European Atherosclerosis Journal
www.eathj.org

EAJ 2023;1:14-17
https://doi.org/10.56095/eaj.v2i1.28

The VIII Spring Meeting of Young Researchers of the Italian Society of Diabetology (SID), the Italian Society of Arterial Hypertension (SIIA), the Italian Society of Internal Medicine (SIMI), the Italian Society of Cardiovascular Prevention (SIPREC) and the Italian Society for the Study of Atherosclerosis (SISA)

Chiara Pavanello[1], Vanessa Bianconi[2], Lorenzo Da Dalt[3], Giovanna Gallo[4], Costantino Mancusi[5], Michele Ciccarelli[6], Alessandro Maloberti[7], Francesco Spannella[8], Fabio Fimiani[9], Damiano D'Ardes[10], Rosa Lombardi[11], Giovanni Talerico[12], Massimiliano Cavallo[13]

[1] *Centro Grossi Paoletti, Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano*

[2] *SC Medicina Interna, Dipartimento di Medicina e Chirurgia, Università degli Studi di Perugia*

[3] *Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano*

[4] *Department of Clinical and Molecular Medicine, School of Medicine and Psychology, Sapienza University, Rome, Italy*

[5] *Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy*

[6] *Department of Medicine, Surgery and Dentistry, University of Salerno, Baronissi, Italy*

[7] *Department of Medicine, University of Milano-Bicocca, Milan, Italy; Cardiology 4, "A.De Gasperis" Cardio Center, ASST GOM Niguarda Ca' Granda, Milan, Italy*

[8] *Internal Medicine and Geriatrics, IRCCS INRCA, via Della Montagnola Ancona, Italy; Department of Clinical and Molecular Sciences, University "Politecnica Delle Marche", Ancona, Italy*

[9] *Unit of Inherited and Rare Cardiovascular Diseases, AORN Dei Colli "V. Monaldi", Naples, Italy*

[10] *Institute of 'Clinica Medica', Department of Medicine and Aging Science, "G. D'Annunzio" University of Chieti-Pescara*

[11] *Department of Pathophysiology and Transplantation, University of Milan, Italy; Medicine and Metabolic Disease Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy*

[12] *Internal medicine, Policlinico Casilino, Rome, Italy*

[13] *Division of Medical Andrology and Endocrinology of Reproduction, University of Perugia and "S. Maria" Hospital, Terni, Italy*

CONFERENCE REPORT

Received 26 April 2023; accepted 28 April 2023

Corresponding Author
Chiara Pavanello: chiara.pavanello@unimi.it

The VIII Spring Meeting of Young Researchers from the Italian Society of Diabetology (SID), the Italian Society of Arterial Hypertension (SIIA), the Italian Society of Internal Medicine (SIMI), the Italian Society of Cardiovascular Prevention (SIPREC) and the Italian Society for the Study of Atherosclerosis (SISA) "*Basic and clinical research: Until grant let us apart*" was held in Rimini on April 16-18, 2023. As is usual, the Congress was organized by the young members of the above scientific societies working in the field of cardiometabolism. The Congress included five sessions discussing the latest findings in basic and clinical research on the treatment and prevention of cardiometabolic diseases. Many young researchers had the opportunity to present their scientific work in dedicated oral and poster sessions. In this report, we provide a summary of the most important topics discussed during the meeting lectures.

The meeting opened with a session organized by SISA that was focused on the role of lipoprotein metabolism beyond atherosclerosis and addressed two hot topics in the field of lipidology, namely the biological functions of proprotein convertase subtilisin/kexin type 9 (PCSK9) beyond lipid metabolism and the role of lipoprotein(a) in thrombosis and inflammation.

The role of PCSK9 in regulating low-density lipoprotein (LDL) cholesterol is well established, and it is currently the target of novel lipid-lowering therapies. However, little is known about the role of PCSK9 in other biological processes. Dr. Lorenzo Da Dalt presented available and new evidence on the role of PCSK9 beyond its known involvement in lipid metabolism, focusing on glucose metabolism and cardiomyocyte function. First, he showed that clinical studies on the role of PCSK9 in glucose metabolism are contradictory. In fact, Mendelian randomization studies suggest that loss-of-function polymorphisms of the *PCSK9* gene are associated with an increased risk of developing diabetes, whereas clinical trials do not show an increased risk of diabetes with drugs that target circulating PCSK9. Secondly, he discussed data from his preclinical studies suggesting that local expression of PCSK9 by pancreatic beta cells, but not circulating PCSK9, may be involved in the pathophysiology of diabetes. Indeed, he showed that reduced expression of PCSK9 in the pancreas promotes the accumulation of cholesterol and subsequent toxic effects in pancreatic beta cells (1). Finally, he showed new evidence that local expression of PCSK9 by cardiomyocytes, but not circulating PCSK9, is involved in the pathophysiology of heart failure (HF). He reported that selective deletion of the *PCSK9* gene in cardiomyocytes is associated with cholesterol accumulation in cardiomyocytes, leading to a rewiring of cardiac metabolism towards an anaerobic pathway (2).

Lipoprotein(a) is a pro-atherogenic lipoprotein with putative pro-inflammatory and pro-thrombotic properties (3). However, there is considerable uncertainty about the pathogenic involvement of lipoprotein(a) in venous thromboembolism and inflammatory diseases. Dr Vanessa Bianconi discussed this issue starting from the available evidence from preclinical and clinical studies on the effects of lipoprotein(a) in thrombosis and inflammation. She then reviewed the available data on the role of lipoprotein(a) in thrombo-inflammation in the context of coronavirus disease 2019 (COVID-19). Despite the lack of clear evidence on the latter issue, she showed original data from her retrospective study of a large population of patients hospitalized for COVID-19 and described the lack of any correlation between lipoprotein(a) levels and biomarkers of thrombo-inflammation, as well as the non-significant predictive role of lipoprotein(a) levels at hospital admission for the occurrence of in-hospital thrombotic events and the risk of the composite endpoint of intensive care unit admission/in-hospital death (4).

The following two sessions, organized by SIPREC and SIIA, were dedicated to the emerging evidence on pathophysiological pathways involved in the development of HF and new therapies for the treatment of HF.

Prof. Maurizio Forte discussed the molecular mechanism underlying the development of HF, with a special focus on autophagy and its stimulation by atrial natriuretic peptide (ANP), a cardiac hormone belonging to the family of natriuretic peptides, which is secreted mainly by atrial cardiomyocytes in response to mechanical stress, such as pressure or volume overload (5). In detail, he showed that ANP exerts critical pleiotropic effects in the cardiovascular system by limiting cardiomyocyte hypertrophy and death, reducing cardiac fibrosis and promoting vascular integrity. In addition, he discussed evidence that stimulation of autophagy by ANP is a protective mechanism that may underlie these beneficial effects and counteract the progression of heart disease towards HF (6).

Prof. Beniamino Pagliaro then discussed interventional treatment options for HF, illustrating the most recent advances in interventional technologies and strategies for the treatment of HF and emphasizing the importance of multidisciplinary treatment including surgery, catheter interventions and mechanical circulatory support devices (7,8).

Prof. Michele Ciccarelli described new insights into molecular mechanisms involved in cardiac remodeling and HF progression. Cardiac remodeling is characterized by several processes, including cardiomyocyte growth, neoangiogenesis, and immune system activation, which are perfectly coordinated under physiological conditions but become aberrant under pathological conditions such as hypertension and diabetes (9). The molecular mechanisms involved in adverse cardiac remodeling were reviewed, focusing on cardiomyocyte metabolic alterations that play a crucial role in the progression of HF and represent potential therapeutic targets. In this context, attention was paid to serine-threonine kinase G protein-coupled receptor kinase 2 (GRK2), a molecule involved in desensitization and downregulation of cardiac beta-adrenergic receptors and the modulation of the metabolic signature of cardiomyocytes (10).

Prof. Costantino Mancusi discussed the main mechanisms associated with the transition from hypertensive heart disease to the development of HF with preserved ejection fraction (HFpEF) and the recommended clinical approach for this condition. First, he reported epidemiological data from the Framingham Heart Study cohort (5,143 subjects), which showed that 1) hypertension precedes the development of HF in 91% of all newly diagnosed HF over a 20-year follow-up, 2) the risk of developing HF is increased 2-fold in men and 3-fold in women in hypertensive compared with normotensive subjects, and 3) the absence of hypertension, obesity, and diabetes from age 45 to 55 years is associated with up to 86% lower risk of incident HF (11). Second, he remarked that, in agreement with international guidelines, the diagnosis of HFpEF might be made using a specific approach that includes the assessment of cardiac morphological remodeling and dysfunction along with circulating levels of specific biomarkers (12). In this context, he discussed the importance of the clinical evaluation of hypertension-induced damage to target organs (in particular, left ventricular hypertrophy and decline of renal function biomarkers), as the main determinants of HFpEF. He also pointed out that in patients with hypertensive heart disease, several comorbidities, including obesity and diabetes, act synergistically to promote the development of hypertension-induced target organ damage and subsequent overt HFpEF.

The role of the immune system in metabolic liver disease was the topic of the session organized by SIMI.

Dr. Moris Sangineto showed preclinical evidence supporting

the role of immunometabolism (a link between metabolic processes and immune cell responses) as a potential therapeutic target in metabolic liver disease (13,14). In particular, he described recent findings showing that in non-alcoholic steatohepatitis (NASH) the bioenergetic profile of monocytes is profoundly altered and characterized by increased levels of glycolysis and oxygen consumption along with mitochondrial dysfunction; furthermore, the activity of complex II (succinate dehydrogenase, SDH) is high and associated with increased production of hydrogen peroxide. In addition, he reported that inhibition of hydrogen peroxide production by SDH through dimethyl malonate normalizes monocyte bioenergetics and reduces hepatic infiltration by immune cells in a preclinical model of NASH.

Dr. Andrea Dalbeni analyzed the role of the immune system in the setting of non-alcoholic fatty liver disease (NAFLD). First, he discussed literature data showing that the immune system plays a crucial role in the development of NAFLD and its progression to NASH and hepatocellular carcinoma (HCC) (15). Second, he highlighted that understanding the intricate relationship between the immune system and NAFLD/NASH/HCC is critical for developing targeted therapies that modulate the immune response to prevent the progression of metabolic liver disease. In this regard, he reported that in 2021, the combination of programmed cell death ligand 1 (PD-L1) inhibitors with vascular endothelial growth factor (VEGF) inhibitors was approved as a new first-line therapeutic strategy for HCC, providing a significant improvement in overall survival (>17 months). However, he also reported a recent meta-analysis by Pfister et al. suggesting that treatment with immune checkpoint inhibitors, either as monotherapy or in combination with bevacizumab, is associated with a significant increase in overall survival only in patients with HCC caused by viral hepatitis. Thus, he concluded that future research efforts are warranted to unravel the specific mechanisms underlying immune system involvement in NAFLD and to identify novel therapeutic targets to mitigate liver inflammation and prevent the progression of NAFLD towards NASH and HCC (16).

The last session, organized by SID, was dedicated to glucagon-like peptide 1 receptor agonists (GLP-1RAs).

Dr. Nicola Marrano discussed the pleiotropic effects of these antidiabetic drugs beyond their glucose-lowering effects. First, he showed that GLP-1RAs are characterized by pronounced anti-lipotoxic effects not only in different peripheral organs (skeletal muscle, heart, liver, adipose tissue, and pancreas) but also in the brain, where they may be crucially involved in neuroregulation and neuroprotection (17). Second, he reported that GLP-1 counteracts palmitate-induced apoptosis by inhibiting ceramide generation in human cardiac progenitor cells. Finally, he discussed the ability of GLP-1RAs to prevent lipotoxicity-induced beta-cell failure by targeting numerous dysfunctional pathways, including inflammation, oxidative stress, endoplasmic reticulum stress, and, to a lesser extent, autophagy and amyloid accumulation (18).

Finally, Prof. Alessandro Mantovani discussed the available clinical data supporting the beneficial role of GLP1RAs in metabolic liver diseases, including NAFLD and NASH. In detail, he showed that GLP-1RAs can exert direct and indirect beneficial effects on NAFLD and NASH by attenuating underlying comorbidities and additional risk factors beyond type 2 diabetes (19). Accordingly, he remarked that given the multiple pathways involved in the pathophysiology of metabolic liver disease, combining a GLP-1RA with other therapeutic approaches may be the best approach to treat these conditions (20).

The congress, traditionally, hosted an unconventional session, that in this edition was dedicated to a debate on the relationship between basic and clinical research. Dr. Marco Busnelli highlighted the need for a common language between clinicians and basic researchers by presenting virtuous and successful examples of research achieved thanks to a profitable link between the two fronts. He concluded by remarking that the strict collaboration between these two sides of science is essential to promote real progress.

This issue of *Eur Ath J* publishes the award-winning abstracts selected from the many high-profile studies presented during the congress.

References

[1] Da Dalt L, Ruscica M, Bonacina F, et al. PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance: the role of the low-density lipoprotein receptor. Eur Heart J. 2019;40:357-368.

[2] Da Dalt L, Castiglioni L, Baragetti A, et al. PCSK9 deficiency rewires heart metabolism and drives heart failure with preserved ejection fraction. Eur Heart J. 2021;42:3078-3090.

[3] Pirro M, Bianconi V, Paciullo F, et al. Lipoprotein(a) and inflammation: A dangerous duet leading to endothelial loss of integrity. Pharmacol Res. 2017;119:178-187.

[4] Bianconi V, Mannarino MR, Ramondino F, et al. Lipoprotein(a) Does Not Predict Thrombotic Events and In-Hospital Outcomes in Patients with COVID-19. J Clin Med. 2023;12:3543.

[5] Shirakabe A, Zhai P, Ikeda Y, et al. Drp1-Dependent Mitochondrial Autophagy Plays a Protective Role Against Pressure Overload-Induced Mitochondrial Dysfunction and Heart Failure. Circulation. 2016;133:1249-63.

[6] Forte M, Marchitti S, Di Nonno F, et al. NPPA/atrial natriuretic peptide is an extracellular modulator of autophagy in the heart. Autophagy. 2023;19:1087-1099.

[7] Saku K, Yokota S, Nishikawa T, Kinugawa K. Interventional heart failure therapy: A new concept fighting against heart failure. J Cardiol. 2022;80:101-109.

[8] Stone GW, Abraham WT, Lindenfeld J, et al. Five-Year Follow-up after Transcatheter Repair of Secondary Mitral Regurgitation. N Engl J Med. 2023;388:2037-2048.

[9] Gogiraju R, Bochenek ML, Schäfer K. Angiogenic Endothelial Cell Signaling in Cardiac Hypertrophy and Heart Failure. Front Cardiovasc Med. 2019;6:20.

[10] Ciccarelli M, Sorriento D, Fiordelisi A, et al. Pharmacological inhibition of GRK2 improves cardiac metabolism and function in experimental heart failure. ESC Heart Fail. 2020;7:1571-1584.

[11] Messerli FH, Rimoldi SF, Bangalore S. The Transition From Hypertension to Heart Failure: Contemporary Update. JACC Heart Fail. 2017;5:543-551. Erratum in: JACC Heart Fail. 2017;5:948

[12] Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40:3297-3317. Erratum in: Eur Heart J. 2021;42:1274

[13] Sangineto M, Grabherr F, Adolph TE, et al. Dimethyl fumarate ameliorates hepatic inflammation in alcohol related liver disease. Liver Int. 2020;40:1610-1619.

[14] Zhang IW, Curto A, López-Vicario C, et al. Mitochondrial dysfunction governs immunometabolism in leukocytes of patients with acute-on-chronic liver failure. J Hepatol. 2022;76:93-106.

[15] Peiseler M, Schwabe R, Hampe J, et al. Immune mechanisms

linking metabolic injury to inflammation and fibrosis in fatty liver disease - novel insights into cellular communication circuits. J Hepatol. 2022;77:1136-1160.
[16] Pfister D, Núñez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature. 2021;592:450-456.
[17] Marrano N, Biondi G, Borrelli A, et al. Irisin and Incretin Hormones: Similarities, Differences, and Implications in Type 2 Diabetes and Obesity. Biomolecules. 2021;11:286.
[18] Marrano N, Biondi G, Borrelli A, et al. Type 2 Diabetes and Alzheimer's Disease: The Emerging Role of Cellular Lipotoxicity. Biomolecules. 2023;13:183.
[19] Gastaldelli A, Marchesini G. Time for Glucagon like peptide-1 receptor agonists treatment for patients with NAFLD? J Hepatol. 2016;64:262-264.
[20] Mantovani A, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. Lancet Gastroenterol Hepatol. 2022;7:367-378.