Centro Cardiologico Monzino

UNIVERSITÀ DEGLI STUDI DI MILANO

International Symposium on:

CHRONIC HEART FAILURE IN 2016: PROGNOSIS

Milan (Italy), February 25 - 27, 2016

Organized by

CENTRO CARDIOLOGICO MONZINO, IRCCS, MILANO, ITALY

DEPARTMENT OF CLINICAL SCIENCES AND COMMUNITY HEALTH, CARDIOVASCULAR SECTION, UNIVERSITY OF MILAN, ITALY

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FONDAZIONE INTERNAZIONALE MENARINI

ABSTRACT BOOK

Palazzo Clerici
Sala L. Pirelli – Via Clerici, 5

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CONTENTS

Carbonic anhydrase and the heart: functions, inhibition and treatment in cardiac diseases

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The story of carbonic anhydrase (CA) and the heart begins over 60 years ago with the introduction of the first oral and well-tolerated diuretic agent for congestive heart failure, the CA inhibitor acetazolamide (1). At that time it was well established that carbonic anhydrase was present in red cells, stomach, pancreas and importantly the kidney, where its inhibition leads to decreased sodium and bicarbonate reabsorption, lower acid secretion and roughly a loss of 5-10% of extracellular volume and sodium. Acetazolamide is a relatively weak diuretic and is associated with side effects such as the development of a mild metabolic acidosis and dyspnea from the acidotic stimulation of ventilation (2). CA inhibitors were soon found to be beneficial in glaucoma, hydrocephalus and in various seizure disorders. The respiratory stimulant effect of acetazolamide has found good use in the prevention of acute mountain sickness and in patients with various sleep disordered breathing syndromes such as the obesity-hypoventilation syndrome. In the deliberate attempt to synthesize more potent CA inhibitors than acetazolamide that might have greater diuretic action, serendipitously the newer sulfonamides, such as the thiazides and loop diuretics, were in fact found to be much weaker CA inhibitors. Fortuitously, some were found to have diuretic activity at different transport steps in the nephron; the NaCl co-transporter in the distal nephron and on the Na-K-2Cl co-transporter in the loop of Henle, respectively. The high ceiling diuretics, particularly furosemide and bumetanide, became and are still commonly employed in heart failure; with the thiazides for hypertension treatment and sometimes to amplify the diuretic effect of loop diuretics in states of severe diuretic resistance. The only indication presently for acetazolamide and other potent CA inhibitors in heart disease is temporary administration to counteract the metabolic alkalosis that sometimes develops with sustained use of loop diuretics (2) and to

reduce contrast induced nephropathy by causing alkaline diuresis (3) and possibly moderating ROS generation (4).

It took another thirty years for the existence of CA in the heart to be demonstrated in the 1980s (2) owing to its much lower concentration (100 –fold less) in the myocardium and vasculature than other organs and tissues. Histochemical and genetic studies have identified numerous isozymes of CA expressed differentially in the heart, including in the mitochondria, cytoplasm and on sarcolemmel and sarcoplasmic reticular (SR) membranes. The initial work on functional relevance in myocardial contraction and relaxation found the acetazolamide and other CA inhibitors in vitro at very high concentrations cause reversible depression of isometric force generation, but surprisingly faster diastolic relaxation. These effects may be related to the slight intracellular acidosis that develops with a reduction in metabolic CO_2 disposal and alterations in SR calcium release and reuptake during the contractile cycle (5). Other functions have identified; faster intracellular and extracellular space pH regulation, in part related to rapid production or disposal of H^+ and HCO_3^- in the operation of membrane Na^+/H^+ exchangers and Cl^-/HCO_3^- exchangers and more rapid intracellular H^+ mobility (6). These effects would lead to the prediction that myocardial CA inhibition might depress cardiac output, but in all animal and human hemodynamic studies to date, there has been no evidence that acetazolamide used in clinically relevant doses alters maximal cardiac output or heart rates even at heavy exercise or in hypoxic conditions (7), nor have there been any reports of angina or myocardial dysfunction developing in patients using CA inhibitors for other indications.

The reasons for the lack of deleterious consequences predicted from isolated heart, cellular and subcellular work in vivo remain unanswered, but could be in some cases of cardiac disease be explained by possible benefits arising from CA inhibition. In healthy persons, the lack of any impact on exercise capacity may be due to the fact that the dosing and concentrations (> 20 mg/kg vs < 5 mg/kg) used to show negative inotropic effects in vitro have never been tested

in humans. The administration of these doses causes such severe intramuscular respiratory acidosis ($pH < 7.00$, $PCO_2 > 100$ mmHg) (8) that it is not possible to determine if isolated myocardial CA inhibition in humans would alone cause a cardiac limitation to exercise.

Could there be benefits of CA inhibition in heart disease that might outweigh the modest negative aspects discussed above? By inhibiting CA and slowing the rate and magnitude at which membrane Na^+/H^+ exchanger alkalinizes the cell, activates calcium signaling (9) and initiates hypertrophy (10) acetazolamide may be therapeutic in limiting catecholamine-driven remodeling and detrimental hypertrophy in heart failure (11,12). In a rat model of permanent LAD occlusion chronic treatment with several different CA inhibitors started 8 months later reduced myocardial fibrosis and improved echocardiographic measurement of LV function compared to control (13). In a similar fashion, CA activation in the hearts of diabetic patients is detectable and associated with increased Na^+/H^+ exchanger expression and myocyte hypertrophy (14). In a model of ischemia-reperfusion injury in the rat heart, we have preliminary evidence that acetazolamide reduces total infarct volume and lessens the decline in LV ejection fraction (unpublished data). Of interest is the expression of CA IX, a hypoxia inducible factor (HIF) responsive gene in the hypoxic and ischemic myocardium that is also expressed in cancers and is growth-promoting. Selective inhibition of this isozyme might be useful when specific CA IX inhibitors, now in phase 3 clinical studies, become available. Additional possible benefits of acetazolamide and other CA inhibitors in the setting of myocardial ischemia and CHF are enhancement of Ca-activated potassium channel opening and systemic vasodilation (15). In the pulmonary vasculature, acetazolamide reduces pulmonary vascular resistance and hypoxic pulmonary vasoconstriction (16) making it possibly useful in the treatment of WHO class II and III pulmonary hypertension. Lastly, we (17) have shown that acetazolamide reduces periodic breathing and central sleep apnea in heart failure, by several mechanisms including CA inhibition in peripheral and central chemoreceptors that acts to slow the rate and magnitude of heightened chemoreceptor responsiveness to O_2 and CO_2 and thus stabilize

breathing. These therapeutic aspects of careful CA inhibition in the heart warrant larger and more convincing clinical trials.

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Chronotropic Incompetence and Chronic Heart Failure Prognosis

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The heart rate (HR) response is crucial to tightly match the subject's cardiac output to metabolic demands during exertion. Indeed, the physiological 4-fold increase in oxygen uptake (VO_2) observed during maximal aerobic exercise is usually achieved by a 0.3-fold increase in stroke volume, a 1.5-fold increase in arterio-venous oxygen difference, and a 2.2-fold increase in HR [1]. Accordingly, the inadequate HR response to exercise, a clinical condition termed as chronotropic incompetence (CI), could represent one of the main contributor to the reduced exercise capacity.

In patients with chronic heart failure (HF), CI presence has been attributed to a reduced myocardial sensitivity to sympathetic modulation together with a β-receptor down-regulation as well to the anatomic and electrophysiological changes in the properties of sinus node. However, although all these conditions are known to be associated with an advanced HF stage and, most likely, with a poor outcome, the actual role of exercise-induced HR response, and specifically of the CI, remain still a debated topic. Particularly, the lack of a consistent methodology, the number of different cut-off points adopted in clinical studies, as well as the drugs impact on HR dynamic are all factors potentially weakening the CI clinical meaning mainly in the HF patients [2].

From a mathematical point of view, CI is usually diagnosed during a maximal exercise test when peak HR fails to reach an arbitrary percentage (ranging from 80% to 85%) of the age predicted maximal HR (APMHR). Alternatively, given that the proportion of HR achieved during exercise depends partially on the resting HR, CI might be diagnosed also as the failure to obtain the 80% of the adjusted HR reserve (change in HR from rest to peak exercise divided by the difference between age predicted maximal HR and resting HR).

The abovementioned represent the most frequently approaches used to diagnose CI and both of them based on the concept of APMHR usually obtained through the (220 – age) equation. Nonetheless, the latter represents a superficial formula based on an observation of a linear best fit to a series of raw and mean data compiled more than forty years ago [3]. Furthermore, given that peak HR concept calls for a maximal exercise test, the cardiopulmonary exercise test (CPET) analysis should be always preferred, being more appropriate than a subjective ratings of perceived exertion to evaluate objectively the physiological level of effort during exercise. However, if a CPET assessment should be mandatory for a true CI diagnosis, it is unclear whether CI owns a prognostic role independently from a strong predictor such as the peak VO_2 (i.e. peak HR concurring to this variable according to the Fick law) [4]. Last, as previously stated, β-blocker treatment may further blunt the HR response to exercise in spite of its undoubted positive role in HF prognosis, thus further confounding a possible CI clinical use.

Aiming to strengthen the CI role in the clinical management of patients with chronic HF, we recently showed in a large multicenter HF cohort that the exercise-induced HR parameters maintain their independent association to cardiovascular mortality in HF patients when they are challenged as continuous parameters. However, contextually, our analysis pointed out that only the 65%-70% cut-off values are able to identify the HF patients with the worst prognosis independently of other well-known risk factors, the historical CI definitions (75%-80%) not achieving an independent prognostic role [5].

In conclusion a well-reasoned and accurate analysis of the exercise-induced HR response still represents, possibly together with other most readily available variables, an useful approach for cardiologists operating in HF centers.

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Anemia and sideropenia role in chronic heart failure prognosis

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Many articles in the last 10 years have sought to assess the prevalence anemia in HF patients. Numbers range from 4 to 55% depending on the definition criteria and the population studied (age, sex, LVEF). In the princeps study Silverberg et al., the prevalence was 55.6%, but this was in aged subjects, in the vast majority of cases with kidney failure. It is 15% in the study by Tanner et al. [3] concerning younger patients. Conversely, in selected populations,
such as in clinical trials, prevalence is much lower: 9.9% in the Val-HeFT. In Euro Heart Survey, male patients were anemic in 33% of the case. So the incidence of anemia increases with the level of definition of anemia, with the age of patients, with the NYHA functional class and naturally with the alteration of renal function. Several studies have shown that anemia was an independent mortality risk factor in CHF. Even if one takes into account the age and function renal, having a low hemoglobin increases mortality.
However, in one study that tried to correct anemia in these patients with darbepoietin alpha (vs placebo) in more than 2000 patients, there was no effect on mortality and even a tendancy to increased thromboembolic risk. Therefore, the issue of whether anemia is a marker or a prognostic factor in CHF remains an open one.
Anemia is most often of iron deficiency (ID) origin and the issue of ID in CHF has been studied after.
In patients with heart failure, ID is frequent but overlooked, with a prevalence of 30-50%. Since it contributes to cardiac and peripheral muscle dysfunction, ID is also associated with poorer clinical outcomes and a greater risk of death, but interestingly independently of hemoglobin level. Therefore, ID emerges as a new comorbidity and a therapeutic target of chronic heart failure in addition to chronic renal insufficiency, anemia, and diabetes. In a series of placebo-controlled, randomized studies in patients with heart failure and ID, intravenous

iron had a favorable effect on exercise capacity, functional class, left ventricular ejection fraction, renal function, and quality of life.
A prospective study in 157 chronic heart failure patients showed that non-anemic, iron-deficient patients had a 2-fold greater risk of death than anemic, iron-replete patients. In another study of 546 heart failure patients, ID predicted unfavorable outcome independently of anemia, with an increased risk of death or heart transplantation. In an international, pooled cohort of 1,506 chronic heart failure patients, ID (but not anemia) was an independent predictor of mortality and was associated with disease severity (assessed with New York Heart Association [NYHA] functional score and level of N-terminal fragment of pro-B-type natriuretic peptide [NT-proBNP]). Recently, it has been shown that ID correction by IV iron not only improves exercise capacity but also reduces HF rehospitalizations. There has been to date no study having assessed the effect of IV iron on mortality in CHF patients but recent meta-analyses suggest of positive effect.

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Kidney dysfunction effects on chronic heart failure prognosis

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Kidney dysfunction plays a central role in the pathophysiology and treatment of heart failure. The interaction between the heart and kidney is however a dynamic process, which has been depicted as a "*rollercoaster ride*". Impairment of kidney function is a highly prevalent condition in chronic heart failure, regardless of whether left ventricular ejection fraction is reduced or preserved. On the other hand, heart failure is the most prevalent cardiovascular comorbidity in patients with a primary diagnosis of chronic kidney disease. Multiple factors can influence the evolution of renal function over time in heart failure. Fifteen percent to 25% of chronic heart failure patients with preserved kidney function develop renal dysfunction over time; yet, the opposite may also be true.

Renal dysfunction is a powerful predictor of morbidity and mortality both in chronic and acute heart failure. Impairment of kidney function is, however, much more than just decreased glomerular filtration rate; it also consists of altered renal hemodynamics, tubular damage or injury, and sodium and water retention. Because of the complexities of kidney dysfunction in heart failure, several biomarkers of glomerular filtration rate and tubular damage and injury have been studied in regard to their prognostic implications. Serum creatinine, estimates of glomerular filtration rate, and albuminuria are closely associated with morbidity and mortality risk in chronic heart failure. Blood urea nitrogen has emerged as one of the most powerful predictor of prognosis. Because of the close relation between blood urea nitrogen and neurohormonal activation, it has also been suggested that blood urea nitrogen-to-creatinine ratio may be useful to characterize the phenotype of renal dysfunction in HF. Whether markers of tubular damage and injury provide independent and incremental prognostic information beyond that derived from traditional markers of renal function still remain insufficiently understood. Finally, severe renal dysfunction may lead to "therapeutic nihilism".

Yet, heart failure patients with severe renal dysfunction are at highest risk of developing adverse outcomes and might benefit most from evidence-based treatments in terms of absolute reduction of morbidity and mortality. Although these patients have been systematically excluded from randomized clinical trials, there is moderate evidence of a mortality benefit for beta-blockers in chronic heart failure patients with stage 3b to 5 chronic kidney disease.

Uric Acid and Chronic Heart Failure Prognosis

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Uric acid has long been known to be a burden to mankind, given our unusual metabolic handling of this product of purine synthesis and breakdown of critically low solubility so it can easily form damaging crystals with the human body. Treatment of elevated UA has historically been focussed on prevention of gout, but a new array of more effective less-side effect prone agents to lower UA offer the prospect of beneficial outcome from therapeutic UA reduction independent of its use in gout-prone subjects.

The regulation of UA metabolism and excretion are two processes that determine the prevalent levels of soluble UA within the human body[1]. Soluble (not crystalline UA) may penetrate endothelial cells, and thereby stimulate oxidative stress, inflammation, vasoconstriction and endothelial dysfunction. This may underlie the commonly noted association between hyperuricaemia and a number of cardiovascular disorders, such as hypertension, coronary artery disease and heart failure.

Xanthine Oxidase (XO) inhibitors, such as allopurinol and uricosuric compounds can all lower UA levels, both circulating and located within organ tissues[2]. Existing drugs have significant limitations, so the development of newer agents with increased potency, differing pharmacological mechanisms, and less toxicity is fortunately an active field of research. UA lowering by drugs, especially XO inhibitors in hypertension, ischemic heart disease and heart failure, may have protective actions against UA-induced endothelial dysfunction and systemic inflammation. Serum UA levels also predict adverse cardiovascular outcomes (MRFIT[3] and PIUMA[4]). There is an important interaction between UA and the complex metabolic, inflammatory and haemodynamic profile of the patient with advanced chronic heart failure (CHF)[5].

Although the prognostic importance of elevated UA in CHF patients has demonstrated many times, its effects appear independent of these other disturbances characteristic of heart failure, so that XO is a potential therapeutic target in the treatment of heart failure patients. UA is related to HF severity predicting aerobic metabolic capacity, impairment of oxidative metabolism and glucometabolic efficacy. Elevated UA levels is also correlated with measures of myocardial mechanical and energetic efficiency along with left ventricular ejection fraction, endothelial dysfunction and disease progression, and most strongly mortality. Whether this reflects a direct adverse effect or merely that UA elevation is related to so many other adverse prognostic markers in heart failure is unclear based on present evidence. Several clinical studies have shown improvements endothelium-dependent vasodilation after allopurinol in CHF. These improvements were associated with many related pathophysiological benefits in the CHF patients tested including energetic efficiency, ejection fraction ventricular remodelling, peripheral tissue perfusion and BNP levels. These results suggest the benefit may be through reducing XO activity rather than UA levels per se, and hence identifying the true therapeutic target. XO inhibition has repeatedly showed favourable effects on a range of surrogate markers, where in contrast uricosuric agents (or uricase) had failed despite comparable UA lowering.

The major question of course that remains unanswered is whether therapeutic impact of XO inhibition in CHF could improve clinical conditions, or reduce mortality/morbidity outcomes. The effect of allopurinol therapy on all-cause mortality in CHF was investigated in one large retrospective cohort study including 4785 patients with hyperuricaemia[6] and although subject to bias, this study suggested allopurinol therapy dose dependently was associated with improved survival. The effect of therapeutic XO inhibition on outcomes in CHF was tested in the OPT-CHF[7] trial using oxypurinol. The study failed to show a beneficial effect, although the fact that it included patients without UA elevation may have reduced its power to show beneficial effects. Subgroup analysis of patients with elevated UA levels ($\geq$9.5 mg/dl) showed a favourable effect of XO inhibition. The EXACT-HF trial[8] tested the effects of XO inhibition with

Allopurinol on mortality and clinical outcome in patients with systolic HF and failed to show improvement, although with only 253 randomized patients with symptomatic HF it may have been inadequately powered.

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ACE inhibitors and ACE genotypes interaction: effects on prognosis

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Use of angiotensin converting enzyme inhibitor (ACEI) and beta blockers as first line therapies of heart failure (HF) was a major breakthrough in medical pharmacological treatment, translating into clinical practice the concept that neurohumoral compensatory mechanisms could be detrimental in the long term progression of the disease, creating a vicious circle that needs to be interrupted. Indeed, after ACEI and beta blockers introduction, HF mortality has decreased respectively of about 15-30% and 35%. However, individual patient response to such therapies have shown to be highly variable. This observation together with the evidence of a different racial response to drugs is highly suspicious of a genetic variation interference. As a matter of fact, pharmacogenetic has convincingly explained drug efficacy variability in fields other than HF. Since the beginning of '90 several studies have identified many genetic variants associated with main HF pharmacotherapies. Clinical usefulness of this approach is doubtful, mainly because available data are fragmentary, mostly deriving from small observational cohort studies. However, possible applications are intriguing: for example, identifications of subjects that can benefit more from one treatment than from another or that can need higher or lower doses of a drug to obtain the expected benefit or to experience less side effects.

Most studies have focused on the genetic variants related to the sympathetic adrenergic system, however some studies have also taken into account the renin-angiotensin-aldosterone system. This is a very interesting field if one consider that ACEI fails to suppress angiotensin II in as many as 15% of HF patients and aldosterone in 38%. Of course, literature has mainly focused on the gene encoding the target of ACEI therapy, that is Angiotensin Converting Enzyme, the enzyme that converts angiotensin I to angiotensin II, resulting in downstream effects such as vasoconstriction or sodium and water

retention. ACE gene is localized to chromosome 17q23. The most studied cardiovascular-relevant variant is a 287-basepair insertion/deletion in intron 16 of ACE, that accounts for one-half of the variance in serum ACE levels (Rigat et al.). Three genotypes are possible: homozygous insertion (II) and deletion (DD) and heterozygous insertion/deletion (ID). Deletion allele (DD) is associated with significantly higher level of serum ACE levels. As a consequence it has been hypothesized that patients with ACE deletion would require a higher dose of ACE inhibitor to achieve the same inhibition. A further consequence would be that, in HF population, DD genotype could be associated with a worse prognosis. Moreover, on account of the inhibitory effects of beta blockers on renin-angiotensin-aldosterone system, ACE deletion HF patients could even present a greater response to beta blockers. Other genetic variants with possible interaction with ACE inhibitors have been described, but failed to show any clinical relevance (for example: M235T variant for angiotensinogen; A1166C variant for angiotensin II receptor type 1 and C-344T variant for cytochrome P450 family 11 subfamily B polypeptide 2).

Possible interference of ACE polymorphism with cardiac function and prognosis has been extensively explored, but with controversial results. However several clues have been collected of an association between DD genotype and left ventricular hypertrophy, left ventricular remodeling after myocardial infarction, risk of ischemic heart disease and severity, progression and prognosis in both ischemic and idiopathic HF.

First evidence of a pharmacogenetic interaction of intron 16 insertion/deletion variant with ACE inhibitor therapy in HF was obtained in 2001 from a 328 patients cohort (McNamara et al), where only DD subgroup demonstrated a significant improvement in transplant-free survival form beta-blockade, a result later replicated in 2004 in a larger cohort (McNamara et al).

Pharmacogenetic studies carried out on heart failure patients in the last 3 decades demonstrated a modulation by ACE polymorphism towards ACE inhibitors effects on mean arterial pressure, aldosterone escape

and even survival (O'Toole L et al. Cicoira M et al.). Less clear are the effects on left ventricular ejection fraction (LVEF), with one study showing an higher increase of LVEF after ACEI treatment in the DD genotype subgroup (Cuoco MA et al.) and a neutral effect in another one. The larger and most interesting study in literature was published in 2004 and examined prospectively a population of 479 HF patients with mean LVEF of 25%. Only in the subgroup treated with a low dose of ACEI (≤50% of the target dose), but not in the subgroup treated with standard ACEI dose, DD genotype was associated with an increased risk of events. Moreover, the benefit of high-dose ACE inhibition and of beta blockers appeared maximal for DD genotype patients (McNamara DM et al.).

More recently these results were extended also to patients with HF and preserved LVEF. In 285 HF patients followed for about 7 years, DD allele was associated with higher mortality in the absence of ACEI therapy, an effect no more detectable in the subgroup receiving an ACEI (Wu CK et al.).

In the last five years the role of ACE polymorphism in HF has almost not been addressed any more in literature. However, taking into account the observations by Abraham and coworkers that DD genotype is associated, in HF, with a worse lung diffusion at rest and ventilatory efficiency during exercise and the awareness that ACEI benefit in HF is at least partially mediated by amelioration in cardiopulmonary function, that is counteracted by ASA, we recently conducted in our lab a study evaluating the interference of ACE polymorphism on vulnerability to water overload in stable heart failure with left ventricular systolic dysfunction. 100 patients with optimized HF therapy including enalapril and without ASA were evaluated before and immediately after intravenous rapid infusion of 500cc of saline. Rest lung function test with measure of lung diffusion for CO (DLCO) and its subcomponent (DM: membrane diffusion, and Vc: capillary volume) and maximal cardiopulmonary exercise test were performed. After water overload challenge, a greater decrease in DLCO, because of DM decrease, and a grater increase in VE/VCO2 slope (that means a decrease in ventilatory efficiency) were observed in DD genotype in comparison to II genotype (delta DM –7.0±5.0 vs –

1.3±5.0 ml/mmHg/min and delta VE/VCO2 slope 1.8±1.1 vs 0.8±2.3, respectively in DD and II genotypes) (Contini M et al.). If translated in the clinical field, these results suggest that HF patients with DD genotype could present an higher vulnerability to pulmonary edema despite apparently optimal medical therapy.

In conclusion, the role of ACE polymorphism in HF is still on debate and most of available data derives from observational cohorts or small population studies. However, strong suggestions that patients with DD genotype are at higher risk of cardiovascular events and need higher doses of ACE inhibitors or a more complete suppression of the renin-angiotensin-aldosterone system does exist. If genetic characterization of HF patients should became part of standard diagnostic evaluation is an intriguing topic, but still not enough supported by available data and therefore needing confirmation by larger prospective studies.

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Blood biomarkers in the prognosis definition of the heart failure patient

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Several biomarkers have been tested for screening, diagnosis and prognosis purposes, as well as to guide treatment in heart failure, but up-to-date- only the assay of circulating B-type natriuretic peptides has widespread recognized application for clinical decision-making. Natriuretic peptides are sensitive in detecting the clinically overt or subclinical myocardial damage, but their plasma levels are increased following every generic insult to the cardiovascular system.
Novel biomarkers are required to identify specific pathways of disease progression, such as diverse neurohormonal axes activation, inflammation and fibrogenesis, and to act as a tool for therapeutic tailoring.
In this view, galectin-3 and ST-2 assays seem very promising, given their involvement in mechanisms of cardiac fibrosis and their prognostic value.

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Arrhythmias and chronic heart failure prognosis

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Arrhythmias are a common event in patients affected by chronic heart failure (HF) and significantly impact on disease progression. Both ventricular and supraventricular events can be found in HF patients exhibiting a different impact on symptoms occurrence, long-term prognosis and management.

About supraventricular tachycardic events, atrial fibrillation (AF) is the most common arrhythmia in patients affected by chronic heart failure (HF) [1,2]. Data from the EuroHeart Failure Survey reported that about 20% of patients with HF exhibit AF and that its prevalence reaches 40% in patients with advanced disease. Occurrence of AF in patients with HF worsens symptoms and complicates therapeutic management, due to several detrimental effects including heart rate increase, reduced left ventricular loading, irregular periods of ventricular filling and decreased cardiac output. Yet, it remains unclear whether the association of AF and prognosis in HF is due to the consequences of the arrhythmia itself or to the fact that AF is usually associated with a more severe clinical status. To date, there is no consensus on the prognostic role of AF in patients affected by chronic, systolic HF. Two meta-analyses [3,4], including 53969 and 32946 patients, reported that the presence of AF in chronic HF is associated with a 30-40% increased risk of mortality. However, in both studies, significant demographic and clinical differences were observed between patients with AF or SR, although the analyses were not adjusted for potential confounders. In a recent study from our group [5], we investigated the prognostic role of AF in a large, multicenter Italian population of patients, part of the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score database, with chronic HF and reduced systolic function [6]. In the entire study population, univariable analysis showed a more frequent occurrence of the composite outcome of CV death and heart transplantation (20% vs. 16%; p=0.026) and higher

rates of all-cause mortality (23% vs. 19.2%; p=0.039) in patients with AF. Nevertheless, HF patients with AF, compared to sinus rhythm patients, significantly differed for several characteristics that are associated with adverse prognosis, including age, NYHA class, peak VO_2 and renal function, making it difficult to distinguish an independent prognostic influence of AF on adverse outcomes. To overcome these differences, we analyzed the independent impact of AF using two different statistical models: 1) a multivariate, Cox regression model assessing the independent role of AF in the whole study cohort; 2) a matching analysis considering demographic data (age and gender), HF severity parameters (LVEF, peakVO2) in a subgroup of patients with either AF or SR. Both models showed that AF is a marker of advanced disease, but it is not independently associated to adverse prognosis in chronic HF patients with reduced ejection fraction.

Ventricular arrhythmias are also frequent in HF patients, particularly in those with a dilated left ventricle and reduced ejection fraction [7]. The occurrence of sustained ventricular arrhythmias significantly impact on the risk of sudden death in HF patients. Ambulatory ECG recording detects premature ventricular complexes in virtually all HF patients, and episodes of asymptomatic, non-sustained ventricular tachycardia are common. The presence and severity of ventricular arrhythmias increase along with the severity of HF, but their value to predict sudden death is unclear. Indeed, identification of increased risk of sudden death in HF patients has been notoriously difficult, and the only consistent association has been reported with the severity of systolic dysfunction. Currently there are no RCTs demonstrating the value of an ICD in primary prevention in asymptomatic patients (NYHA class I) with systolic dysfunction (ejection fraction ≤35–40%) or in patients with HF and preserved systolic function (40–45%). Moreover, there are no randomized trial data regarding the value of ICDs in patients with NYHA class IV. It is generally accepted that ICD therapy is not recommended in primary prevention in patients with severe, drug-refractory symptoms who are not candidates for CRT, a ventricular assist device or heart transplantation.

On the other side, in view of the scarcity of data and the rather high rate of recurrence following catheter ablation for sustained ventricular tachycardia, ICD implantation should be considered in all patients with LV dysfunction (ejection fraction FE<45%) and sustained ventricular tachycardia.

Thus, many aspects should be considered treating HF patients, since many different arrhythmic events may appear and might negatively impact on quality of life, disease progression and prognosis. Great attention should be focused on each single patient in order to reduce the risk of sudden cardiac death and improve symptom management and, of course, quality of life.

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Prognosis in Heart Transplant and LVAD Patients

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Estimating prognosis in patients (pts) under evaluation for heart transplantation (HTx) candidacy and/or for Left Ventricular Assist Device (LVAD) implantation is a multi-step process that may involve various possible pathways and critical decisions according to patient clinical characteristics and preferences, medical judgment, and healthcare organization (1). Medical and societal ethical principles and priorities, and, ultimately, destiny, may also play a role in influencing events, outcomes, their interpretation and their translation into clinical guidelines, laws and regulations (2, 3). Since many of the above listed factors are different across countries (and may differ also between areas within the same country), and change over time, *universal* and/or *ideal* prognostic models (and, consequently, recommendations) do not exist. In theory and simplistically, the prediction of prognosis with HTx or LVAD for a given patient at a given time should be weighed against the prognosis that can be estimated with medical plus other "conventional" interventional or surgical therapies. In practice, the picture is much more complex, as summarized below.

- When HTx is under evaluation, it must be kept in mind that listing is a declaration of intent, but not a therapy. During the waiting time, patient characteristics and, consequently, his/her risk-benefit profile with HTx, may change significantly.
- Donor characteristics, including cause and mode of death and management before and during heart harvesting, transplant-related factors (e.g. cold ischemia time), and donor/recipient matching (e.g. regarding size and HLA compatibility) may influence early and long term results of HTx beyond recipients' characteristics, involving additional variables that cannot be predicted at the time of prognostic balance and listing.
- Our knowledge regarding prognostication in advanced heart failure (HF), after HTx and after LVAD implantation, relies mostly on

multicenter observational registries, of which the most important are the International Society for Heart and Lung Transplantation (ISHLT) Registry for HTx (4), and the Interagency Mechanically Assisted Circulatory Support (INTERMACS) Registry for LVAD. The reliability of prognostic factors and models derived from multicenter registries when applied to my patient(s) depends on how much the outcomes and the distribution of prognostically relevant variables at my hospital are similar to those observed in the registry population (5).

- "Conventional" therapy, HTx, and LVAD implantation share many prognostic factors, which may attenuate the estimated benefit of these therapies both in low and high risk pts.
- The threshold for defining a patient at "too high" risk for HTx is related to donor availability, mortality on the waiting list, and overall post-transplant survival - beyond, of course, the estimated risk of dying without HTx. The limited number of donor hearts requires strict selection of HTx candidates and equitable allocation policies (6). Regarding LVAD, the threshold is defined, beyond clinical reasons, by the amount of resources that providers and payers feel appropriate to invest for this therapy.
- Where both options are available, the interactions between HTx and LVAD may be complex. Again, patient and medical decisions are guided not only by prognostication with or without either therapy, but also by social and individual perception of the value of these therapies, and by the rules for organ allocation and, specifically, for prioritization of pts awaiting HTx after LVAD implantation.

Within this framework, the following statements and suggestions are offered for discussing prognostication in pts under evaluation for HTx and/or LVAD:

1. Clinical evaluation of "natural" prognosis can be supported by the use of a multiparanetric score. Among the variety of published HF scores, preference must be given to ones specifically validated in pts with advanced HF, such as the Heart Failure Survival Score (7).
2. When evaluating pts for HTx listing, specific risk factors are pulmonary hypertension, recent history of cancer, and renal

insufficiency. A big size and sensitization may also reduce the probability to get HTx.

3. When evaluating pts for LVAD, some anatomical and post-surgery conditions and "primary" right ventricular dysfunction represent specific risk factors. Although various clinical, hemodynamic, and echocardiographic parameters, alone or in combination, have been shown to be associated with increased probability of post-operative right ventricular (RV) failure, predictive accuracy is low in clinical setting. In our experience, persistently high right atrial pressure is a relevant risk factor, while severe pulmonary hypertension may imply adequate residual RV functional reserve, which can also be evaluated with dobutamine stress echocardiography.

4. HTx is more and more often performed in pts supported with LVAD. At present, probability of survival is similar after HTx or LVAD up to 2-3 years, while hospitalizations are more frequent after LVAD. Long term survival is also superior after HTx (4,5, 8). Hemodynamics, end-organ function, and physical rehabilitation generally improve on mechanical support, but when urgent HTx is dictated by LVAD-related complications (especially infections), post-HTx probability of survival may be negatively affected (8,9).

5. The scope of LVAD implant is often still defined in relationship with HTx: "bridge to transplant", "bridge to candidacy", or "destination therapy". If ongoing studies on earlier LVAD implantation will provide positive results in comparison with "conventional" therapies, then LVAD - such as any other HF therapy- could be routinely considered before evaluating HTx candidacy (10).

6. Limiting HTx to pts unsuitable/suboptimal for LVAD, or with relapsing HF after LVAD implant, or with LVAD-related complications, could imply lower post-HTx survival. Another approach could be early separation of the two pathways, Iimiting (and facilitating) the access to HTx almost only to "ideal" candidates, and being very strict regarding admission to the HTx waiting list (and prioritization for organ allocation) of pts with LVAD-related complications, and/or with multiple risk factors at HTx.

7. In order to be implemented by the medical community and accepted by the pts and their families, these changes of paradigm

should be supported by the evaluation of the observed and expected benefits of these strategies on the overall population of pts with advanced HF - and, moreover, by demonstration of a substantial reduction in postoperative LVAD-related complications.

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Effects of reflex control on prognosis of the chronic heart failure patient

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Exercise-induced dyspnea in patients with heart failure is related to an abnormal increase in ventilation at any metabolic rate, which persist after cardiac transplantation.
Abnormalities in the skeletal muscles and alterations of peripheral feedbacks, namely the chemoreflex and the ergoreflex, have been proposed as central mechanisms in the origin of the limitation to exercise and dyspnoea on effort. Increased sympathetic activity, a main determinant of disease evolution and life-threatening events, is elicited by changes in autonomic afferent feedbacks through chemoreceptor [1], ergoreceptor sensitization [2] and baroreceptor desensitization [3]. An increased chemoreflex sensitivity either to CO2 (mainly expression of central, medullary oversensitivity) or to hypoxia (mostly peripheral, carotid) is often present in CHF patients with a prevalence up to 60%, regardless of optimal treatment [4]. This is associated with the occurrence of respiratory abnormalities, such as altered ventilatory response to exercise [5] or Cheyne–Stokes respiration, independent of the degree of left ventricular (LV) systolic dysfunction. Moreover, enhanced chemosensitivity may trigger atrial fibrillation and ventricular arrhythmias and holds a prognostic value [6]. Many of these negative effects are mediated by an increased sympathetic drive associated with parasympathetic withdrawal, elicited, both at rest and during exercise by the exaggerated chemoreceptor activity [7].

The muscle ergoreflex system senses metabolic products of exercising skeletal muscles. It modulates the haemodynamic, ventilatory and autonomic responses during exercise to maintain the homeostasis between muscle work and energy supply to perform it. The response to the activation of the ergoreceptors is an increase in ventilation, blood pressure and heart rate: as for the chemoreflex, the efferent arm

of the ergoreflex involves the activation of sympathetic nervous system [8]. An overactivity of these receptors and of the resulted reflex responses during exercise has been described in CHF patients. This reflex is likely sensitized by the muscle acidosis seen in CHF during exercise, inducing abnormally elevated ventilatory drive, with vasoconstriction and sympathetic activation. Moreover other stimuli, besides decrease in pH, such as potassium, prostaglandins and blood flow itself have been hypothesized to influence ergoreceptor firing. The metabolic alterations of skeletal muscle in CHF are probably caused by several factors, such as muscle atrophy, impaired muscle activation, reduced blood flow, intrinsic changes of the muscle, and deconditioning effects.
However, it is worth mentioning that the exaggerated ergoreflex response can be blunted by aerobic physical training. Another group of researchers has pointed out an important contribution from muscle mechanoreceptors in symptom generation in CHF; the anatomical and physiological differentiation of these reflexes versus ergoreflex group is unclear [9]. Finally, an impaired baroreflex leads to a reduced buffering effect of its cardiac vagal component, sustains sympathetic overactivity and worsens the haemodynamic response to exercise [10].

The alteration of the chemo, baro and ergoreflex systems and, likely, their direct/indirect interaction helps to explain the sustained sympathetic drive at rest, the heightened ventilatory response during exercise and the origin of dyspnoea on effort in CHF patients.

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Day and night-time periodic breathing impact on prognosis of heart failure

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For years, ventilation inefficiency has become an established matter of interest in heart failure (HF) patients performing a cardiopulmonary exercise testing (CPET), the most remarkable being exertional oscillatory ventilation (EOV). EOV is a cyclic fluctuation of minute ventilation (VE) and expired gas kinetics occurring during exercise: it is a slow, prominent, consistent rather than random, fluctuation in VE that may be evanescent or transient and can follow several distinct patterns. The reported incidence of EOV ranges 7 to 51%, and this broad interval originates by no universal definition currently describing EOV. Even though EOV is considered a marker of disease severity and worst prognosis.

Three are the main attributes for EOV definition: amplitude and interval (length) of the single VE oscillation and duration of abnormal VE phenomenon during exercise protocol. The wide variability of EOV pattern distinctiveness is further mystified by arbitrary assessment methods, that include manual scoring or visual interpretation. A recent systemic review screened 75 studies, accounting for 17,440 patients of which 4,638 (26.6%) presented EOV; seven of these studies incorporated other population than HF. The EOV definitions were categorized in nine subdivisions of which four referred to an original definition as suggested by Kremser et al. (n = 23), Leite et al. (n = 13), Ben-Dov et al. (n = 6) and Sun et al. (n = 2). Other EOV definitions were combinations, relying on different oscillations quantifications, with diverse computational analysis.

EOV is a robust CPET risk index in distinct HF cohorts, including heart transplantation candidates, and in patients chronically treated with beta-blockers. EOV and numerous CPET-derived parameters have been shown to be predictive in HF, but most have been studied in a binary analysis, considering risk indexes in isolation, disregarding the potential value of combining variables.

In addition, few observations have been validated, yet. Up to now, only peak VO2, VE/VCO2 slope and EOV (representing the so-called 2008 ESC model) have been validated: the 2008 ESC multi-parametric model was superior than other predictive prototypes, creating by adding, in isolation, predicted peak VO2, peak oxygen pulse, peak respiratory exchange ratio, peak circulatory power, peak VE/VCO2, VE/VCO2 slope normalized by peak VO2, VO2 efficiency slope, ventilatory anaerobic threshold detection, peak end-tidal CO2 partial pressure, peak heart rate, and peak systolic arterial blood pressure. Hence, although difficult to properly compute, EOV should always be taken into account during CPET, if macroscopically evident, at visual or analytical inspection.

Sleep-disordered breathing (SDB) includes obstructive (OSA) and central sleep apnea (CSA). CSA is characterized by apneas secondary to diminution or cessation of thoraco-abdominal respiratory movements (due to dysfunction of central respiratory control mechanisms), while OSA is caused by upper airway collapse during inspiration and is accompanied by strenuous breathing efforts. By convention, the severity of CSA and OSA is commonly assessed by the apnea hypopnea index (AHI). The prevalence of SDB in patients with chronic HF is more than tenfold that seen in the general community. In HF populations, OSA occurred in 38% to 43% of patients and CSA occurred in 28% to 38%.

The pathogenesis of CSA in HF is complex and remains incompletely understood. It is unclear whether CSA directly affects chronic HF patho-physiology and can therefore be causally linked to prognosis, or whether it is rather an index of the severity of HF. However, a substantial body of research suggests that an increased respiratory control response to changes in PaCO2 above and below the apneic threshold is central to the pathogenesis of CSA in HF. In patients with HF, CSA occurrence is due to changes associated with background disease, and three main factors are currently theorized to interact and lead to respiratory instability in HF: hyperventilation, circulatory delay, and cerebrovascular reactivity.

Since the underling mechanisms of CSA with Cheyne-Stoke respiration (CSR) resemble (partially) that of EOV, it was assumed that both respiratory disorders may cohabit in HF patients. Nonetheless, the relationship between EOV and CSA with CSR in HF has been scantly studied. In 2006, 133 HF patients were studied during the night and symptom-limited CPET, and one third showed respiratory alterations both during exercise and during sleep. EOV patients showed a significantly higher apnea-hypoapnea index (AHI) and EOV was the only predictor of AHI >30/hr. During the follow up, 31 patients (23%) had major cardiac events (cardiac death or urgent heart transplantation): total mortality was 9% in patients without either EOV or AHI ≤30/h, 17% in those with EOV alone, 31% in those with AHI >30/h alone, and 54% in those with combined EOV and AHI >30/h. Thus, the combination of EOV and significant CSA heralds worst prognosis.

The management of EOV should be individualised and specialised. The presentation of this atypical breathing pattern is an indicator for application of more aggressive therapy: servoventilation , sildenafil intake, inhalation of acetazolamide and carbon dioxide. Milrinone treatment and heart transplantation showed to be effective in blunting EOV. More physical activity in the form of aerobic exercise leas to a remarkable 71.2% disappearance of EOV.

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The prognosis of heart failure patients with pulmonary hypertension

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Pulmonary hypertension (PH), eventually leading to right ventricular failure, is a well-known complication in patients with left heart failure, negatively impacting symptoms, exercise capacity and outcome [1,2] – independent of left ventricular ejection fraction [3]. PH may occur in patients with heart failure and reduced ejection fraction (HFrEF) as well as in patients with heart failure and preserved ejection fraction (HFpEF). Due to an increasing incidence of left heart failure in a growing elderly population, the prevalence of PH due to left heart diseases (PH-LHD) will likely expand in the future. However, the prevalence of PH-LHD differs among different studies, due to heterogeneous study populations and heterogeneous hemodynamic criteria for the presence of PH [4-6].
The diagnosis and classification of PH due to left heart diseases may be challenging. In particular, a clear differentiation between pre- and postcapillary PH in patients with HFpEF may be difficult and requires a combined invasive and non-invasive diagnostic workup [7].

The presence of PH in HFrEF *and* in HFpEF correlates with markers of disease severity, and is associated with worse long-term outcomes, including heart failure hospitalization and mortality [3,8]. Right ventricular failure has an independent prognostic value over PH in left heart failure [3]. Patients with PH due to HFpEF may even show a higher 5-year mortality rate than patients with HFrEF [8]. Exercise testing may add important clinical information on the risk stratification of patients with PH-LHD. A diagnostic approach combining stress echocardiography and cardiopulmonary exercise testing may identify patients at a particularly high risk of future cardiac events [9].

Currently, there is no established specific treatment for LH-PHD. However, current guidelines provide insights into the management of

the disease [1,2]. Further studies are needed to identify further therapeutic targets and/ or to detect subgroups of patients who might benefit and improve prognosis by existing PH treatment.

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The Metabolic Exercise Test Data Combined with Cardiac and Kidney Indexes (MECKI) Score: a new prognostic tool in patients with systolic heart failure

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Heart failure (HF) is a leading cause of morbidity and mortality worldwide and its prognostication is a challenging medical judgment, constrained by a magnitude of uncertainty. Many HF risk stratification tools have been developed in last years, each differing in the sample used for validation, in the variables selected for risk assessment and in the effective utility in predicting mortality at varying time points (1-3). However, their application in daily clinical practice is limited by their complexity. Thus, we developed a new predictive model, built and validated on contemporary HF population, the Metabolic Exercise Test Data Combined with Cardiac and Kidney Indexes (MECKI) score (4).

The MECKI score is a simple, 6-variables score, based on simple parameters selected form several measurements of clinical status, cardiac kidney function, anemia, fluid homeostasis and exercise performance with the aim to help clinicians in the risk stratification of ambulatory HF patients. We developed and validated the MECKI score from a cohort of 2716 (mean age 60.3±12.4 years) systolic HF patients followed in 13 Italian centers with a median follow up of 1041 days. Our study population consisted of clinically stable systolic HF patients capable to perform a CPET (4,5). The combined end-point of cardiovascular death+urgent cardiac transplant occurred in 529 cases (19%, 441 cardiac death and 88 urgent cardiac transplant). At multivariable Cox analysis, with subsequent cross validation, only hemoglobin, Na+, MDRD, ejection fraction, peak VO_2 (% predicted), and VE/VCO_2 slope resulted independently related to the risk of cardiovascular death+urgent heart transplant. The MECKI score identified the risk of study end-point with area under the ROC curve (AUC) values of 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. A free web-based calculator was also developed to allow an easy and convenient calculation of the estimated risk of death. http://www.cardiologicomonzino.it/Inglese/News/Pages/UserNewsHome.aspx

After this validation, we expanded the MECKI score database including new enrolling centers and, recently, evaluated the prognostic value of MECKI score compared with two of the actually most-used and available scores, Heart Failure Survival Score (HFSS) (2) and Seattle Heart Failure (SHF) Model (1). Data from 4862 consecutive patients (mean age 61.3±12.6 years) with systolic HF admitted in 21 Italian cardiology departments (mean follow up 3.6±2.6 years) were analyzed. In each patient we collected data on clinical history, physical examination, blood sample, 12 derivations ECG, transthoracic echocardiogram, CPET and calculated the MECKI, HFSS and Seattle Score and measured ROC curves and the AUC. Nine hundred ninety-eight patients died or underwent urgent transplantation during the follow-up period. Available data allowed calculation of MECKI score in 4139 patients, HFSS in 4007 and SHF in 2833. All the three scores were calculated in 2762 patients. At 1, 2 and 4 years AUC were 0.757, 0.742, 0.729 respectively. Including all the patients (by estimating the missing variables) AUC were 0.782, 0.767 and 0.756 ($p<0.001$ vs. HFSS and SHF) (Fig. 1).

Conclusion

MECKI score is a simple, reliable, easy to calculate, personalized heart failure prognostic tool. The MECKI score is a "CPET-centered" score, and emphasizes a modern interpretation of CPET results. Since prediction models should be designed to improve outcome definition in individual patients, the integration of CPET risk factors with demographic data, medical history, laboratory values, and HF treatment background is crucial. The MECKI score fills the gap, and its clinical insight and originality lies in the ability to amalgamate a modern CPET risk interpretation with easily accessible HF predictive data. At present, MECKI is the long-term risk stratification score for systolic HF with the highest prognostic power.

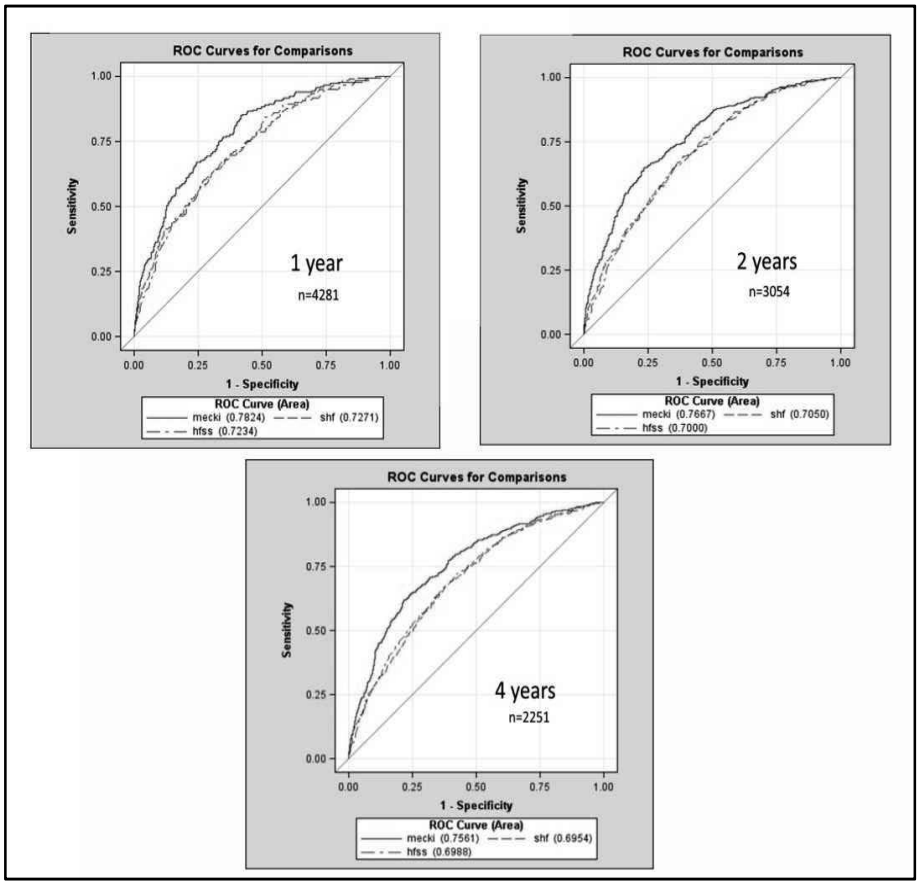

Fig.1 - Comparison between Mecki score and Seattle and HFSS scores

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