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Angio-Cardio-Thoracic Pathophysiology and Imaging

"Prognostic Evaluation of Heart Failure in Women: Insight from the MECKI Score Database"

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ABSTRACT

Background: Heart failure is a multi-organ disease often associated with comorbidities. Heart failure in women assumes extremely peculiar characteristics. The pathophysiology of the damage is profoundly different; the endothelial dysfunction, the damage to the microcirculation and the comorbidities that cause chronic heart failure are in fact frequently associated with a type of decompensation that has a better ejection fraction than those in the male population. Symptoms are often vague and not "typical", which often delays diagnosis, bringing patients to the doctor's attention only belatedly. This aspect frequently leads to having a much older age than the male gender at diagnosis, which determines higher co-pathology degree and polypharmacy. In this situation, female patients are highly exposed to risk of iatrogenic damage and poor compensation and therapeutic unsuccess. Age is often a limiting factor also for enrollment in clinical trials, which therefore frequently have a gender-related bias.

To identify the prognosis, it is necessary to take into account several variables. The cardiopulmonary test allows a comprehensive assessment of the patient during physical activity as physical exercise involves the cardiovascular, hematopoietic, sympathetic/parasympathetic, neuro-hormonal, respiratory and motor systems. The oxygen consumption at the peak and at the anaerobic threshold mainly depend on the cardiovascular and motor systems while the VE/VCO2 is an index not only of ventilatory efficiency and of the ventilation/perfusion mismatch of the lung, but also of activation of metabo- and chemoreceptors.

The proposed risk scores are very numerous but mostly based on data obtained in male populations. Few use the cardiopulmonary exercise test. Among these, the Metabolic Exercise Cardiac Kidney Indexes -MECKI score- was obtained by evaluating about 80 variables of which 6 have independent prognostic significance: hemoglobin, natremia, renal function (MDRD), left ventricular ejection fraction (LVEF), oxygen consumption at the peak of the exercise [%] and VE/VCO2 slope. The MECKI score demonstrated in patients with systolic heart failure, considering the combined cardiovascular death, urgent heart transplant and LVAD as an end-point, AUC = 0.804 (0.754-0.852) at 1 year, 0.789 (0.750-0.828) at 2 years, 0.762 (0.726-0.799) at 3 years and 0.760 (0.724-0.796) at 4 years.

Aim of the study: identify parameters and variables which could be associated to a different prognosis in men and women enrolled in the MECKI Score database. Thus, the objectives of the present study: 1) achievement in 2 years of at least 7000 cases with about 1400 cases of female gender; 2) evaluation of the prognosis in systolic heart failure in the female gender, differentiating by: a) etiology (ischemic non-ischemic), b) presence/absence of atrial fibrillation, c) presence of CRT, d)

presence/absence of diabetes/hypertension/dyslipidemia; 3) evaluation in the female gender of the prognostic cut-offs of the variables that generate the MECKI score.

Results: In reviewing the MECKI Score database, numerous, mostly expected, gender differences emerged which reinforce the initial hypothesis. In the population examined, there is no substantial difference in age, women have, although overweight, a lower BMI than men, a better LVEF, significant differences in renal function and hemoglobin concentration (these parameters are already corrected for sex); no difference in terms of natremia. Other differences were observed about pharmacological therapy among the two groups.

Kaplan-Meier survival curves showed that the MECKI Score is accurate in predicting the risk also in the female population, as there are no overall differences in the prevalence of events in the two sexes at two years. Differences in survival curves begin to be observed over longer follow-up periods.

Conclusions: gender-specific characteristics have a critical impact on heart failure in women and it should be valuable to concentrate future analysis for the identification of any specific subpopulation that have peculiarities that can impact on the prognosis. However, the MECKI Score maintains its prognostic power at two years follow up, even in the female population, guaranteeing appropriate clinical and therapeutic choices.

Cardiovascular disease in women

Cardiovascular diseases (CVD) are the main cause of morbidity and mortality in Europe in female population. (Townsend N et al 2016) Every year in Europe 51% of deaths in women and 49% in men are caused by cardiovascular events. (Townsend N et al 2016). Chronic heart failure (CHF) is one of the most common causes of hospitalization (Klein L et al 2011) and mortality in women (Scardovi AB et al 2012). The widespread, misleading idea that women are substantially protected from heart disease generates life-threatening conditions: in fact, cardiovascular risk in women is often underestimated.

Today, clinicians have to face epochal changes in the way of approaching medicine, which requires more and more evidences, study and precision. The evaluation and stratification of cardiovascular risk must therefore take into due account the gender peculiarities in order to be able to estimate the risk of the individual patient in the most appropriate way possible, also considering gender-related differences.

a) *Female sex hormones and the cardiovascular system*

Gender differences in the development of cardiovascular diseases have been demonstrated both in the animal world and among humans. These differences explain the lower incidence in women, before menopause, of cardiovascular (CV) pathologies such as stroke, arterial hypertension and atherosclerosis. The cardio-protection observed in women is due to the action of estrogens. These hormones stimulate the release of endothelial-derived vasodilator factors and they modulate the renin-angiotensin-aldosterone system. Although it is an integral part of hormone replacement therapy, it is not yet clear whether progesterone has a protective role on the CV system. Its vasodilating and vasoconstricting actions vary depending on the concentration and location along the vascular tree. Figure 1 (Dos Santos et al 2014)

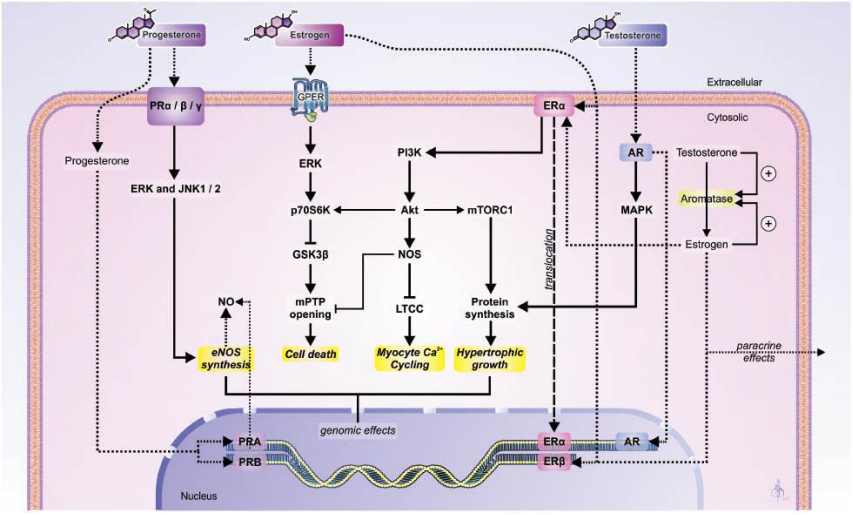


Figure 1. Intracellular sex hormones signaling. (dos Santos RL 2014)

The human body has two different estrogen receptors; like all systems, even the cells of the cardiovascular system they express the estrogen receptor-a and the estrogen receptor-b, which have a characteristic tissue distribution.

As previously demonstrated, (Harvey RE et al 2015) the presence and correct functionality of the a-receptor in the endothelial cells of the vessels is reflected in a reduced risk of atherosclerosis; on the other hand, the estrogen receptor-b acts as a counter-regulator of the same receptor for estrogen-a.

Endothelial dysfunction is known to constitute the pathophysiological basis of atherosclerosis. The presence of estrogen guarantees the activation of the endothelial nitric oxide (NO) synthase enzyme, allowing the production of this important cellular mediator. (Harvey RE et al 2015) NO plays fundamental roles in both male and female organisms. It has been shown that in subjects with genetic mutation of the estrogen receptor there is an absence of the physiological flow-mediated dilation of the arteries with consequent accelerated atherosclerosis. In postmenopausal women, in whom nitric oxide production is reduced, similar functional alterations can be found. (Harvey RE et al 2015)

In addition, it should be remembered that the complex angiogenesis' process is modulated by the estrogen receptor-a, which also plays a fundamental role in vascular remodeling, balancing the proliferation and migration of endothelial cells, as well as in trophism of muscle smooth cells, through the activation of the mitogen protein kinase. (Harvey RE et al 2015)

The above gives a small example of how complex and multifaceted the role of estrogens is in the cardiovascular system, suggesting that even minimal changes in the woman's hormonal profile, albeit physiological, can contribute to the induction of risk states for cardiovascular diseases. (Harvey RE et al 2015)

b) Traditional cardiovascular risk factors

Analyzing the epidemiology of cardiovascular diseases in women, the evident differences in the distribution of risk factors between the two sexes are immediately clear. Furthermore, these are more evident in specific periods of a woman's life, when, in fact, the protection given by estrogens on the cardiovascular system is stronger.

It is well known that in women the prevalence of *hypertension* is lower than that of men up to the fifth decade, when there is an inversion of the prevalence of the disease. (Whelton PK ACC et al 2018)

Peculiarities of female hypertension are the high prevalence of isolated systolic hypertension, white coat hypertension and an often-delayed diagnosis due to socio-cultural factors. (Reckelhoff JF et al 2018)

The current guidelines available on the treatment of hypertension (ESC guidelines 2018), while directly citing some pathological conditions peculiar to the female gender (e.g., gestational hypertension, oral contraception or hormone replacement therapy) and their treatment, refer to the choice of the doctor as regards therapy, drug dosage, providing less information on how to achieve the desired blood pressure target in women. However, with respect to the previous guidelines, authors have certainly tried to identify specific categories in which a gender-related approach is desirable. This type of approach seems to be the most suitable and it is highly desirable that it matures over time, guaranteeing an increasingly specific and targeted point of view on female patient.

Coronary ischemic heart disease is another cardiovascular disease that presents specificity in the female gender; in fact, coronary artery disease is a condition that presents substantial peculiarities in female patients. (Nakao YM et al 2018) The specific pathophysiological bases of vascular damage produce substantial differences in clinical presentation and outcome in the female gender. In fact, microvascular damage is much more markedly present in female ischemic heart disease, while in the male the coronary pathology characterized by occlusive stenosis of the epicardial vessels, acute plaque events and thrombosis determine the well-known and "classic" symptoms and clinical picture. The clinical presentation, for these reasons, in the woman will be characterized more by dyspnea, inappropriate fatigue, more prolonged symptoms, compared to the male patient who will suffer more easily the "typical" chest pain. Hence the greater length of in-hospital stay in women and the highest mortality from acute event compared to men. Myocardial infarction with nonobstructive coronary arteries (MINOCA), spontaneous coronary artery dissection, stress-induced cardiomyopathy (Takotsubo Syndrome) are widely spread conditions among women. (Mattioli AV et al 2019) (Figure 2)

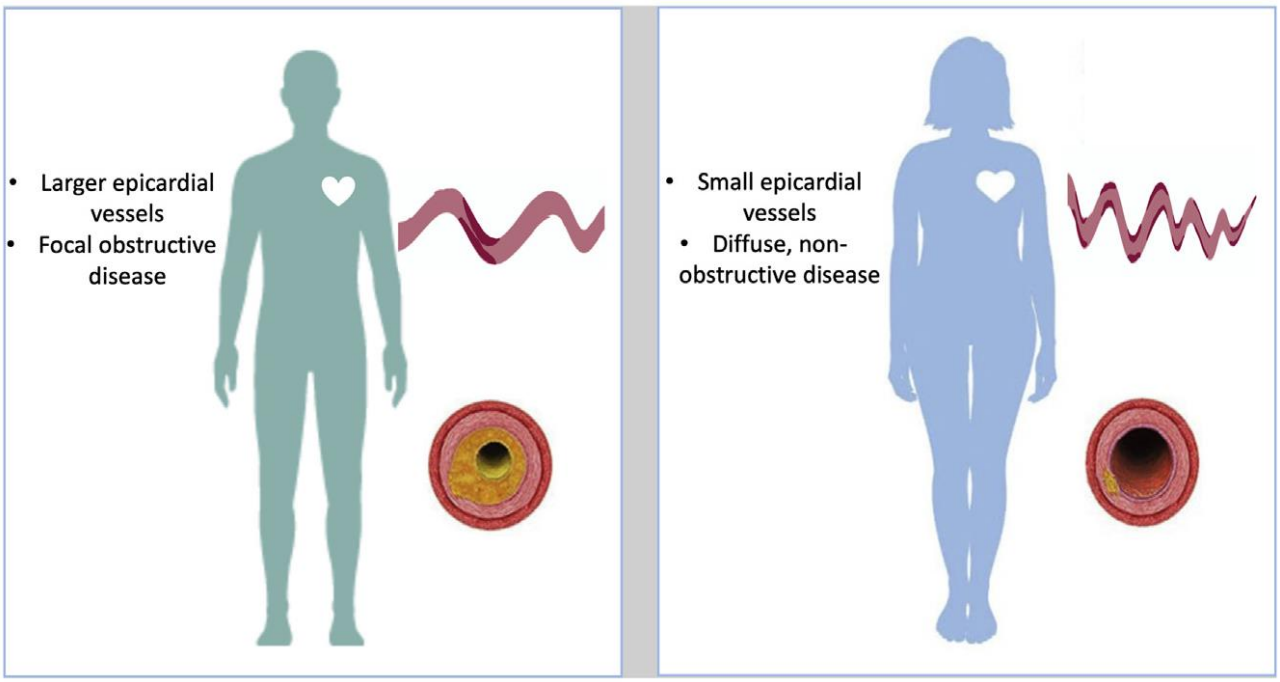


Figure 2 from Geraghty L Heart, Lung and Circulation (2021) 30, 9–17 1443-9506/20/

Noteworthy, there are fewer women involved in primary and secondary prevention treatments and have less access to rehabilitation programs. (Kouvari M et al 2018)

Another risk factor that deserves the clinician's attention is the alteration of the patient's *lipid profile*. In fact, it would be desirable to have specific cut-offs in each age, sex and condition of copathology, in order to accurately and exhaustively estimate the relative risk on cardiovascular health of dyslipidemia. In fact, the assumption that premenopausal women are protected from estrogen is unfortunately very widespread. These alterations often become clinically evident after menopause, when the atherosclerosis process comes to an end, causing vascular disease, diagnosable through color Doppler imaging methods. Correct stratification of cardiometabolic risk, at any age, would therefore be desirable. (Harvey RE et al 2015) This aspect it becomes crucial especially after menopause, when the protection of the endothelium, previously, conferred by estrogen is reduced and the classic atherosclerotic process can occur.

The presence of dyslipidemia is known to be an independent risk factor for the development of *peripheral artery disease* (PAD); female patients are mostly asymptomatic and undertreated. There PAD is the product of various risk factors (e.g., diabetes, hypercholesterolemia, hypertension, smoking habit, obesity, etc.) which resulted in damage to peripheral arterial vessels, which reasonably suggests that the atherosclerotic process also affected the coronary vessels and the epi-aortic

circulation. Recently, some authors developed a risk model, useful in clinical practice, showing how age, body mass index, hypertension, diabetes mellitus, smoking, oral contraception and parity were all independently associated with PAD. (Mansoor H et al 2018)

Another risk factor with a preponderant role in women's cardiovascular health it is undoubtedly *diabetes mellitus*. In fact, although there is no substantial difference in incidence in Western countries, diabetes mellitus shows a much more severe impact on the life of the female patient. Diabetic women, in fact, show a worse cardiovascular risk profile, with higher mortality and higher incidence of acute cardiovascular events than men. (Ballotari R et al 2017) Adherence to therapy is lower in women than in men, while the so-called "allostatic load" is greater, resulting in overexposure to environmental stressors that negatively contribute to cardiometabolic health, particularly in middle-aged women. (Kirkman MS et al 2015)

Finally, *atrial fibrillation* is a very frequent arrhythmic condition in women with diastolic heart failure / hypertensive heart disease; anticoagulant therapy with warfarin, necessary in the treatment of thrombotic complications of AF, is often associated with an increased risk of intracranial bleeding, especially in the female gender. On the contrary, a recent study has shown that the use of direct oral anticoagulants has a much more acceptable risk profile for intra cranial hemorrhages, particularly in the female gender. (Law SWY et al 2018) Therefore, gender-oriented therapeutic management would be desirable.

c) Peculiar cardiovascular risk factors in women

Alongside the well-known, traditional cardiovascular risk factors, there are others which, no less than the others, can determine a negative effect and a worsening of the cardiovascular risk profile of the female patient.
Some of these are related to a woman's reproductive life and make understanding the impact of estrogen on a woman's cardiovascular health even more important.

Polycystic ovary syndrome (PCOS) is a very common endocrine alteration among women during the reproductive age; alongside the known fertility problems, women with PCOS have an increased cardiometabolic risk. In fact, diabetes mellitus and hyperlipemia frequently accompany the disease. Insulin resistance is a metabolic condition that is very frequently associated to PCOS. These

conditions, in particular, are due to the increase in abdominal fat mass, which shows a behavior comparable to a real endocrine tissue.
It is therefore clear that PCOS must be fully included among the predisposing conditions for cardiovascular disease; (Cooney LG et al 2021) the prevalence of CAD is four times higher in women with PCOS than in the general population, with a hazard ratio that progressively increases over time. (Zhu T et al 2021) The most important aspect derives from the young age of these patients: it is mandatory to propose to them an appropriate correction of lifestyle and risk factors related to their underlying pathology, to ensure the best long-life prognosis.

For all the above-mentioned reasons, age at *menopause* should be considered a fundamental datum in female cardiovascular anamnesis. Premature/delayed/surgical menopause could have a dramatic impact on cardiovascular health of a women. Thus, this datum, together with hormone replacement therapy or hormonal contraceptives must be taken into proper account, stratifying patients' cardiovascular risk. (Sciomer S et al 2016)
The correct knowledge of the cardiovascular pathologies and risk factors that may occur during *pregnancy* is now a necessity. There are, in fact, specific conditions typical of the gestational period, which are not configured as cardiovascular pathology per se, but constitute a risk factor for the development of future cardiovascular pathology. *Preterm delivery* (delivery occurring <37 weeks gestation) has been recognized as an independent risk long-term for maternal cardiovascular disease. (Brown HL et al 2020) In addition to infectious etiology that can cause inflammation and premature rupture of the membranes, it can be generated by placental micro-vasculopathy. All this can translate into preterm birth, placental insufficiency with low birth weight of the fetus.
Another condition to keep in mind is gestational hypertension, which arises after the 20^{th} week of gestation (SBP> 140 mmHg, DBP> 90 mmHg) and represents a lasting cardiovascular risk, which does not resolve with the completion of delivery, but determines a doubled risk of cardiovascular disease in the 3 years following childbirth. (Dines V et al 2020)
To the conditions previously mentioned, *gestational diabetes* must be added, which not only determines a 7-fold increased risk of incurring diabetes mellitus later in life, but also an overall increase in cardiovascular risk (twice for stroke and four times for myocardial infarction), 18 regardless of overt development of diabetes. (Brown HL et al 2020)

A specific theme is that of the cardiovascular impact of *chemo-* and *radiotherapy* for breast cancer treatment. The long-term survival of these patients' category has seen a major leap forward in the past 20 years. This has brought out the long-term complications that, in particular from a

cardiovascular point of view, can afflict patients who have undergone radio and chemotherapy treatments. Reduction of ejection fraction and heart failure, valvular and coronary artery disease can occur. Consequently, this particular population requires surveillance for cardiotoxicity secondary to cancer therapy, including radiation, anthracycline, trastuzumab and hormone treatment. (Jafari L et al 2021) In particular, long-term surveillance is required due to the long clinical latency of adverse events, particularly for radiotherapy (up to 20 years after treatment). (Meattini I et al 2021)

Autoimmune disorders are very common in female population, with a female/male proportion up 2.5:1 for rheumatoid arthritis and 9:1 for systemic lupus erythematosus. Autoimmune disorders are highly associated to cardiovascular morbidity and mortality (Mal K et al 2020). The pathophysiological basis of vascular damage is placed in inflammation and in the increase of oxidative stress, which cause endothelial dysfunction, microcirculatory disease and alterations of the lipoproteins and peptides involved in inflammation. (Deane KD et al 2021) Furthermore, the therapy often used for the treatment of these morbid states is based on glucocorticoids, which in turn can exacerbate cardiovascular damage, starting with the induction or worsening of risk conditions such as hyperglycemia and hyperlipidemia. On the other hand, among the drugs used for the treatment of rheumatoid arthritis, methotrexate should also be included, which is associated with a 28% reduction of cardiovascular events (RR 0.72, 95% CI 0.57-0.91). (Plein S et al 2020) As these conditions are extremely more frequent in the female gender, they must be specifically considered in a gender-specific approach to CVD prevention.

In addition to the aforementioned pathological conditions, *depression* plays an important role as a risk factor for coronary artery disease and as a comorbidity that exposes to a more ominous risk of cardiovascular disease. This morbid condition is also more prevalent in women; this pathology determines in the patient damage on several levels, constituting a risk factor for poor self-care and adherence to therapies and, if associated with an anxious state, it correlates with a higher number of stress-induced ischemic heart disease events (Takotsubo), for which the female-to-male ratio is 9:1. (Bucciarelli V 2019)

Another significant aspect to consider is also the *sedentary lifestyle*, prevalent among female gender, especially in middle age, which constitutes an impacting risk factor, much more than in men, on cardiovascular health. Already in adolescence, physical activity in girls is lower-lasting than in boys of the same age. This aspect worsens over the course of life, resulting in a more severe impact on women's cardiovascular health. (Badon SE et al 2021)

e) Heart failure in women

The evolution of cardiovascular diseases over time leads inexorably to the development of chronic heart failure (with preserved, HFpEF, "mid-range", HFmrEF or reduced ejection fraction, HFrEF), to be counted among the most significant causes of hospitalization and mortality in women. (Klein F et al 2011) CHF has specific characteristics in the female gender, to be taken into due account both in clinical practice and in research. Clinical presentation, response to treatment (implantable electrical devices and drugs), less adherence by the clinician to guidelines and less referral to rehabilitation paths determine inequalities and a worse outcome in women.

Very frequently, women develop a type of heart failure with a preserved ejection fraction (Crousillat DR et al 2018). The ischemic pathology starting from the great epicardial vessels is in fact less frequent in women, who are more frequently affected by hypertensive or diabetic heart disease, which more easily affect the cardiac microcirculation thus determining a purely diastolic alteration, with reduced compliance of the left ventricle and a greater atrial contribution to the left ventricular filling phase. Additionally, women tend to be at increased risk of developing left ventricular dysfunction due to specific conditions related to peri-partum heart disease (preterm delivery, gestational diabetes, pree-eclampsia) and any treatments they have undergone to treat breast cancer, including induced heart disease. From chemo- or radiotherapy. (Gardia M et al 2016)

Age at menopause, whether or not to have performed hormone replacement therapy, are factors to be taken into account and which can influence the onset, progression and outcome of the patient's heart disease. (Sciomer S et al 2016). Despite this, this too is an element that is not considered in the risk assessment of the female patient.

A further bias to keep in mind is very frequently, in randomized clinical trials, the female population is underrepresented; the tendency is therefore to evaluate treatments on populations of younger men and subsequently use drugs, validated in that way, even in populations with different characteristics (women, of more advanced age, with different risk factors, with a higher degree of polypathology).

Also, less frequently than in men, women are sent for defibrillator or transplant. (Han Z et al 2017, Morris AA et al 2015).

All in all, the prognostic evaluation of systolic heart failure in the female gender is therefore particularly complex, starting from often very different and multifaceted pathophysiological bases and having to take into account innumerable variables, frequently not considered in the most used risk scores.

CPET evaluation: risk stratification and MECKI score in women

The prognostic stratification of patients with systolic decompensation plays a key role in clinical management and in the indication for heart transplantation. To date, various scores are used for the prognostic evaluation of patients suffering from CHF with reduced ejection fraction, including the Seattle Heart Failure Model (SHFM) (Lewy WC et al 2006), the (Heart Failure Survival Score (HFSS) (Lund LH et al 2005), the global group in chronic heart failure (MAGGIC) (Sartipy U et al 2014) and the metabolic exercise cardiac kidney index (MECKI) (Agostoni PG et al 2013).

The HFSS and MECKI scores include some parameters of the cardiopulmonary exercise test (CPET), more suitable for assessing the functional status of the patient. (Arena R et al 2004)

Among these we can find the oxygen consumption (VO2) and the ventilation / carbon dioxide production slope (VE/VCO2). Furthermore, some parameters have a different prognostic power between men and women. For example, all of these scores take into account the ejection fraction. Very frequently women, even in the presence of a systolic decompensation of the left ventricle, have a better ejection fraction than men, in the face, however, of more severe symptoms and a more severe functional impairment.

Therefore, inserting functional parameters in the scores can better estimate the risk of the individual patient: the HFSS and MECKI scores use the peak oxygen consumption (MECKI score peak VO2% predicted, table 1).

Table 1. Main characteristics of MECKI score registry population according to the enrolment steps.

	N.	AGE (YEARS)		MALES (N)	%	VO2/KG (ML/MIN/KG)	EVENTS (N)	%	CV DEATHS (N)	%	FOLLOW-UP
2019	7004	61	±13	5740	82	14.8±4.8	1899	27	1419	20	1421 [627-2713]
2016	6112	62	±13	5001	82	14.8±4.9	1390	23	1104	18	1342 [630-2353]
2014	4862	61	±13	4015	83	14.8±4.7	998	21	812	17	1112 [548-1797]
2012	2716	60	±13	2285	84	14.4±4.4	598	22	618	23	1040 513-1811]

Reproducted from Eur J Prev Cardiol 27
MECKI: metabolic exercise cardiac kidney index; VO2: oxygen consumption.

Nevertheless, the VO2 peak appears to be relatively lower in women, compared with a better prognosis; this could raise doubts about the accuracy of a prognostic assessment using CPET-derived parameters in the female population.

For this reason, Corrà et al. investigated the predictive power of known parameters of the CPET ie whether the VO2 peak and ventilatory response (VE / VCO2 slope) are gender independent features or not. (Corrà U et al 2016) Lower VO2 peak and better prognosis in CHF could be a confounding factor; the female the prognostic advantage is lost when sex-specific differences they are correctly taken into account with the propensity score match. Then, with the match of the propensity score, the female sex had a significant impact, but the VE/VCO2 slope was, suggesting that for an effective and efficient HF model, adjustment must be made for sex-related characteristics. (Corrà U et al 2016)

Furthermore, the research group on the MECKI score (Salvioni et al 2020) further investigated this specific aspect, working on the predictive power of VE/VCO2 slope by gender and also the age of the patients. Indeed, produced equations for predicting the slope VE/VCO2 based on a large population of healthy subjects, then apply the formulas to the MECKI score database. In this way, using the percentage of predicted value, the prognostic power of the VE/VCO2 slope was more effective in predicting the prognosis of patients with CHF appropriately. Furthermore, this evaluation led to the identification of patients with the most severe degree of decompensation (with low peak VO2), those who are most appropriately assessed by the score.

Cardiopulmonary Exercise TEST

The prognostic stratification in systolic heart failure is a crucial point in clinical management and treatment strategy, and the cardiopulmonary exercise test (CPET) is the most accurate tool for risk stratification in this pathological condition.

The cardiopulmonary test allows a holistic assessment of the individual during physical activity as physical exercise involves the cardiovascular, hematopoietic, sympathetic/parasympathetic, neuro-hormonal, respiratory and motor systems. The oxygen consumption at the peak and at the anaerobic threshold mainly depend on the cardiovascular and motor systems while the VE/VCO2 is an index not only of ventilatory efficiency and of the ventilation / perfusion mismatch of the lung, but also of activation of metabo- and chemoreceptors.

The CPET most commonly used is the maximal CPET, performed with ramp protocol on a cycle ergometer or on a treadmill, which gives information on functional capacity during high level exercise. Many CPET variables have been proposed to stratify the risk of CHF patients and some of them have also been integrated into multiparameter prognostic scores, currently known as the best way to predict the outcome. (Paolillo S et al 2017)

- ***Oxygen uptake***

The most significant prognostic index for the patient with CHF is undoubtedly the oxygen consumption (VO2) measured at the peak exercise. However, the measurements made during Submaximal CPET and also at the anaerobic threshold are essentially valid from the prognostic point of view. In both HFrEF and HFpEF the peak VO2 has shown validity in the prognostic stratification capacity of patients. In HFrEF patients, Mancini and colleagues (Mancini DM et al 1991) conducted a milestone study that identified the peak VO2 cutoff of 14 ml/kg/min, for patients with systolic cardiac compensation to be referred for cardiac transplantation. Subjects with CHF with a VO2 peak below this cutoff demonstrated a significantly lower 1-year survival with the same systolic function. This value was subsequently revised in light of beta-blocker therapies (Cattadori G et al 2013), at 12 ml/Kg/min; in some specific cases 10 mL/kg/min was individuated as cutoff (Goda A et al 2011), suggesting that, in the era of implantable devices, a VO2 peak would not greater than that may represent a more appropriate cutoff for risk stratification than traditional cutoff value of 14 mL/kg/min.

Other important prognostic parameters in CPET are oxygen consumption at the anaerobic threshold and identification of anaerobic threshold, itself. An unreached anaerobic threshold is common in patients with CHF and it has a strong predictive power on prognosis. Analyzing the MECKI score database (Agostoni P et al 2013), the anaerobic threshold was identified in 1,935 of 2,137 patients (90.5%) and failure to reach the anaerobic threshold corresponded to a worse prognosis. In addition, on multivariate analysis, VO2 peak, the ratio of carbon minute ventilation slope production of dioxide (VE / VCO2), hemoglobin, ejection fraction, renal function, sodium, and the unidentified anaerobic threshold were predictors of the outcome.

-Ventilatory Parameters

Disturbances in ventilation are very common in people with CHF; the VE/VCO2 slope is the expression of the *ventilatory efficiency* during exercise, corresponding to the quantity of air that must be ventilated to eliminate 1 l of CO2.

The combination of peak VO2 and VE/VCO2 slope allows for better risk stratification in heart failure patients.

Another important element to consider during exercise is the presence or absence of *periodic breathing*, which is observed in a high proportion of subjects suffering from heart failure. This element is frequently associated with the presence of ventilatory sleep disturbances (i.e., obstructive

sleep apnea). The presence of a periodic breathing is associated with a worse prognosis (Corrà U et al 2006), in particular when present for more than 60% of the duration of the exercise. (Figure 3)

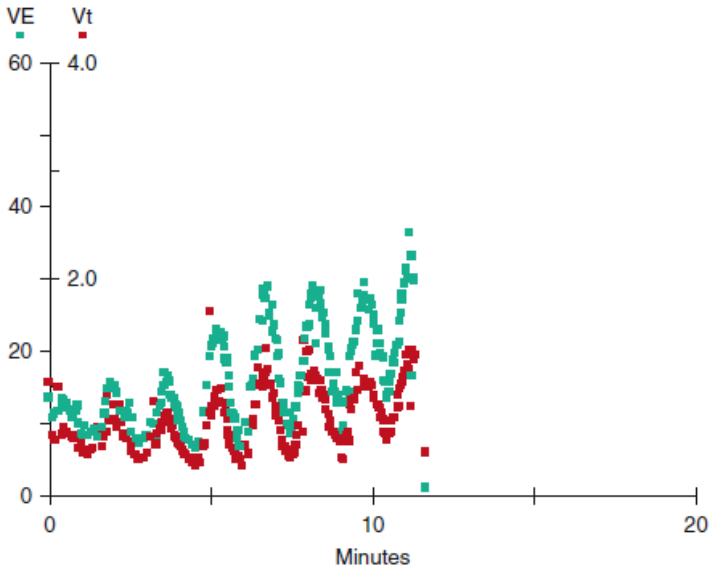


Figure 3 Example of exercise oscillatory ventilation during exercise in a patient with chronic heart failure. _VE and VT are measured in liters. VE = ventilation; Vt = tidal volume.

Another interesting element is the association between periodic breathing and HFpEF, with exclusive diastolic alteration. Guazzi and colleagues (Guazzi M et al 2008) showed that periodic breathing was the strongest predictor of adverse cardiac events in heart failure with impaired diastolic function.

-Recovery parameters

It could be valuable to observe some parameters concerning the period immediately following the execution of the CPET to understand how the recovery phase is rich in prognostically relevant information.

In particular, Arena and colleagues (Arena R et al 2006) observed that subtracting from the maximum heart rate obtained during CPET, the one obtained after the first minute of recovery after exercise, we obtain a value that seems to exceed the peak VO2, the ejection fraction and the etiology of heart failure in predicting mortality and the need for hospitalization; in addition, it adds prognostic power to the VE/VCO2 slope. Similarly, an increase in heart rate in the recovery phase is to be interpreted as a sign of severe heart failure and a limitation to physical exercise itself. However, at the moment, these parameters are being studied and deepened for their more adequate applicability in the clinical field.

The MECKI score and its parameters

Many variables have been singularly used in the prognostic stratification of CHF patients, but all of them failed to demonstrate a strong correlation with adverse events. Thus, a multiparametric approach has been considered the most suitable way to predict heart failure outcome. Many risk stratification models have been proposed, and some of them also include exercise parameters. The Heart Failure Survival Score (Aaronson KD et al 1997) was developed in 1997 in a population of 268 patients with advanced heart failure, and it is composed of seven variables, also including peak VO2 expressed as ml/kg/min. The Heart Failure-Action Predictive Risk Score Model (O'Connor CM et al 2012) also includes exercise performance analysis such as the duration of cardiopulmonary exercise testing on a treadmill.

The proposed risk scores are very numerous but mostly based on data obtained in male populations. Few use the cardiopulmonary exercise test. Among these, the Metabolic Exercise Cardiac Kidney Indexes -MECKI score- was obtained by evaluating about 80 variables of which 6 have independent prognostic significance: hemoglobin, natremia, renal function (MDRD), left ventricular ejection fraction (LVEF), oxygen consumption at the peak of the exercise [%] and VE/VCO2 slope. (Agostoni P et al 2013) (Figure 4.)

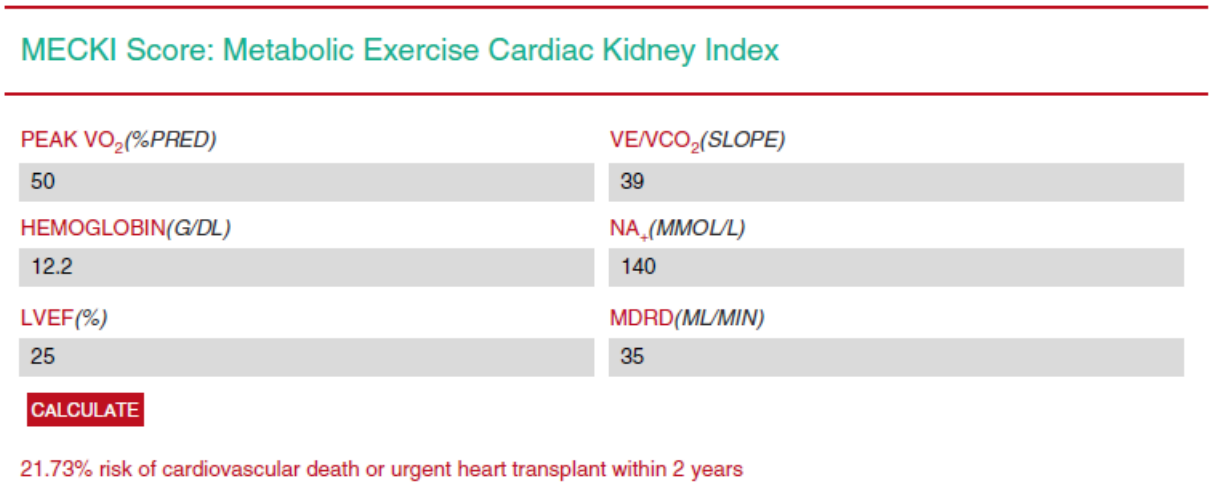


Figure 4. MECKI Score as displayed in online version and app for devices.

MECKI score calculator to predict the risk of cardiovascular death or urgent heart transplantation within 2 years (https://www.cardiologicomonzino.it/it/mecki-score/). LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; MECKI = Metabolic Exercise, Cardiac, Kidney Index (Paolillo S 2017)

The MECKI score demonstrated in patients with systolic heart failure, considering the combined cardiovascular death, urgent heart transplant and LVAD as end-point, AUC = 0.804 (0.754-0.852) at 1 year, 0.789 (0.750-0.828) at 2 years, 0.762 (0.726-0.799) at 3 years and 0.760 (0.724-0.796) at 4 years. (Agostoni P et al 2013)

Two recent studies (Freitas P et al 2017, Agostoni P et al 2017) compared the prognostic capacity of various scores (HF survival score - HFSS, Seattle Heart Failure Model SHFM, Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) used for risk stratification of affected patients from heart failure, with the MECKI score, concluding that the latter has a better prognostic capacity with modest over or underestimation of the risk.

Study design

The MECKI score project was initially conducted by 13 Italian centers with proven experience in heart failure and in the multiparametric assessment guaranteed by the CPET. Since then, a huge amount of data has been collected, in particular concerning the clinical data of patients during a standard hospitalization in the Heart Failure Unit of the participating centers: demographics, echocardiography, electrocardiography (ECG), full CPET variables, main procedures, previous cardio resynchronization therapy(CRT), implantable cardioverter defibrillator (ICD) implantation, hospitalization history, therapy at the time of enrollment, etiology of heart failure, laboratory data have become part of the large database of the MECKI score.

Patient follow-up was also collected.

The inclusion criteria were:

-present or past symptoms of HF according to the New York Heart Association functional classification (NYHA) functional class I - III, American stage C (College of Cardiology / American Heart Association classification);

- documented systolic dysfunction of the left ventricle (left ventricular ejection fraction <40%);

- stable clinical conditions drug therapy infected for at least three months;

-capacity to perform a CPET;

- no major cardiovascular intervention scheduled.

Patients with previous left ventricular dysfunction, which improved over time and within normal limits at the time of enrollment, were also included in the study.

The exclusion criteria were:

- history of pulmonary embolism;

-moderate to severe aortic and mitral valve stenosis,

-pericardial disease;
-severe obstructive pulmonary disease,
-exercise-induced angina and significant changes in the ECG,
-any clinical comorbidities that could prevent the correct execution of the CPET.

Follow-up ended with the last clinical evaluation in the center where the patient was enrolled, either with referral for urgent heart transplantation or with the death of the patient. The study end point was the composite of cardiovascular death or urgent heart transplant.

The promoter center was the Monzino Cardiology Center, responsible for data collection. The quality of the data was also ensured by two "external" experts, not engaged in data collection.

Following, the Biostatistics Unit of the Cardiology Center Monzino was asked to develop a score to be quantified patient risk of the designated outcome (death or need for urgent heart transplant). The score was to be based on a set of variables collected at baseline, including all parameters that could potentially predict the occurrence of the endpoint.

Objectives of the present evaluation and purposes of the study

Little is known about heart failure in women, which is poorly represented in trials. In the MECKI Score, it is about 20% of a total population of 6200 patients enrolled up to 2017 (when this specific analysis began), with average follow-up 3.5 years, which is equivalent to about 1250 female patients (Corrà U et al 2016)

So, the aim was:

- increase the number of cases and follow-up through a new call in the 24 centers participating in the MECKI score and the involvement of other 5 centers;

-achievement in 2 years of a population of 1400 cases of female gender;

-evaluation of the prognosis in systolic heart failure in the female gender, differentiating by: a) etiology (ischemic / non-ischemic), b) presence / absence of atrial fibrillation, c) presence of CRT, d) presence / absence of diabetes / hypertension / dyslipidemia;

-Evaluation in the female gender of the prognostic cut-offs of the variables that generate the MECKI score.

Statistical analysis

Continuous variables were presented as means ± SDs, and categorical variables were presented as percentages. Anova or unpaired *t* test were used as appropriate for comparison between groups, and $\chi 2$ test was used for comparing categorical variables. Skewed distributed variables were reported as median and interquartile range and compared by the Wilcoxon signed-rank test. Potential predictors of mortality were identified by univariable Cox regression analysis. When MECKI score was considered in multivariable analysis, parameters generating this score were excluded. Hazard ratios and 95% confidence intervals were calculated. Kaplan–Meier survival curves were implemented for sex and survival curves were compared using log rank test. Statistical analysis was performed using SAS 9.2 (SAS Institute, Inc, Cary, NC) or IBM SPSS 20.0 (SPSSPC+ Inc, Chicago, IL).

Results

The first analysis carried out "*ad interim*" during the PhD course were made at 5 years of follow-up on 5297 patients (620 events), including 983 women (77 events) and 4314 men (543 events).

In the first table, the individual parameters of MECKI in men and women are represented. (Table 2 A and B). In men, all variables were associated with the event, while in women only MDRD and VO2 peak percentage are associated. From these data, however, it was not possible to deduce the specific weight of the individual parameters, since each variable has its own unit of measure (for example in men the peak VO2 expressed as percentage of the predicted value has an OR of 0.969, which means that when one unit of the peak VO2 % predicted increases, the risk decreases by about 3%, while hemoglobin -Hb- has an OR of 0.939, that is, with an increase of one unit of Hb the risk decreases by about 5%; nevertheless, a unit of peak VO2 % predicted is not comparable to an Hb unit, therefore not even the ORs are comparable).

Tables 2 A and B. Odds Ratio of MECKI score parameters between men and women.

A

Variables	MEN				WOMEN			
	Odds ratio	**95% CI**		**P value**	**Odds ratio**	**95% CI**		**P value**
VO2 peak % predicted	0,969	0,961	0,977	**<.0001**	0,963	0,946	0,979	**<.0001**
VE/VCO2 slope	1,019	1,006	1,032	**0,0038**	1,013	0,985	1,042	0,3722
Hb g/dL	0,939	0,884	0,998	**0,0436**	0,871	0,722	1,051	0,1485
Na mEq/L	0,954	0,928	0,98	**0,0006**	1,016	0,94	1,097	0,6921
LVEF %	0,955	0,944	0,965	**<.0001**	0,98	0,958	1,001	0,0654
MDRD mL/min/1.73m^2	0,989	0,985	0,993	**<.0001**	0,987	0,975	0,998	**0,0268**

B

Variables	Standard Odds ratio	95% CI		P value	Standard Odds ratio	95% CI		P value	change
VO2 peak % predicted	0,579	0,503	0,667	<.0001	0,514	0,382	0,691	<.0001	-11,23%
VE/VCO2 slope	1,154	1,047	1,273	0,0038	1,104	0,888	1,372	0,3722	-4,33%
Hb g/dL	0,904	0,82	0,997	0,0436	0,8	0,591	1,083	0,1485	-11,50%
Na mEq/L	0,857	0,785	0,935	0,0006	1,052	0,819	1,352	0,6921	22,75%
LVEF %	0,615	0,546	0,692	<.0001	0,806	0,64	1,014	0,0654	31,06%
MDRD mL/min/1.73m^2	0,766	0,692	0,849	<.0001	0,727	0,548	0,964	0,0268	-5,09%

Peak VO2, % of predicted oxygen uptake at peak exercise; VE/VCO2 slope, ventilatory efficiency by means of CO2 production/ventilation relationship Hb: hemoglobin; Na: sodium; LVEF: left ventricular ejection fraction; MDRD glomerular filtration rate estimated by modification of diet in renal disease formula.

For this reason, the standardized ORs were calculated (table 3 A and B), eliminating the effect given by the disparity in the measure unit. Looking at table 3, it can be seen that Peak VO2, % of predicted oxygen uptake at peak exercise, the VE/CO2 slope, Hb and MDRD have a greater weight in women than in men (but this difference is not statistically relevant). Conversely, Natremia and LVEF have a greater impact among men and the difference for sodium has statistical relevance. We can conclude that Sodium has a different association weight with the event between men and women. In men it counts 23% more than in women, as sodium standard deviation increases, in men the risk decreases by about 15%, in women it increases (not significantly) by 5%.

Tables 3 A and B. Standardized Odds Ratio of MECKI score parameters between men and women.

A

Variables	Men				Donne			
	Odds ratio	**95% CI**		**P value**	**Odds ratio**	**95% CI**		**P value**
peak VO2 % predicted	0,971	0,964	0,978	<.0001	0,962	0,947	0,977	<.0001
VE/VCO2 slope	1,017	1,005	1,029	0,0042	1,016	0,99	1,042	0,2268
Hb g/dL	0,93	0,877	0,985	0,0131	0,84	0,703	1,003	0,0544
Na mEq/L	0,956	0,933	0,98	0,0004	1,026	0,954	1,103	0,4905
LVEF %	0,948	0,938	0,957	<.0001	0,97	0,95	0,99	0,004
MDRD mL/min/1.73m^2	0,989	0,985	0,993	<.0001	0,991	0,98	1,001	0,0885

B

Variables	Standard Odds ratio	95% CI		P value	Standard Odds ratio	95% CI		P value	change	p di confronto
peak VO2 % predicted	0,595	0,525	0,674	<.0001	0,51	0,391	0,666	<.0001	-14,29%	0,4748
VE/VCO2 slope	1,136	1,041	1,24	0,0042	1,127	0,928	1,369	0,2268	-0,79%	0,6133
Hb g/dL	0,893	0,817	0,977	0,0131	0,764	0,58	1,005	0,0544	-14,45%	0,9183
Na mEq/L	0,868	0,802	0,939	0,0004	1,084	0,862	1,364	0,4905	24,88%	**0,0148**
LVEF %	0,57	0,511	0,635	<.0001	0,729	0,588	0,904	0,004	27,89%	0,1684
MDRD mL/min/1.73m^2	0,772	0,704	0,847	<.0001	0,805	0,627	1,033	0,0885	4,27%	0,1495

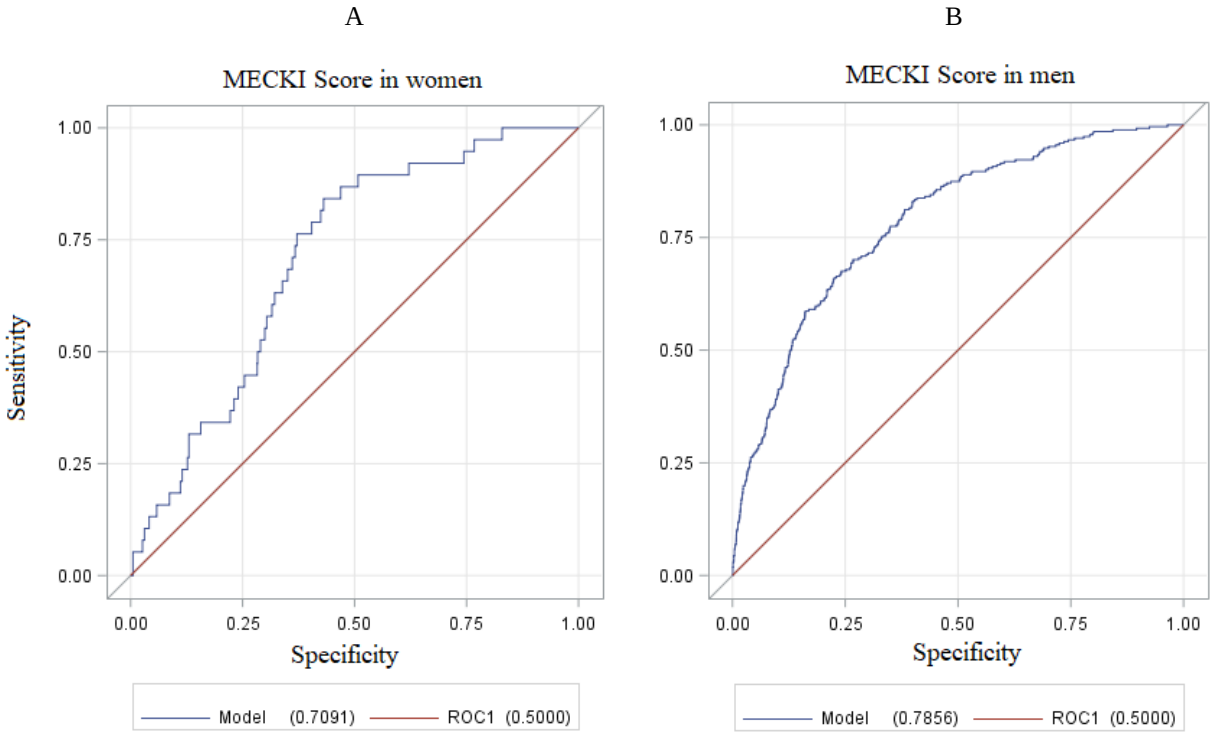
Peak VO2, % of predicted oxygen uptake at peak exercise; VE/VCO2 slope, ventilatory efficiency by means of CO2 production/ventilation relationship Hb: hemoglobin; Na: sodium; LVEF: left ventricular ejection fraction; MDRD glomerular filtration rate estimated by modification of diet in renal disease formula.

In addition, further *ad interim* analysis was carried out evaluating the predictive capacity of the MECKI score in the female and male population of the database.

The MECKI score "Women" evaluated 1111 women of 6112 total patients in the database. There were 51 events of cardiac death or transplantation out of 410 total events.

The area under the curve (AUC), expression of the predictive capacity, of the MECKI Score for men and women on the whole database at 2 years, is 0.7091 for women and 0.7856 for men. (Figure 5 A and B)

Figure 5. A and B

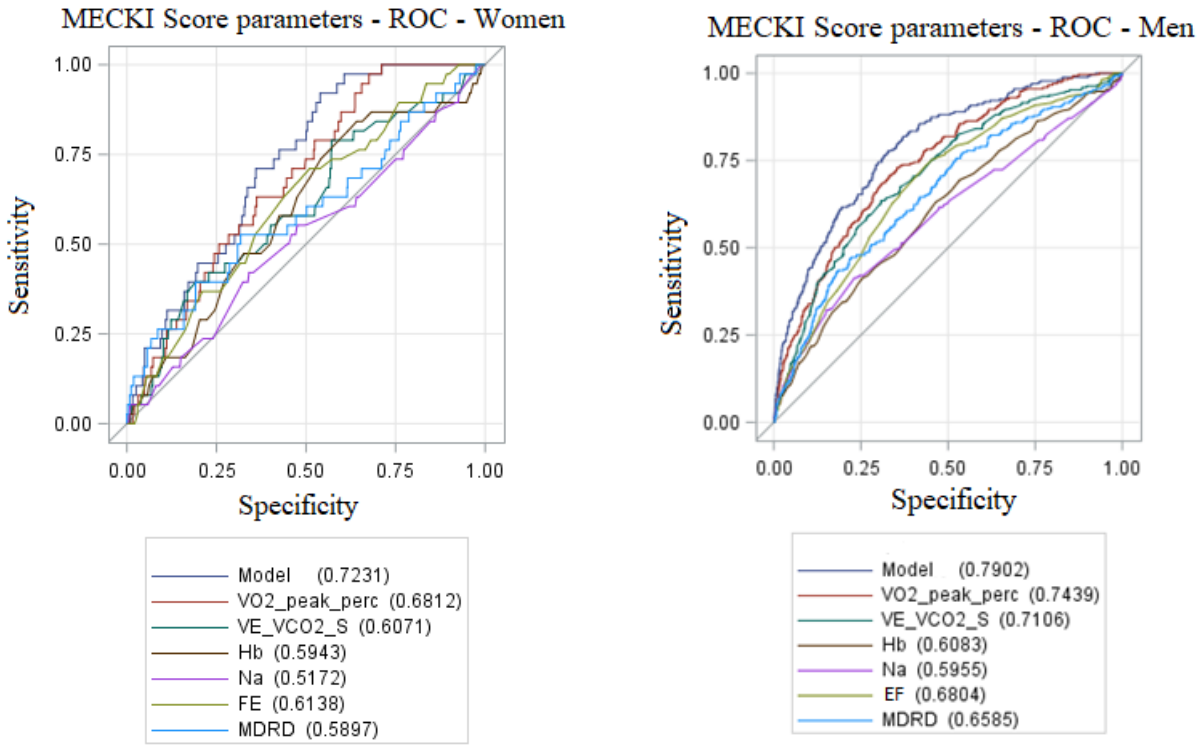


Roc curves for the predictive capacity of MECKI Score show AUC: 0.709 for women and AUC 0.785 for men.

On the other hand, considering separately the variables that make up the MECKI Score, lower predictive capacity in women than in men arise. (Figure 6 A and B)

Figure 6. A and B

A **B**



A: peak VO2 AUC: 0.68, VE/VCO2 slope AUC: 0,61; HB AUC: 0.59; Na AUC: 0,52; EF AUC: 0,61; MDRD AUC: 0,59,

B: peak VO2 AUC: 0.74, VE/VCO2 slope AUC: 0,71; HB AUC: 0.61; Na AUC: 0,60; EF AUC: 0,68; MDRD AUC: 0,66

Furthermore, observing the weights that each variable has in the two sexes separately, we note that the individual variables present substantial differences.

MECKI Score actual population – last data

Currently, the MECKI score database consists of 1400 women (aim point reached for the enrollment of this project) and 6284 men.

As shown table 4, there are no substantial age differences in the two groups (*p* value: 0.4); women, although overweight, have a lower body mass index (BMI) than men (women, w 25.7 ± 4.8 vs men, m 26.9 ± 4.22, *p* value < 0.0001). Among the CPET parameters examined, only the VE/VCO2 slope does not show statistically significantly differences between men and women. The female population of the MECKI Score shows a higher ejection fraction (w 36.4 ± 11.5 vs m 32.3 ± 9.9, *p* value: <0.0001), although obviously falling within the HFrEF. Renal function calculated with MDRD is better in men (w 68.3 ± 24.2 vs m 72.2 ± 24.1, p value: <0.0001), as well as hemoglobin is physiologically higher in men. No statistical difference was found in serum sodium concentrations (w, 139.6 ± 3.02 vs m, 139.4 ± 3.2, p value: 0.067) (table 4).

Table 4. Differences among sexes about MECKI Score parameters and CPET variables.

N.	Variable	Mean ± standard deviation	*p* value
♂**1400**/♀**6284**	Age yrs, w/m	61,8±13,5/61,5±12,38	0,4244
	BMI Kg/m2, w/m	25,7±4,8/26,9±4,22	<.0001
	VO2 peak, w/m	873,8±289,3/1208,2±434,2	<.0001
	VO2 peak_%, w/m	62,9±18/54,4±16,8	<.0001
	VE/VCO2_S, w/m	33,6±7,7/33,1±7,9	0,0782
	LVEFEF %, w/m	36,4±11,5/32,3±9,9	<.0001
	MDRD ml/min per 1.73m^2, w/m	68,3±24,2/72,2±24,1	<.0001
	Hb g/dL, w/m	12,7±2,7/13,7±1,64	<.0001
	Na mEq/L, w/m	139,6±3,02/139,4±3,2	0,067
	FU_total		0,4921

Mean ± standard deviation, SD.

Peak VO2, oxygen uptake at peak exercise; Peak VO2, % of predicted oxygen uptake at peak exercise; VE/VCO2 slope, ventilatory efficiency by means of CO2 production/ventilation relationship Hb: hemoglobin; Na: sodium; LVEF: left ventricular ejection fraction; MDRD glomerular filtration rate estimated by modification of diet in renal disease formula

Pointing out the drug therapy (table 5), substantial differences can be observed as regards the therapy with beta blockers and for ACE inhibitors, more widely used among males. No substantial differences were highlighted in the use of diuretics among sexes (w 78.77% vs m 81.08 %, *p* value: 0.055). The 23% of women undergo therapy with angiotensin receptor blockers, compared to 19% of men (*p*

value: 0.001). Mineralocorticoid drugs have been administered to 48.9% of women and to 53.2% of men (*p* value: 0.004).

The prevalence of atrial fibrillation, ICD implantation and use of CRT in the studied population was also assessed. The15.7% of women and 17.7% of men have atrial fibrillation (*p* value: 0.078). In this population the 23.9% of women and the 35.1% of men an ICD was implanted (*p* value <0.0001). CRT was performed in 11.6% of women and in 14.8% of men (*p* value: 0.002).

Table 5. Characteristics of female and male population in MECKI Score database, regarding drugs, atrial fibrillation, ICD and CRT.

	Female	**Male**	**Female vs Male %**	***p* value**
Diuretics, n. (no/yes) (7583, 101 missing)	293/1087	1177/5026	78,77 vs 81,08	0,055
Beta Blockers, n. (no/yes) (7618, 66 missing)	198/**1189**	757/**5474**	**85,72 vs 87,85**	**0,03**
ACEi, n. (no/yes) (7615, 69 missing)	471/**916**	1693/**4535**	**66,04 vs 72,82**	**<0,0001**
ARB, n. (no/yes) (7308, 376 missing)	1035/**311**	4821/**1141**	**23,11 vs 19,14**	**0,001**
MRA, n. (no/yes) (7498, 185 missing)	692/663	2872/3271	48,93 vs 53,25	**0,004**
Atrial fibrillation, n. (no/yes) (7665, 19 missing)	1179/220	5157/1109	15,73 vs 17,7	0,078
ICD, n. (no/yes) (7677, 7 missing)	1063/335	4073/2206	23,96 vs 35,13	**<0,0001**
CRT, n. (no/yes) (7620,64 missing)	1231/162	5303/923	11,63 vs 14,82	**0,0021**

Data are expressed in number and %. ACEi: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, CRT: cardio resynchronization therapy ICD: implantable cardiac defibrillator, MRA: mineralocorticoid receptor antagonist

The prevalence of events at 2, 5 and 10 years within the subgroups by sex showed overlapping percentages in females and males at 2 years. Greater are the differences between the groups at 5 and 10 years (table 6).

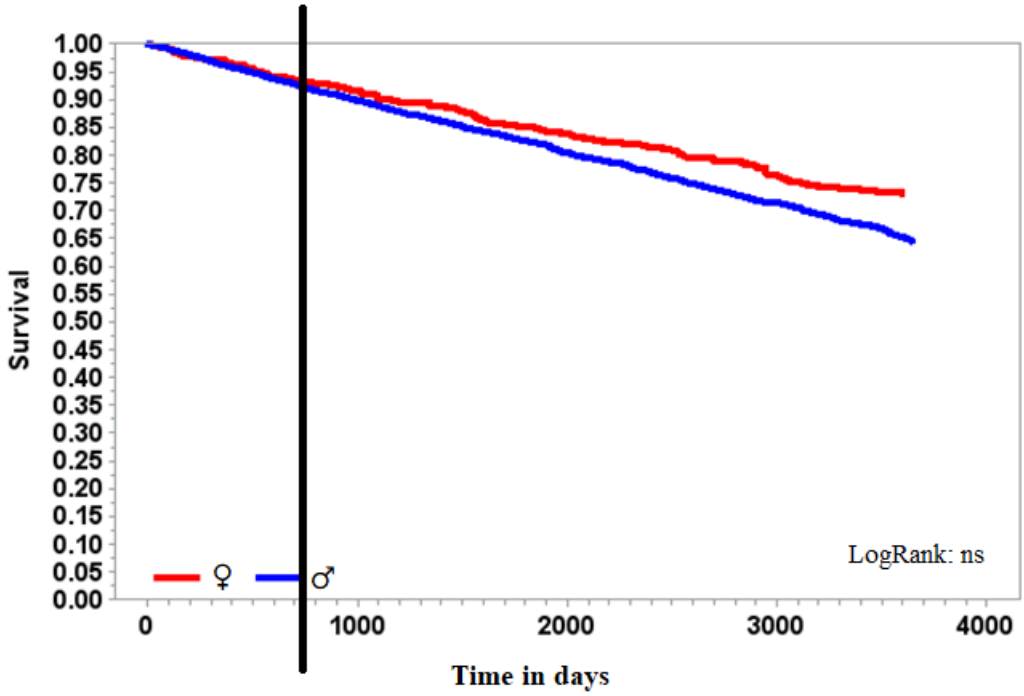
Table 6. Prevalence of events at 2, 5 and 10 years of follow up.

MECKi score	***End point 2 yrs***	***end point 5 yrs***	***end point 10 yrs***
Women, events/patients (**%**)	56/1104 (**5,07%**)	105/1055 (**10%**)	156/1004 (**15,5%**)
Men, events/patients (**%**)	375/4893 (**7,66%**)	731/4537 (**16,1%**)	1061/4207 (**25,5%**)

n. of events and %.

Survival analysis highlighted an absolute overlap of the two study populations, adjusting the analysis for the MECKI Score (figure 7). At 2 years, the survival curves are equivalent. Over time, they tend to drift apart.

Figure 7. Kaplan–Meier survival curves adjusted for MECKI Score in women and men.



Kaplan–Meier survival curves by sex, adjusted for MECKI Score,

Discussion

Heart failure in the female gender assumes extremely peculiar characteristics. (Crousillat DR et al 2018). As previously said, the pathophysiology of the damage is profoundly different; the endothelial dysfunction, the damage to the microcirculation and the comorbidities that cause CHF are in fact frequently associated with a type of decompensation that has a better ejection fraction than those in the male population. (Han Z et al 2017)

Symptoms are often vague and not "typical", which often delays diagnosis, bringing patients to the doctor's attention only belatedly. This aspect frequently leads to having a much older age than the male gender at diagnosis, which determines higher co-pathology degree and polypharmacy. In this situation, female patients are highly exposed to risk of iatrogenic damage and poor compensation and therapeutic unsuccess. (Nakao YM et al 2018)

Age is often a limiting factor also for enrollment in clinical trials, which therefore frequently have a gender-related bias. (Crousillat DR et al 2018)

The MECKI Score database also shows a clear prevalence of male patients (about 82%). However, it is an extremely large database of more than 7,000 patients; this corroborates the statistical data relating to the female gender, too.

For this reason, it is of primary importance to have clear, reproducible risk stratification tools even in a population with specific characteristics.

The MECKI Score has demonstrated efficacy in predicting cardiac death or transplantation among the population for which it was validated. Nevertheless, we know that the CPET, of which the MECKI Score uses peak VO2 and VE VCO2 slope, could constitute a bias in the evaluation of prognosis in the female gender. Even with a less performing CPET, women appear to have, in fact, a generally better prognosis. This could cause them to lose appropriateness to the therapeutic indications (i.e. heart transplant).

In reviewing the MECKI Score database, numerous, mostly expected, gender differences emerged which reinforce the initial hypothesis. In the population examined, there is no substantial difference in age, women have, although overweight, a lower BMI than men, a better LVEF, significant differences in renal function and hemoglobin concentration (these parameters are already corrected for sex); no difference in terms of natremia.

The drug therapies administered to the patients of the two groups studied showed substantial differences. This aspect largely depends on the different pathogenesis of heart damage, which, in the female gender, is specifically based on the micro-vessels damage, while atherosclerosis of the large coronary vessels is at the basis of ischemic heart disease found in men. This leads to the need for slightly different drugs. For example, we are not surprised by reading the data on the use of beta blockers, which tend to be more used in men than among women. A specific evaluation about the different dosages of beta-blockers administered has not been carried out at the moment, but it will be very interesting, in order to evaluate this aspect as well. Hypertensive heart disease is considered one of the cardiovascular pathologies more frequently associated with heart failure in women. Therefore, it is not surprising the data found in the MECKI Score database, in which more women than men underwent ARBs therapy.

Observing the percentages of events in the two sexes, as the MECKI Score was born with the intention of predicting the risk of cardiovascular death or transplantation at 2 years, it is valuable that the percentages of events in the two sexes are substantially overlapping at two years. ***Therefore, the MECKI Score is able to be accurate in predicting the risk also in the female population, as there are no overall differences in the prevalence of events in the two sexes at two years***. Differences in survival curves begin to be observed over longer follow-up periods. This aspect is in line with the literature.

The data is also evident in the Kaplan-Meier survival curves, where at two years, the survival curve of the group of men are substantially similar to that of women.

Conclusions

From the insight into the MECKI Score database, it emerged that female patients suffering from heart failure often have profoundly different characteristics as regards the etiopathogenesis of heart failure, drug therapy, CPET performance and long-term prognosis.

On these gender-specific characteristics it will be appropriate to concentrate future analysis for the identification of any specific subpopulation that have peculiarities that can impact on the prognosis.

However, it is evident that the MECKI Score maintains its prognostic power at two years follow up, even in the female population, guaranteeing appropriate clinical and therapeutic choices.

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