ECG, echocardiographic, and CPET data were collected at enrollment. Inclusion criteria were: HF symptoms (NYHA functional classes I–III, stage C of ACC/AHA classification) and former documentation of LVEF <0.40, stable clinical condition with unchanged medications for at least 3 months, and no major cardiovascular treatment or intervention scheduled. Only patients who attained a peak exercise respiratory quotient >1.05 were included in the present study. Exclusion criteria were: history of pulmonary embolism, moderate-to-severe aortic and mitral stenoses, pericardial disease, severe obstructive lung disease, exercise-induced angina and significant ECG alterations, or the presence of any clinical comorbidity interfering with exercise performance. The primary outcome was a composite of cardiovascular death and urgent heart transplantation (HT) at 3 years.

Statistical Analysis

Details of data management were previously reported.[12,13] Data are reported here as mean ± standard deviation for continuous variables or number (percentage) of patients for categorical variables. ANOVA test was used for comparison between groups and χ^2 test was used for comparing categorical variables. Skewed data are reported as median and interquartile range (IQR) and compared by the Kruskall-Wallis test. The eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation.[14] Patients were stratified according to their eGFR into 4 clinically meaningful strata: <30, 30 to <45, 45–59, and ≥60 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$.[15] Because only 79 patients (2.7%) were in the lowest eGFR stratum, they were grouped into the next stratum of 30 to <45 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$.

We used multivariable linear regression analysis to assess the association of eGFR with peak $\dot{V}O_2$ as the dependent variable. The following variables were examined: age, sex, body mass index, etiology of HF, NYHA class, atrial fibrillation, diastolic (DBP) and systolic (SBP) blood pressures at rest, left ventricular end-systolic volume (LVESV), LVEF, resting heart rate, QRS duration, eGFR, B-type natriuretic peptide (BNP) concentration, sodium level, hemoglobin, and treatment with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin type 1 (AT_1) receptor blockers, β-blockers, or cardiac resynchronization therapy (CRT). Because of collinearity between left ventricular end-diastolic volume and LVESV, the former was not included in the analysis. Because BNP values were available only for 1,297 patients, a separate regression analysis was performed. Because of a skewed distribution, SBP, LVESV, QRS duration, and peak $\dot{V}O_2$ were logarithmically transformed.

Kaplan-Meier survival curves were applied for the categories of eGFR and peak $\dot{V}O_2$ and compared using log-rank test. The area under the receiver-operating characteristic (ROC) curve (AUC) of peak $\dot{V}O_2$ <12 $ml \cdot kg^{-1} \cdot min^{-1}$ for the primary outcome at 3 years was determined for the entire study population and each strata of eGFR. Because it has been suggested that peak $\dot{V}O_2$ tends to lose its predictive value 3 years post-CPET,[16] we also calculated the AUC of peak $\dot{V}O_2$ <12 $ml \cdot kg^{-1} \cdot min^{-1}$ at 2 years for each strata of eGFR. The statistical significance of the interaction between eGFR and peak $\dot{V}O_2$ in predicting the primary outcome was tested with the likelihood ratio test. The hazard ratio (HR) and 95% confidence interval (CI) for the primary outcome at 3 years associated with peak $\dot{V}O_2$ <12 $ml \cdot kg^{-1} \cdot min^{-1}$ in each strata of eGFR was estimated using univariable and multivariable Cox proportional hazard models.

San Camillo-Forlanini Hospital, Roma (F.R.); Department of Health Science, University of Milano Bicocca & Department of Cardiology, San Luca Hospital, Istituto Auxologico Italiano, Milano (G. Parati, G.M., S.C.); Heart Failure Unit, IRCCS Policlinico San Donato, San Donato Milanese (M. Guazzi); Cardiology, Department of Medical and Surgical Specialities, Radiological Sciences, and Public Health, University of Brescia, Brescia (M.M.); ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies), Palermo (C.M.); Division of Cardiology, Salvatore Maugeri Foundation, IRCCS, Institute of Milan, Milan (M.B.); Department of Cardiology, University of Foggia, Foggia (M. Correale); Cardiology Division, Santo Spirito Hospital, Roma (A.B.S., R. Ricci); SDN Foundation, Institute of Diagnostic and Nuclear Development, Napoli (P. Gargiulo); Department of Advanced Biomedical Sciences, "Federico II" University, Napoli (P.P.-F., S.P.); "S. Maugeri" Foundation, IRCCS, Institute of Tradate, Department of Medicine and Cardiorespiratory Rehabilitation, Unit of Cardiac Rehabilitation, Tradate, Varese (R. Raimondo); and Cardiologia Riabilitativa, Azienda Ospedali Riuniti, Ancona (R.B.), Italy

The Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) Score Research Group see Appendix.

Mailing address: Piergiuseppe Agostoni, MD, PhD, Centro Cardiologico Monzino, IRCCS, Via Parea 4, 20138, Milan, Italy. E-mail: piergiuseppe.agostoni@unimi.it

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Analyses were conducted using SAS v. 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

Baseline characteristics by eGFR are reported in Table 1; 1,992 patients (67.8%) had an eGFR ≥60 ml·min^{-1}·1.73 m^{-2}, 574 (19.5%) in the range of 45–59 ml·min^{-1}·1.73 m^{-2}, and 372 (12.7%) <45 ml·min^{-1}·1.73 m^{-2}. The peak respiratory exchange ratio was comparable across the eGFR strata. Median (IQR) peak $\dot{V}O_2$ was 15.2 (9.2–24.6) ml·kg^{-1}·min^{-1} in the highest, 13.2 (8.2–20.4) ml·kg^{-1}·min^{-1} in the intermediate, and 11.5 (7.5–17.9) ml·kg^{-1}·min^{-1} in the lowest eGFR strata (P<0.0001). The proportion of patients with peak $\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1} was 25.1%, 24.2%, and 50.7%, respectively (P<0.0001). The patients in the lowest eGFR strata were older, had higher NYHA class and BNP concentrations, lower LVEF and hemoglobin and sodium levels, higher minute ventilation/CO_2 production ($\dot{V}E/\dot{V}CO_2$) slope, and more frequently presented exercise oscillatory ventilation and atrial fibrillation (Table 1). Overall, 94.4% of the patients were on chronic treatment with ACEIs or AT$_1$-receptor blockers and 85% with β-blockers.

In the multivariable linear regression analysis, eGFR was a significant predictor of log-transformed peak $\dot{V}O_2$ (t value: 5.45; P<0.0001). Figure 1 shows the geometric mean peak $\dot{V}O_2$ according to eGFR strata. Other significant variables were age (t value: −10.58; P<0.0001), sex (t value: 8.15; P<0.0001), body mass index (t value: −9.7; P<0.0001), etiology of HF (t value: −2.42; P=0.0157), NYHA class (t value: −7.12; P<0.0001), atrial fibrillation (t value: −2.65; P=0.0081), resting heart rate (t value: −3.26; P=0.0011), log QRS duration (t value: −2.78; P=0.0055), hemoglobin (t value: 5.64; P<0.0001), treatment with ACEIs (t value: 2.77; P=0.0056) or AT$_1$-blockers (t value: 2.7; P=0.007), and LVEF (t value: 5.85; P<0.0001). The multivariable linear regression model explained 42% of the variation in peak $\dot{V}O_2$. When the analysis was restricted to the 1,297 patients with available BNP data, eGFR remained significantly correlated with log-transformed peak $\dot{V}O_2$ (t value: 4.79; P<0.0001). The model incorporating BNP explained 48% of the variation in peak $\dot{V}O_2$.

Mean follow-up was 3.7 years in the entire population and 3.7, 3.9, and 3.3 years, respectively, in the patient subgroups of eGFR. The primary outcome occurred in 521 cases (17.8%); 221 deaths occurred in the subgroup of patients with eGFR ≥60 ml·min^{-1}·1.73 m^{-2} (11.1%), 131 among those with eGFR in the range of 45–59 ml·min^{-1}·1.73 m^{-2} (22.8%), and 103 with eGFR <45 ml·min^{-1}·1.73 m^{-2} (27.7%). Urgent HT had to be performed in 52 (2.6%), 9 with (1.6%) and 5 (1.3%) patients in the respective subgroups of eGFR.

Figure 2 shows survival curves in the 3 eGFR subgroups, stratified by peak $\dot{V}O_2$, and Figure 3 shows the ROC curves of peak $\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1} at 3 years in the entire study population and in each strata of eGFR. The comparison of AUC with 95% CI of peak $\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1} for the primary outcome at 2 and 3 years in the entire population and in each strata of eGFR is shown in Table 2. There was no significant interaction between peak $\dot{V}O_2$ and eGFR for the primary outcome, indicating that the association of peak $\dot{V}O_2$ with the primary outcome did not depend on eGFR (P value for interaction 0.7716). Peak $\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1} was associated with an unadjusted HR for the primary outcome at 3 years of 2.56 (95% CI: 1.98–3.31; P<0.0001) in patients with eGFR ≥60, 2.20 (95% CI: 1.51–3.21; P<0.0001) in those with eGFR of 45–59, and 2.35 (95% CI: 1.59–3.67; P=0.0002) in those with EGFR <45 ml·min^{-1}·1.73 m^{-2}. After adjusting for age, sex, body mass index, SBP, DBP, etiology of HF, NYHA class, atrial fibrillation, LVESV, LVEF, heart rate, QRS duration, sodium and hemoglobin levels, and treatments, the HR for the occurrence of the primary outcome at 3 years for patients who achieved a peak $\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1} vs. those who achieved a peak $\dot{V}O_2$ ≥12 ml·kg^{-1}·min^{-1} was 1.75 (95% CI: 1.06–2.91; P=0.0292) in patients with eGFR ≥60, 1.77 (95% CI: 0.87–3.61; P=0.1141) in those with eGFR of 45–59, and 2.72 (95% CIs: 1.01–7.37; P=0.0489) in those with eGFR <45 ml·min^{-1}·1.73 m^{-2}.

Discussion

Although the effect of renal dysfunction on morbidity and mortality in HF patients has been firmly established, its effect on exercise capacity has been poorly defined. In this study, we investigated the association of renal function with exercise capacity and the effect of impaired renal filtration rate on the prognostic accuracy of peak $\dot{V}O_2$ in HF patients with reduced LVEF. There are 2 major findings of this study.

First, renal dysfunction, as assessed by eGFR, positively correlated with decreased peak $\dot{V}O_2$, independent of other established factors influencing peak $\dot{V}O_2$ such as age, sex, obesity, NYHA class, atrial fibrillation, hemoglobin, and treatments, including CRT. Peak $\dot{V}O_2$ as well as other key CPET-derived variables, including $\dot{V}E/\dot{V}CO_2$, significantly worsened with declining renal function. These findings suggest that renal dysfunction may contribute to exercise intolerance in HF. A significant correlation, however, does not prove a cause-effect relationship and our study was not designed to investigate the mechanisms underlying the association between decreasing renal function and decreasing exercise capacity in HF. Thus, whether this association reflects a cause-effect relationship or merely a more advanced stage of HF remains to be elucidated. Nonetheless, it is tempting to speculate about some mechanisms potentially linking renal dysfunction to reduced exercise performance. In HF, chronic sympathetic activation results in maladaptive changes in target organs rich in α- and β-adrenergic receptors.[17–19] Chronic sympathetic activation leads to decreased responsiveness of the failing heart to catecholamines, thus limiting its ability to increase cardiac output during dynamic exercise, increased peripheral vascular resistance, and impaired skeletal muscle vasodilatation capacity during exercise resulting in muscle hypoperfusion.[17–23] In addition, chronic sympathetic activation may contribute to skeletal myopathy.[24–26] These central and peripheral abnormalities are causally linked to reduced exercise capacity in systolic HF.[27–32] Dysfunctional kidneys have a pronounced effect on sympathetic activity[9,10,33,34] and, as demonstrated by Grassi et al,[35] the magnitude of the adrenergic drive is proportional to the degree of renal dysfunction. In HF, the dysfunctional kidneys are both the target and source of central sympathetic drive,[9,10,33,34,36–40] thus fuelling the vicious circle of sympathetic overactivity. In a landmark study, Petersson et al demonstrated that increased renal norepinephrine spillover has a pathophysiological and prognostic role in parallel with and independent of cardiac sympathetic drive in HF.[37] It is conceivable that renal dysfunction may act as an amplifier of sympathetic activation in HF,[17,33,41] thus potentiating the sympathetically mediated mechanisms underlying reduced exercise capacity. Additional mechanisms may be implicated. As CKD is a catabolic condition, it may potentially contribute to the exercise intolerance of HF by activating metabolic pathways leading to skeletal muscle wasting. Systemic inflammation, a prominent feature in both HF and CKD, may induce proteolysis in skeletal muscle.[11,29,42] Chronic metabolic acidosis is a common condition in moderate-to-severe

Table 1. Baseline Characteristics of Study Patients by Level of Renal Function

	All (n=2,938)	eGFR ≥60 (n=1,992)	eGFR 45–59 (n=574)	eGFR <45 (n=372)
Age (years), mean (SD)	60.6 (12.4)	57.9 (12.4)	65.5 (10.3)	67.2 (10)
Male sex, n (%)	2,488 (84.7)	1,702 (85.4)	480 (83.6)	306 (82.3)
BMI (kg/m^2), mean (SD)	26.6 (4.3)	26.7 (4.3)	26.4 (4.1)	26.4 (4.4)
Etiology				
Ischemic, n (%)	1,459 (49.7)	927 (46.5)	308 (53.7)	224 (60.2)
Idiopathic, n (%)	1,230 (41.9)	907 (45.5)	206 (35.8)	117 (31.5)
Valvular, n (%)	82 (2.8)	47 (2.4)	25 (4.4)	10 (2.7)
Other, n (%)	167 (5.6)	111 (5.9)	35 (6.1)	21 (5.6)
NYHA III class, n (%)	817 (27.8)	472 (23.7)	183 (31.9)	162 (43.6)
Atrial fibrillation, n (%)	446 (15.2)	254 (12.7)	117 (20.4)	75 (20.2)
Implanted ICD, n (%)	841 (29.1)	552 (28.3)	162 (28.4)	127 (34.6)
Implanted CRT, n (%)	329 (12.2)	193 (10.7)	72 (13.3)	64 (18.7)
Implanted PM, n (%)	509 (17.5)	287 (14.5)	118 (20.7)	104 (28.2)
QRS duration (ms), median (IQR)	113 (90–140)	110 (90–140)	120 (90–140)	125 (100–151)
LVEF (%), mean (SD)	31.4 (9.5)	31.7 (9.3)	31.0 (10.2)	30.1 (9.3)
LVEDV (ml), mean (SD)	180.72 (72.14)	180.56 (72.1)	179.29 (72.18)	183.69 (72.35)
LVESV (ml), median (IQR)	115 (83.06–157)	114 (82.5–156)	114.7 (83.2–158)	123 (87.05–160.77)
Hemoglobin (g/dl), mean (SD)	13.52 (1.58)	13.74 (1.52)	13.34 (1.56)	12.62 (1.62)
eGFR (ml·min^{-1}·1.73 m^{-2}), mean (SD)	71.02 (22.86)	82.78 (17.1)	52.97 (4.34)	35.91 (7.56)
Serum creatinine (mg/dl), median (IQR)	1.1 (0.92–1.34)	1.0 (0.88–1.11)	1.4 (1.3–1.5)	1.85 (1.7–2.11)
Serum sodium (mmol/L), mean (SD)	139.44 (3.21)	139.57 (3.08)	139.43 (3.24)	138.74 (3.68)
Serum potassium (mmol/L), mean (SD)	4.3±0.48	4.27 (0.45)	4.33 (0.51)	4.4 (0.55)
BNP (pg/ml) (n=1,297), median (IQR)	319 (120–800)	271 (101–677)	371 (140–842)	621 (273–1,300)
CPET data				
HR (bpm) at rest, mean (SD)	70 (12)	71 (12)	70 (12)	70 (13)
SBP (mm Hg) at rest, median (IQR)	120 (108.5–130)	120 (110–130)	120 (110–130)	115 (100–130)
AT, n (%)	2,613 (88.94)	1,791 (89.91)	510 (88.85)	312 (83.87)
EOV, n (%)	499 (17)	288 (14.47)	129 (22.51)	82 (22.1)
ns$\dot{V}O_2$ at AT (ml·kg^{-1}·min^{-1}), median (IQR)	9.72 (7.93–11.86)	10 (8.25–12.27)	9.35 (7.6–11.12)	8.55 (6.9–10.36)
$\dot{V}O_2$ at AT (% of peak), mean (SD)	67.5 (13.6)	66.4 (13.4)	69.2 (13.7)	71 (13.6)
HR at AT (bpm), mean (SD)	97 (19)	99 (19)	94 (19)	90 (17)
Work rate at AT (W), mean (SD)	51.08 (22.96)	53.45 (23.94)	47.78 (20.02)	42.84 (18.81)
O_2 pulse at AT (ml/bpm), mean (SD)	8.2 (2.87)	8.36 (2.89)	7.99 (2.75)	7.61 (2.85)
Peak HR (bpm), mean (SD)	121 (24)	125 (23)	116 (240)	108 (22)
ΔHR peak-rest, mean (SD)	50 (24)	54 (24)	45 (24)	36 (20)
Peak $\dot{V}O_2$ (L/min), median (IQR)	1,080 (851–1,392.3)	1,162 (915–1,486)	996.15 (797.3–1,231)	873.2 (703.1–1,071)
Peak $\dot{V}O_2$ (ml·kg^{-1}·min^{-1}), median (IQR)	14.3 (11.7–17.5)	15.2 (9.2–24.6)	13.2 (8.2–20.4)	11.5 (7.5–17.9)
Peak $\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1}, n (%)	826 (28.1)	500 (25.1)	139 (24.2)	187 (50.7)
Peak $\dot{V}O_2$ (% of predicted), mean (SD)	54.98 (16.33)	56.95 (16.67)	52.99 (15.03)	47.48 (13.7)
Peak work rate (W), median (IQR)	80 (60–103)	84 (61–110)	72.5 (60–97)	65 (50–80)
Peak O_2 pulse (ml·beats^{-1}·min^{-1}), median (IQR)	9.3 (7.3–11.57)	9.61 (7.6–11.97)	8.82 (7–11.1)	8.32 (6.54–10.27)
$\dot{V}E/\dot{V}CO_2$ slope, median (IQR)	31 (27–37)	30 (26.61–35)	32.1 (28.53–37.99)	35.09 (30–41)
$\dot{V}O_2$/work slope (ml·min^{-1}·W^{-1}), median (IQR)	9.6 (8.4–10.91)	9.8 (8.6–11)	9.3 (8.3–10.75)	9 (8–10.35)
Peak RR, median (IQR)	31 (27–35.69)	31 (27–35)	31 (28–36)	31 (27–35.25)
Peak $\dot{V}E$ (L/min), median (IQR)	45.5 (37.2–56)	47.4 (38.5–57.8)	43.6 (36–52)	41.75 (33.1–50)
Peak RER, median (IQR)	1.14 (1.09–1.21)	1.14 (1.09–1.21)	1.13 (1.09–1.2)	1.14 (1.09–1.21)
Weber class				
A, n (%)	367 (12.5)	323 (16.2)	36 (6.3)	8 (2.2)
B, n (%)	906 (30.8)	702 (35.2)	149 (26)	55 (14.8)
C, n (%)	1,301 (44.3)	794 (39.9)	302 (52.6)	205 (55.1)
D, n (%)	364 (12.4)	173 (8.7)	87 (15.1)	104 (28)
Treatment				
ACEI, n (%)	2,271 (77.5)	1,594 (80.1)	435 (76)	242 (65.4)
AT$_1$-blocker, n (%)	495 (16.9)	302 (15.2)	105 (18.3)	88 (23.7)
β-blocker, n (%)	2,497 (85)	1,722 (86.5)	470 (81.9)	305 (82)
Diuretic, n (%)	2,365 (80.5)	1,520 (76.3)	499 (86.9)	346 (93)
K-sparing drugs, n (%)	1,577 (53.71)	1,031 (51.78)	334 (58.29)	212 (56.99)
Antiplatelet agents, n (%)	1,556 (53.03)	1,052 (52.89)	304 (53.05)	200 (53.76)
Oral anticoagulant therapy, n (%)	846 (28.81)	521 (26.17)	203 (35.43)	122 (32.8)
Digitalis, n (%)	684 (23.3)	441 (22.14)	152 (26.62)	91 (24.46)
Amiodarone, n (%)	714 (24.34)	414 (20.81)	171 (29.9)	129 (34.7)

ACEI, angiotensin-converting enzyme inhibitor; AT, anaerobic threshold; AT$_1$, angiotensin type 1; BMI, body mass index; BNP, B-type natriuretic peptide; CPET, cardiopulmonary exercise testing; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EOV, exercise oscillatory ventilation; HR, heart rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; PM, pace-maker; RER, respiratory exchange ratio; RR, respiratory rate; SBP, systolic blood pressure; SD, standard deviation; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, ventilation; $\dot{V}O_2$, oxygen uptake.

(Table 1 continued the next page.)

	All	eGFR ≥60 vs. eGFR 45–59	eGFR ≥60 vs. eGFR <45	eGFR 45–59 vs. eGFR <45
	P value	P value	P value	P value
Age (years), mean (SD)	<0.0001	<0.0001	<0.0001	0.006
Male sex, n (%)	NS	NS	NS	NS
BMI (kg/m^2), mean (SD)	NS	NS	NS	NS
Etiology				
Ischemic, n (%)	<0.0001	0.0026	<0.0001	0.05
Idiopathic, n (%)	<0.0001	<0.0001	<0.0001	NS
Valvular, n (%)	0.0376	0.0107	NS	NS
Other, n (%)	NS	NS	NS	NS
NYHA III class, n (%)	<0.0001	<0.0001	<0.0001	0.001
Atrial fibrillation, n (%)	<0.0001	<0.0001	0.0002	NS
Implanted ICD, n (%)	0.0461	NS	0.0145	NS
Implanted CRT, n (%)	0.0001	NS	<0.0001	0.0293
Implanted PM, n (%)	<0.0001	0.001	<0.0001	0.008
QRS duration (ms), median (IQR)	<0.0001	0.0249	<0.0001	0.0006
LVEF (%), mean (SD)	0.0055	NS	0.0025	NS
LVEDV (ml), mean (SD)	NS	NS	NS	NS
LVESV (ml), median (IQR)	NS	NS	NS	NS
Hemoglobin (g/dl), mean (SD)	<0.0001	<0.0001	<0.0001	<0.0001
eGFR (ml·min^{-1}·1.73 m^{-2}), mean (SD)	<0.0001	NS	NS	NS
Serum creatinine (mg/dl), median (IQR)	<0.0001	NS	NS	NS
Serum sodium (mmol/L), mean (SD)	<0.0001	NS	<0.0001	0.0013
Serum potassium (mmol/L), mean (SD)	<0.0001	0.017	<0.0001	0.0191
BNP (pg/ml) (n=1,297), median (IQR)	<0.0001	0.0011	<0.0001	<0.0001
CPET data				
HR (bpm) at rest, mean (SD)	NS	NS	NS	NS
SBP (mm Hg) at rest, median (IQR)	0.0191	0.0413	NS	0.0072
AT, n (%)	0.003	NS	0.0006	0.0267
EOV, n (%)	<0.0001	NS	0.0002	NS
ns$\dot{V}O_2$ at AT (ml·kg^{-1}·min^{-1}), median (IQR)	<0.0001	<0.0001	<0.0001	<0.0001
$\dot{V}O_2$ at AT (% of peak), mean (SD)	<0.0001	<0.0001	<0.0001	NS
HR at AT (bpm), mean (SD)	<0.0001	<0.0001	<0.0001	0.0033
Work rate at AT (W), mean (SD)	<0.0001	<0.0001	<0.0001	0.0029
O_2 pulse at AT (ml/bpm), mean (SD)	<0.0001	0.0139	<0.0001	NS
Peak HR (bpm), mean (SD)	<0.0001	<0.0001	<0.0001	<0.0001
ΔHR peak-rest, mean (SD)	<0.0001	0.0001	<0.0001	<0.0001
Peak $\dot{V}O_2$ (L/min), median (IQR)	<0.0001	<0.0001	<0.0001	<0.0001
Peak $\dot{V}O_2$ (ml·kg^{-1}·min^{-1}), median (IQR)	<0.0001	<0.0001	<0.0001	<0.0001
Peak $\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1}, n (%)	<0.0001	NS	<0.0001	<0.0001
Peak $\dot{V}O_2$ (% of predicted), mean (SD)	<0.0001	0.0021	<0.0001	<0.0001
Peak work rate (W), median (IQR)	<0.0001	<0.0001	<0.0001	<0.0001
Peak O_2 pulse (ml·beats^{-1}·min^{-1}), median (IQR)	<0.0001	<0.0001	<0.0001	0.0038
$\dot{V}E/\dot{V}CO_2$ slope, median (IQR)	<0.0001	<0.0001	<0.0001	<0.0001
$\dot{V}O_2$/work slope (ml·min^{-1}·W^{-1}), median (IQR)	<0.0001	0.0027	<0.0001	NS
Peak RR, median (IQR)	NS	NS	NS	NS
Peak $\dot{V}E$ (L/min), median (IQR)	<0.0001	<0.0001	<0.0001	0.0041
Peak RER, median (IQR)	NS	NS	NS	NS
Weber class				
A, n (%) B, n (%) C, n (%) D, n (%)	<0.0001	<0.0001	<0.0001	<0.0001
Treatment				
ACEI, n (%)	<0.0001	0.0335	<0.0001	0.0004
AT$_1$-blocker, n (%)	0.0002	NS	<0.0001	0.047
β-blocker, n (%)	0.0059	0.0063	0.024	NS
Diuretic, n (%)	<0.0001	<0.0001	<0.0001	0.0031
K-sparing drugs, n (%)	0.009	0.0059	<0.0001	0.0004
Antiplatelet agents, n (%)	NS	NS	NS	NS
Oral anticoagulant therapy, n (%)	<0.0001	<0.0001	0.0084	NS
Digitalis, n (%)	NS	0.0252	NS	NS
Amiodarone, n (%)	<0.0001	<0.0001	<0.0001	NS

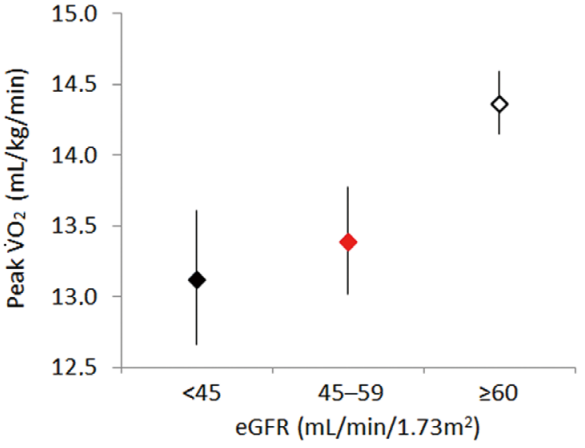

Figure 1. Multivariate adjusted geometric mean peak $\dot{V}O_2$ with 95% confidence intervals according to strata of estimated glomerular filtration rate (eGFR).

CKD and may worsen the catabolic/anabolic imbalance in skeletal muscle.[11,42] In addition, elevated levels of angiotensin II may contribute to skeletal myopathy by enhancing protein degradation and myocyte apoptosis.[43] Hormonal disorders such as growth hormone- and insulin-resistance, oxidative stress, and uremic toxins also may contribute.[11,42]

Second, there was no statistically significant interaction between the level of residual renal function and peak $\dot{V}O_2$ in relation to prediction of the primary outcome. The discriminative value of the cutoff for peak $\dot{V}O_2$ of 12 $ml \cdot kg^{-1} \cdot min^{-1}$ was modest, with the worst performance among the patients with more severely impaired renal function. The finding that peak $\dot{V}O_2$ had a modest predictive accuracy in the overall population is consistent with prior data.[44] Among patients in the lowest eGFR strata, peak $\dot{V}O_2$ <12 $ml \cdot kg^{-1} \cdot min^{-1}$ was associated with an adjusted HR of borderline statistical significance and had a low discriminative value. Because it has been suggested that peak $\dot{V}O_2$ tends to lose its predictive value 3 years post-CPET,[16] we also estimated the discriminative value of peak $\dot{V}O_2$ <12 $ml \cdot kg^{-1} \cdot min^{-1}$ at 2 years. The analysis yielded similar results: peak $\dot{V}O_2$ <12 $ml \cdot kg^{-1} \cdot min^{-1}$ remained poorly predictive in the lowest eGFR strata. It should be noted that the peak respiratory exchange ratio was comparable across eGFR strata, indicating an equivalent intensity of effort. These findings should, however, be interpreted in context. Only a relatively small proportion of patients had poor renal function (12.7%). Moreover, a potential referral bias should be considered; indeed, it is reasonable to hypothesize that patients with more severely impaired renal function were less frequently referred for CPET than those with mildly impaired or normal renal function. In the study by McCullough et al, renal dysfunction was associated with a "clustering of high risk features".[45] Our data are consistent with that finding. Indeed, the patients with poor renal function (eGFR <45 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) were older and had a more advanced NYHA class, lower SBP and hemoglobin values, and higher BNP concentrations, and more frequently needed treatment with diuretics. It is likely that, in such patients, the prognostic weight of other risk markers outranks that of decreased exercise capacity. CPET is widely used to risk stratify HF patients. Although not formally tested, the cutoff for peak $\dot{V}O_2$ of 12 $ml \cdot kg^{-1} \cdot min^{-1}$ is currently regarded as a key prog-

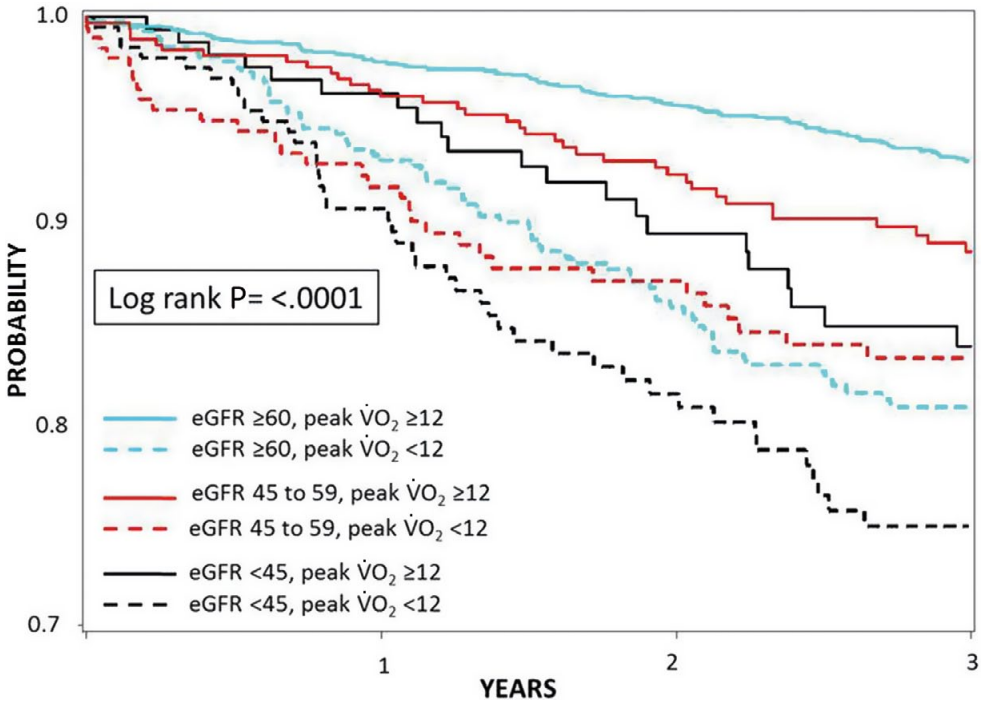

Figure 2. Kaplan Meyer survival curves in the 3 subgroups of estimated glomerular filtration rate (eGFR), stratified by peak $\dot{V}O_2$.

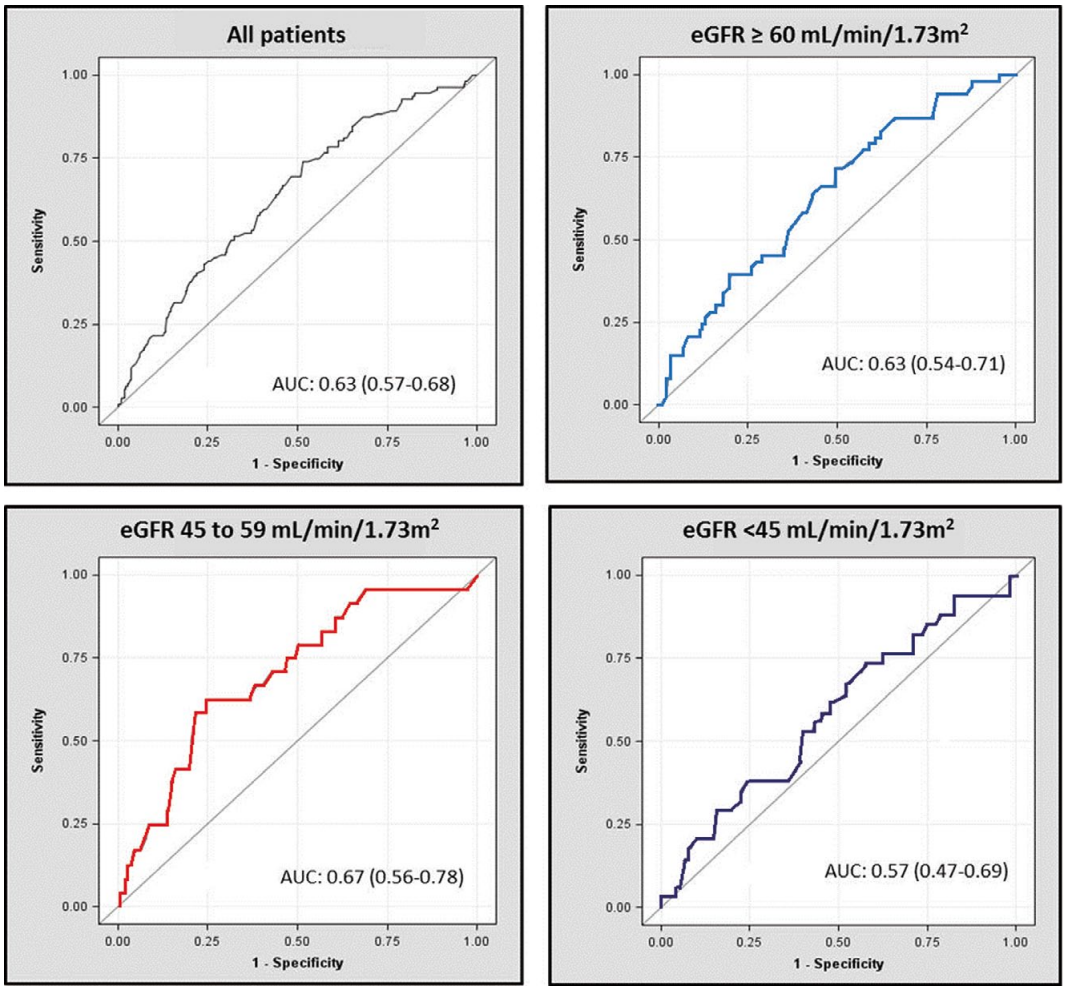

Figure 3. Receiver-operating characteristic curves of peak $\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1} for the primary outcome at 3 years. Numbers in parentheses represent 95% confidence intervals. AUC, area under the curve; eGFR, estimated glomerular filtration rate.

nostic marker to guide transplant listing in optimally treated HF patients,[6,7] albeit recent observations suggest differently.[46] There is, however, evidence that a multiparametric approach to risk stratification incorporating measures of both exercise capacity and renal function can allow a more efficient use of key CPET-derived prognostic variables.[12]

Previous Studies

McCullough et al[45] observed that peak $\dot{V}O_2$ significantly decreases as renal function declines. On logistic regression, only age and peak $\dot{V}O_2$ were independently associated with an eGFR <30 ml·min^{-1}·1.73 m^{-2}. When eGFR was modeled as a continuous variable, lower LVEF, higher NHYA class, and race also were found to be statistically significant. Van Laethem et al[47] studied 79 HT patients, in whom eGFR was a strong independent predictor of decreased exercise capacity. An eGFR value of 53 ml·min^{-1}·1.73 m^{-2} was the optimal cutoff for discriminating patients with a peak $\dot{V}O_2$ < or >18 ml·kg^{-1}·min^{-1}. These studies support the concept that renal dysfunction may influence peak $\dot{V}O_2$.

Study Limitations

Some limitations of the MECKI score database are already reported.[12,13] The patients were relatively young; mean age was 61 years, likely reflecting the inclusion of patients referred for CPET. Only 15% of the patients were female; pathophysiological and clinical sex-related differences have been noted in HF. Only HF patients with reduced LVEF were included; thus, the results cannot be extrapolated to patients with preserved EF.[48,49] Moreover, we evaluated patients able to perform a CPET, so patients with very severe HF were excluded. Similarly, patients with primary CKD as well as those requiring dialysis were also excluded. We focused on peak $\dot{V}O_2$ instead of other CPET-derived prognostic variables, such as percent predicted peak $\dot{V}O_2$ or $\dot{V}E/\dot{V}CO_2$, because peak $\dot{V}O_2$ is the most widely used measure of exercise capacity in HF. Further studies addressing the influence of renal dysfunction on percent predicted peak $\dot{V}O_2$ or $\dot{V}E/\dot{V}CO_2$ would be of interest. Peak $\dot{V}O_2$ was dichotomized at 12 ml·kg^{-1}·min^{-1}. Dichotomization of continuous covariates may be arbitrary in statistics and potentially may result in loss of useful information; however, the cutoff of 12 ml·kg^{-1}·min^{-1} is generally accepted as clinically relevant and meaningful.[6,7]

Table 2. Area Under ROC Curve With 95% CIs for Peak $\dot{V}O_2$ <12 ml·kg^{-1}·min^{-1} in the Entire Patient Population and in Each Strata of eGFR

	2 years	3 years
All patients	0.64 (0.58–0.69)	0.63 (0.57–0.68)
eGFR (ml·min^{-1}·1.73 m^{-2})		
≥60	0.63 (0.55–0.72)	0.63 (0.54–0.71)
45–59	0.70 (0.59–0.81)	0.67 (0.56–0.78)
<45	0.58 (0.47–0.69)	0.57 (0.47–0.69)

CI, confidence interval; eGFR, estimated glomerular filtration rate; ROC, receiver-operating characteristic.

Conclusions

Renal dysfunction is significantly correlated with peak $\dot{V}O_2$, independently of other known factors influencing peak $\dot{V}O_2$. Further mechanistic studies are warranted to understand the pathophysiological link between renal dysfunction and decreased exercise capacity in HF. In HF patients with poor renal function, peak $\dot{V}O_2$ offers limited prognostic information.

Conflict of Interest: none declared.

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Appendix

Other MECKI Score Group Members

Centro Cardiologico Monzino, IRCCS, Milano: Cesare Fiorentini, Anna Apostolo, Pietro Palermo, Mauro Contini, Erika Bertella, Valentina Mantegazza; Cardiologia Riabilitativa, Ospedali Riuniti, Ancona: Francesca Pietrucci; UOC Cardiologia Ospedale S. Spirito, Roma: Aessandro Ferraironi; Azienda Ospedaliera Sant'Andrea, "Sapienza" Università degli Studi di Roma, Roma: Matteo Casenghi; ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies), Palermo: Francesco Clemenza; Cardiologia SUN, Ospedale Monaldi, Napoli: Teo Roselli, Andrea Buono, Raffaele Calabrò; "S. Maugeri" Foundation, IRCCS, Cassano Murge: Daniela Santoro, Saba Campanale, Domenica Caputo; "S. Maugeri" Foundation, IRCCS, Tradate: Donatella Bertipaglia, Raffaella Vaninetti; Ospedali Riuniti and University of Trieste: Marco Confalonieri, Elena Zambon, Emanuela Berton, Chiara Torregiani; Cardiology, University of Civil Hospital, Brescia: Livio Dei Cas, Valentina Carubelli; UOC Cardiologia, G da Saliceto Hospital, Piacenza: Simone Binno; Division of Cardiology, Salvatore Maugeri Foundation, IRCCS, Institute of Milan, Milan: Giovanni Marchese; Dipartimento Cardiologico "A. De Gasperis", Ospedale Cà Granda- A.O. Niguarda, Milano: Fabrizio Oliva; Fondazione Gabriele Monasterio, CNR-Regione Toscana, Pisa: Luigi Pastormerlo.