

Research Center on Heart Failure

Director: Dr.sa Alessandra Villani (Coordinator Dr.sa Alessia Giglio)

**Specialized Research Centre afferent to the Cardiology
Research Laboratory**

Members of the Research Group

- Dr.ssa Alessandra Villani (Director)
- Dr.ssa Gabriella Malfatto (Co-Director)
- Dr.ssa Alessia Giglio (Coordinator)
- Prof. Sergio Caravita,
Dr.ssa Carlotta Munforti

RESEARCH ACTIVITIES

Heart failure (HF) is a widespread clinical syndrome that represents the most common cause of hospitalization in individuals over 65, characterized by a five-year mortality of approximately 50%. It is a heterogeneous condition, with a multiplicity of manifestations and phenotypes and is classified into three groups based on the value of the ejection fraction: reduced, mid-range and preserved.

The research group carries on several activities in the field of clinical trials on new pharmacological therapies, as well as on innovative protocols and strategies regarding the therapy and management of advanced HF patient.

RESULTS OF PARTICULAR IMPORTANCE ACHIEVED (list of publications accessible from the website with a hyperlink, approved projects, awards and recognitions - to be updated annually).

The Group pursues several lines of research, as detailed below.

1. Participation in multicenter studies and in clinical registries on innovative drugs for the treatment of heart failure (Vericiguat, Istaroxime, Sacubitril/Valsartan, Levosimendan, Glifozines), as well as on HF treatment based on Telemonitoring e Telecare.
2. Analysis of the use of these drugs in the real world, with particular reference to the pathophysiology of functional capacity and ventricular function.
3. Analysis of the clinical and prognostic relevance of laboratory methods and non-invasive measures of hemodynamics in the management of chronic heart failure outpatients.
4. Analysis of the utility of daily pulmonary pressure monitoring with a sensor implanted in the pulmonary veins in patients with advanced heart failure.
5. Analysis of the feasibility and efficacy of long-term refracted infusion treatment with inotropic drugs in advanced heart failure, by designing an *ad-hoc* palliative protocol
6. Studies of the efficacy, cardiovascular effects and modulation of autonomic nervous cardiac regulation of various rehabilitation programs dedicated to patients with heart failure
7. Studies on new ways of prognostic classification of heart failure through multiparametric analysis of clinical factors and derived from the cardiorespiratory test (MECKI-SCORE group)

MAIN COLLABORATIONS IN NATIONAL AND INTERNATIONAL RESEARCH NETWORKS

rete MECKI SCORE (see list of publications)

rete SOCRATES (see list of publications)

rete RELEVANT (see list of publications)

rete REAL.IT (see list of publications)

MOST RELEVANTS RESULTS ACHIEVED

List of publications grouped by the specific research topics described above

Topic 1

1. Villani A, Malfatto G, Compare A, Della Rosa F, Bellardita L, Branzi G, Molinari E, Parati G. Clinical and psychological telemonitoring and telecare of high risk heart failure patients. *J Telemed Telecare* 2014; 20: 468-75.
2. Gheorghiu M, Greene SJ, Butler J, Filippatos G, Lam CS, Maggioni AP, Ponikowski P, Shah SJ, Solomon SD, Kraigher-Krainer E, Samano ET, Müller K, Roessig L, Pieske B; SOCRATES-REDUCED Investigators and Coordinators. Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction: The SOCRATES-REDUCED Randomized Trial. *JAMA*. 2015 Dec 1;314(21):2251-62. doi: 10.1001/jama.2015.15734. PMID: 26547357.
3. Carubelli V, Zhang Y, Metra M, Lombardi C, Felker GM, Filippatos G, O'Connor CM, Teerlink JR, Simmons P, Segal R, Malfatto G, La Rovere MT, Li D, Han X, Yuan Z, Yao Y, Li B, Lau LF, Bianchi G, Zhang J; Istaroxime ADHF Trial Group. Treatment with 24 hour istaroxime infusion in patients hospitalised for acute heart failure: a randomised, placebo-controlled trial. *Eur J Heart Fail*. 2020 Sep;22(9):1684-1693. doi: 10.1002/ejhf.1743. Epub 2020 Jan 23. PMID: 31975496.
4. Lam CSP, Giczevska A, Sliwa K, Edelmann F, Refsgaard J, Bocchi E, Ezekowitz JA, Hernandez AF, O'Connor CM, Roessig L, Patel MJ, Pieske B, Anstrom KJ, Armstrong PW; VICTORIA Study Group. Clinical Outcomes and Response to Vericiguat According to Index Heart Failure Event: Insights From the VICTORIA Trial. *JAMA Cardiol*. 2021 Jun 1;6(6):706-712. doi: 10.1001/jamacardio.2020.6455. Erratum in: *JAMA Cardiol*. 2021 Jan 13;: Erratum in: *JAMA Cardiol*. 2021 Jun 1;6(6):728. Erratum in: *JAMA Cardiol*. 2021 Oct 6;:null. PMID: 33185650; PMCID: PMC7666431.
5. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM; VICTORIA Study Group. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2020 May 14;382(20):1883-1893. doi: 10.1056/NEJMoa1915928. Epub 2020 Mar 28. PMID: 32222134.
6. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019 Oct 24;381(17):1609-1620. doi: 10.1056/NEJMoa1908655. Epub 2019 Sep 1. PMID: 31475794.
7. Pözl G, Allipour Birgani S, Comín-Colet J, Delgado JF, Fedele F, García-González MJ, Gustafsson F, Masip J, Papp Z, Störk S, Ulmer H, Vrtovec B, Wikström G, Altenberger J. Repetitive levosimendan infusions for patients with advanced chronic heart failure in the vulnerable post-discharge period.

ESC Heart Fail. 2019 Feb;6(1):174-181. doi: 10.1002/ehf2.12366. Epub 2018 Oct 30. PMID: 30378288; PMCID: PMC6351894.

8. Oliva F, Perna E, Marini M, Nassiacos D, Cirò A, Malfatto G, Morandi F, Caico I, Perna G, Meloni S, Vincenzi A, Villani A, Vecchi AL, Minoia C, Verde A, De Maria R; RELEVANT-HF study group. Scheduled intermittent inotropes for Ambulatory Advanced Heart Failure. The RELEVANT-HF multicentre collaboration. *Int J Cardiol.* 2018 Dec 1; 272: 255-259. doi: 10.1016/j.ijcard.2018.08.048. Epub 2018 Aug 16. PMID: 30131229.
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Topic 2

1. Branzi G, Malfatto G, Villani A, Ciambellotti F, Revera M, Giglio A, Della Rosa F, Facchini M, Parati G. Acute effects of levosimendan on mitral regurgitation and diastolic function in patients with advanced chronic heart failure. *J Cardiovasc Med* 2010; 11: 662-8
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4. Villani A, Ravaro S, Cerea P, et al. Do the remodeling effects of sacubitril/valsartan treatment depend upon heart failure duration?. *J Cardiovasc Med (Hagerstown)*. 2020;21(9):682-687.
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6. Malfatto G, Villani A, Parati G. Heart failure features and sacubitril/valsartan effects. *J Cardiovasc Med (Hagerstown)* 2021; 22: 234-235
7. Caravita S, Faini A, Vignati C, Pelucchi S, Salvioni E, Cattadori G, Baratto C, Torlasco C, Contini M, Villani A, Malfatto G, Perger E, Lombardi C, Piperno A, Agostoni P, Parati G. Intravenous iron therapy improves the hypercapnic ventilatory response and sleep disordered breathing in chronic heart failure. *Eur J Heart Fail.* 2022 Oct;24(10):1940-1949. doi: 10.1002/ejhf.2628. Epub 2022 Aug 8. PMID: 35867685; PMCID: PMC9804720.

Topic 3

1. Osculati G, Malfatto G, Chianca R, Perego GB. Left-to-right systolic ventricular interaction in patients undergoing biventricular stimulation for dilated cardiomyopathy. *J Appl Physiol* 2010; 109: 418-23.
2. Malfatto G, Caravita S, Giglio A, Rossi J, Perego GB, Facchini M, Parati G. Pulmonary congestion at rest and abnormal ventilation during exercise in chronic systolic heart failure. *J Am Heart Assoc* 2015; 4: 1-9
3. Malfatto G, Villani A, Della Rosa F, Rella V, Oldani M, Giglio A, Facchini M, Parati G. Correlation between trans and intra-thoracic impedance and conductance in patients with chronic heart failure. *J Cardiovasc Med (Hagerstown)* 2016; 17: 276-82.
1. Facchini C, Malfatto G, Giglio A, Facchini M, Parati G, Branzi G. Lung ultrasound and transthoracic impedance for noninvasive evaluation of pulmonary congestion in heart failure. *J Cardiovasc Med (Hagerstown)* 2016; 17:510-7.
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Topic 4

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Topic 5

1. Malfatto G, Della Rosa F, Rella V, Villani A, Branzi G, Blengino S, Giglio A, Facchini M, Parati G. Prognostic value of noninvasive hemodynamic evaluation of the acute effect of levosimendan in advanced heart failure. *J Cardiovasc Med* 2014;15:322-30
2. Ortis B, Villani A, Oldani M, Giglio A, Ciambellotti F, Facchini M, Parati G, Malfatto G. Intermittent levosimendan infusions in advanced heart failure: a real world experience. *J Int Med Res.* 2017; 45: 361-371.
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database and evaluation of its therapeutic applications. *J Cardiovasc Pharmacol* 2017 Aug 15

Topic 6

1. Malfatto G, Branzi G, Gritti S, Sala L, Bragato R, Perego Giovanni B, Leonetti G, Facchini M. Different baseline sympathovagal balance and cardiac autonomic responsiveness in ischemic and non-ischemic congestive heart failure. *Eur J Heart Failure* 2001; 3:197-202
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3. Malfatto G, Facchini M, Branzi G, Riva B, Sala L, Perego GB. Long-term treatment with the beta-blocker carvedilol restores autonomic tone and responsiveness in patients with moderate heart failure. *J Cardiovasc Pharmacol* 2003; 42: 125-131
4. Malfatto G, Branzi G, Ciambellotti F, Valli P, Bizzi C, Facchini M. Different ventricular remodelling and autonomic modulation after long-term beta-blocker treatment in hypertensive, ischaemic and idiopathic dilated cardiomyopathy. *J Cardiovasc Med* 2007; 8: 840-5
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6. Giallauria F, Fattirolli F, Tramarin R, Ambrosetti M, Griffo R, Riccio C, Vigorito C; ISYDE-2008 Investigators of the Italian Association for Cardiovascular Prevention and Rehabilitation (GICR-IACPR). Cardiac rehabilitation in chronic heart failure: data from the Italian Survey on cardiac Rehabilitation (ISYDE-2008). *J Cardiovasc Med* 2014; 15: 155-63
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Topic 7

1. Toto F, Salvioni E, Magrì D, Sciomer S, Piepoli M, Badagliacca R, Galotta A, Baracchini N, Paolillo S, Corrà U, Raimondo R, Lagioia R, Filardi PP, Iorio A, Senni M, Correale M, Cicoira M, Perna E, Metra M, Guazzi M, Limongelli G, Sinagra G, Parati G, Cattadori G, Bandera F, Bussotti M, Mapelli M, Cipriani M, Bonomi A, Cunha G, Re F, Vignati C, Garascia A, Lombardi C, Scardovi AB, Passantino A, Emdin M, Passino C, Santolamazza C, Girola D, Zaffalon D, Vizza D, De Martino F, Agostoni P; MECKI score research group. Does moderate hyperkalemia influence survival in HF? Insights from

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 5. Paolillo S, Salvioni E, Perrone Filardi P, Bonomi A, Sinagra G, Gentile P, Gargiulo P, Scoccia A, Cosentino N, Gugliandolo P, Badagliacca R, Lagioia R, Correale M, Frigerio M, Perna E, Piepoli M, Re F, Raimondo R, Minà C, Clemenza F, Bussotti M, Limongelli G, Gravino R, Passantino A, Magrì D, Parati G, Caravita S, Scardovi AB, Arcari L, Vignati C, Mapelli M, Cattadori G, Cavaliere C, Corrà U, Agostoni P; MECKI Score Research Group. Corrigendum to "Long-term prognostic role of diabetes mellitus and glycemic control in heart failure patients with reduced ejection fraction: Insights from the MECKI Score database" [*Int J Cardiol.* 2020 Oct 15; 317: 103-110. PMID: 32360652]. *Int J Cardiol.* 2021 Jun 15;333:252. doi: 10.1016/j.ijcard.2021.02.045. Epub 2021 Feb 26. Erratum for: *Int J Cardiol.* 2020 Oct 15;317:103-110. PMID: 33640418.
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MAIN COLLABORATIONS IN NATIONAL AND INTERNATIONAL RESEARCH NETWORKS

Networks

MECKI SCORE
SOCRATES
RELEVANT
PROMISES
REAL.IT
VAVIRIMS

Research Groups

LEODOR
ARS-HF
ADHF Trial
OUTSTANDING

Registries:

EUROSCORE
PARIS

The preliminary and final results of all these activities are reported in the above list of publications

The Group is affiliated to the AISC network which is the association of patients suffering from Chronic Heart Failure