European Atherosclerosis Journal
www.eathj.org

EAJ 2024;1:21-24
https://doi.org/10.56095/eaj.v3i1.60

The IX 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)

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CONFERENCE REPORT

Received 12 April 2024; accepted 29 April 2024

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The IX 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), entitled "*Research drives us crazy",* was held in Rimini on February 25-27, 2024. The Congress was organized by young researchers from the aforementioned scientific societies working in the cardiometabolic field. The Congress hosted five sessions promoted by the five societies, addressing hot topics in the prevention and treatment of cardiometabolic diseases.

More than one hundred young researchers had the opportunity to discuss their scientific work in dedicated oral and poster sessions. In this conference report, we offer an overview of the key topics covered in the presentations at the meeting.

The meeting began with an insightful session organized by SIPREC, dedicated to the role of nutraceuticals in the cardiovascular field. This session addressed evidence from both basic research and clinical studies. Although several novel pharmacological treatments have been developed over the last 20 years to slow the progression of cardiovascular diseases, prevention remains crucial. Nutraceuticals play an important role in pursuing this goal. Nutraceuticals, derived from the terms "nutrition" and pharmaceuticals", are defined as foods or parts of foods that have health-promoting effects ("pharmaceutic properties"). These include polyphenols, carotenoids, polyunsaturated fatty acids, and natural peptides (1). Although guidelines for the treatment of cardiometabolic disorders recognize the role of nutraceuticals in the prevention of atherosclerotic cardiovascular disease (ASCVD), they also stress the weakness of evidence and the lack of concordance between studies. Therefore, caution is required when interpreting the results of randomized controlled trials (RCTs). In recent years, nutraceuticals have been shown to exert important protective cardiovascular effects (2). Albino Carrizzo discussed the molecular mechanisms underlying the biological properties of nutraceuticals, dietary supplements and functional foods leading to improved endothelial function, increased nitric oxide release, reduced production of reactive oxygen species and inflammatory markers, decreased levels of lipoproteins, and inhibition and slowing of the atherosclerotic process (3).

The clinical rationale for the use of nutraceuticals was discussed by Federica Fogacci. She summarized the available evidence on the action of nutraceuticals on plasma lipids, glucose metabolism, liver enzymes, HOMA-IR and body fat and explained their potential implications in clinical practice for the treatment of cardiovascular risk factors and diseases. Among these, red yeast rice is one of the nutraceuticals with the most solid clinical evidence of efficacy, with a dose-dependent lipid-lowering efficacy supported by large meta-analyses of RCTs (4).

The use of well-studied nutraceuticals with defined molecular targets, taken at appropriate dosage and over an adequate period, can contribute to reducing individual cardiovascular risk. However, it is important to emphasize that the use of nutraceuticals should never be considered a substitute for pharmacological treatment.

Day 2 of the congress began with a session on regenerative medicine, exploring innovative approaches for cardiovascular health. Post-ischemic heart failure remains a leading cause of death and disability worldwide, making regenerative therapies a promising approach. In the session organized by SISA, Paola Cattaneo summarized the major limitations in cardiac regenerative therapies: the inability of adult cardiomyocytes to proliferate and the formation of fibrotic scars that replace damaged cardiomyocytes.

The hearts of newborns retain the ability to regenerate, leading researchers to study embryonic mechanisms governing cardiac development and the reprogramming factors that facilitate the transition to adult cardiomyocytes. Potential targets to reverse maturation may include epigenetic enzymes, which are differentially expressed during differentiation (5). DOT1L, an epigenetic enzyme catalyzing methylation of lysine 79 of histone 3, regulates specific gene regulatory networks required for left ventricular morphogenesis and postnatal cardiomyocyte cell cycle withdrawal during embryonic cardiogenesis. Studies in cardiomyocytes and mice suggest that transient inhibition of DOT1L in postnatal hearts could be a strategy to promote the re-acquisition of mitotic potential in cardiomyocytes (5).

Following this, Mario D'Oria provided an overview of the clinical applications of regenerative medicine, with a particular focus on vascular medicine. Chronic limb-threatening ischemia (CLTI) represents the most severe form of peripheral arterial disease affecting the lower limbs; it manifests with rest pain or tissue loss due to an anatomically complex multilevel atherosclerotic burden, often associated with diabetes mellitus. Therefore, it poses a significant threat to the limbs, decreases the quality of life and carries a dramatic cardiovascular risk. Endovascular treatment is currently established as a first-line option for the revascularization of CLTI patients, either alone or in combination with open surgery in hybrid interventions.

Despite the tremendous advancements in the field of revascularization techniques and technologies, which currently allow limb salvage in a significant proportion of patients, some patients fail in all attempts to achieve good in-line arterial flow to the foot and therefore usually face major amputation as the only therapeutic option to control pain or infection. These patients, also known as "no-option CLTI", may benefit from alternative regenerative medicine approaches to (re)establish sufficient distal perfusion to maintain limb viability and reduce pain (6). Despite some clinical trials that have investigated the use of regenerative medicine approaches to achieve (neo)vascularization in no-option CLTI patients, results so far remain highly heterogeneous. There are several barriers to the successful implementation of regenerative medicine methods in this area, such as the heterogeneous cellular sources that have been investigated, different protocols for delivery routes and difficulties with the assessment of cellular homing, the correct identification of the subsets of patients who would benefit most, and uncertainty about the perfusion threshold (and its duration) required to achieve sustained and meaningful clinical benefit. Newer studies are currently being undertaken and their results may reveal whether regenerative medicine will ultimately be a viable therapeutic alternative or whether it is far from the bedside.

The subsequent session, organized by SIIA, focused on the impact of extreme conditions on the cardiovascular system. Giovanni Vinetti and Grzegorz Bilo addressed the topic using the high-altitude (HA) as a model to study integrated cardiovascular regulation in health and disease, whether in natural environments or environmental chambers such as the recently-built terraXcube at Eurac Research, in Bolzano. Reduced alveolar oxygen tension induces generalised pulmonary arteriolar vasoconstriction, which increases pulmonary arterial pressure and right ventricular end-diastolic volume. In the systemic circulation, hypoxemia-induced vasodilation, chemoreflex-induced sympathetic outflow to the heart and vessels, and cold cutaneous vasoconstriction coexist. Acutely, this results in a decrease in total peripheral resistance and an increase in resting and submaximal exercise cardiac output (exclusively via heart rate), with resting arterial pressure unchanged or slightly increased (7). Chronically, the increase in haemoglobin concentration restores resting and submaximal cardiac output to sea-level values, while arterial pressure remains elevated due to increased blood viscosity and decreased local vasodilatory demand. The increased erythropoiesis compensates for the loss of plasma volume only after one month or longer exposure

to hypoxia. Therefore, total blood volume is reduced during most of the stay, as are cardiac filling pressures and left ventricular end-diastolic volume. Maximal exercise capacity is reduced both acutely and chronically, with exhaustion occurring at a lower cardiac output, heart rate, and vagal withdrawal compared to normoxia. In patients with coronary atherosclerosis, HA may trigger myocardial ischemia due to the combined effects of increased afterload, lower oxygen supply and unfavourable coronary haemodynamics (relatively reduced diastolic perfusion time because of a higher heart rate). Nonetheless, the available data suggest that acute HA exposure is safe in patients who underwent coronary revascularization even in the presence of residual noncritical lesions (8). In hypertensive patients, an increase in blood pressure may occur at HA, but this is generally mild if blood pressure is well-controlled at low altitude and treatment adjustment is only occasionally needed (9). Overall, current clinical recommendations suggest that, with some exceptions (e.g., pulmonary hypertension or cyanotic congenital heart disease), HA exposure is not contraindicated in patients with pre-existing cardiovascular disease in stable clinical conditions. Such patients should be carefully evaluated on an individual basis and, in general, should continue to take their existing medications while on HA.

Day 2 ended with a session organized by SIMI, delving into the promises and perils of artificial intelligence (AI) in cardiovascular diseases. Luca Palazzolo introduced the basic concepts of AI. He formally defined the term, starting from the Turing Test, which asks whether it is possible to distinguish between a hypothetical human or artificial interlocutor (10). Subsequently, he reflected on algorithms capable of simulating human dialogues, particularly highlighting the dialogue between Eliza and Parry, and discussed the use of AI in complex games such as chess. Basic notions of machine learning and deep learning were then provided, briefly touching upon the conception and architecture of neural networks and their application in design and content creation. The last part of the presentation involved a dialogue with ChatGPT, aiming to present AI as a statistical model capable of formulating sentences "connected by logical/mathematical operators based on probabilistic calculations", thus defining how it does not experience emotions or feelings but can still mimic these concepts. During the discussion, the audience asked the question "Can AI replace the professional figure of a doctor?". Both speakers firmly denied this possibility, asserting that AI can only support decision-making, which must still rely on personal and professional experience and knowledge.

Giulio Francesco Romiti further explored the potential of AI in enhancing the diagnosis and prognostic evaluation of ASCVD (11). For example, AI can help physicians identify the 30% of patients with coronary occlusion that escape diagnosis. However, it was underlined that AI is not a flawless machine, but only provides a probability estimate and therefore cannot replace clinical judgment. Moreover, critical aspects were highlighted - from the challenges in integrating AI into current clinical workflows to the imperative for comprehensive external validation of existing models to ensure their reliability. The need for rational use of AI in medicine was emphasized, and a specific focus was also dedicated to the diagnosis and screening of atrial fibrillation and the resulting thromboembolic risk stratification. Atrial fibrillation is the most common arrhythmia and often occurs asymptomatically, posing challenges for diagnosis and treatment. AI systems exhibit commendable performance in identifying atrial fibrillation and stratifying thromboembolic risk, thus offering a significant advance in CVD management.

The last scientific session of the meeting, organized by SID, was dedicated to sodium-glucose transport protein 2 (SGLT2) inhibitors, also known as gliflozins, in primary prevention. Valentina Genchi and Renata Risi summarized the preclinical and clinical evidence supporting the use of SGLT2 inhibitors.

SGLT2 inhibitors (SGLT2i) belong to a class of medications used in the treatment of type 2 diabetes. These drugs work by blocking the SGLT2 cotransporter, a protein found primarily in the renal tubules and responsible for reabsorbing filtered glucose in the kidneys and returning it to the bloodstream. These drugs increase the urinary excretion of glucose, thereby reducing blood glucose levels. This mechanism of action is independent of insulin and leads to an effective reduction of blood glucose, particularly in patients with type 2 diabetes, which is characterized by insulin resistance and a reduced ability to utilize glucose. In addition to their hypoglycemic effect, SGLT2i have shown pleiotropic effects that collectively exert beneficial effects on the kidneys, liver, adipose tissue and heart (12). Clinical trials and real-world data have shown that SGLT2i reduce all-cause mortality, composite outcomes of CV mortality, MACE, and hospitalization for heart failure, regardless of diabetes status, glycosuric activity, and previous CV disease (13). SGLT2i also prevent diabetes-related renal tubular damage and myocardial dysfunction by tackling apoptotic, inflammatory, and fibrotic pathways. They also improve renal filtration and reduce the progression of albuminuria in all classes of renal filtrate. Finally, SGLT2i have shown promising effects in resolving hepatic steatosis and reducing fat mass by stimulating the browning of white adipose tissue. Future challenges will be to tailor treatment to those patients who may benefit most from the use of gliflozin.

The congress, following the tradition, featured an unconventional session, which in this edition was dedicated to a debate on error and cognition in medicine. In this edition, Fabrizio Elia led the discussion on the presence of diagnostic errors in medical practice, despite technological advancements, and physicians' reluctance to acknowledge them. He explored the two modes of human reasoning, fast and analytical, highlighting how cognitive errors can impact clinical practice.

References

[1] Carrizzo A, Izzo C, Forte M, et al. A Novel Promising Frontier for Human Health: The Beneficial Effects of Nutraceuticals in Cardiovascular Diseases. Int J Mol Sci 2020; 21.

[2] Wang L, Wang N, Zhang W, et al. Therapeutic peptides: current applications and future directions. Signal Transduct Target Ther 2022; 7:48.

[3] Schiattarella GG, Cattaneo F, Carrizzo A, et al. Akap1 Regulates Vascular Function and Endothelial Cells Behavior. Hypertension 2018; 71:507-17.

[4] Cicero AFG, Fogacci F, Zambon A. Red Yeast Rice for Hypercholesterolemia: JACC Focus Seminar. J Am Coll Cardiol 2021; 77:620-8.

[5] Cattaneo P, Hayes MGB, Baumgarten N, et al. DOT1L regulates chamber-specific transcriptional networks during cardiogenesis and mediates postnatal cell cycle withdrawal. Nat Commun 2022; 13:7444.

[6] Troisi N, D'Oria M, Fernandes EFJ, et al. International Union of Angiology Position Statement on no-option chronic limb threatening ischemia. Int Angiol 2022; 41:382-404.

[7] Roche J, Rasmussen P, Gatterer H, et al. Hypoxia briefly increases diuresis but reduces plasma volume by fluid redistribution in women. Am J Physiol Heart Circ Physiol 2022; 323:H1068-H79.

[8] Parati G, Agostoni P, Basnyat B, et al. Clinical recommendations for high altitude exposure of individuals with pre-existing cardiovascular conditions: A joint statement by the European Society of Cardiology, the Council on Hypertension of the Europe-

an Society of Cardiology, the European Society of Hypertension, the International Society of Mountain Medicine, the Italian Society of Hypertension and the Italian Society of Mountain Medicine. Eur Heart J 2018; 39:1546-54.

[9] Bilo G, Villafuerte FC, Faini A, et al. Ambulatory blood pressure in untreated and treated hypertensive patients at high altitude: the High Altitude Cardiovascular Research-Andes study. Hypertension 2015; 65:1266-72.

[10] Turing AM. I.–Computing machinery and intelligence. Mind 1950; LIX:433-60.

[11] Johnson KW, Torres Soto J, Glicksberg BS, et al. Artificial Intelligence in Cardiology. J Am Coll Cardiol 2018; 71:2668-79.

[12] Wanner C, Marx N. SGLT2 inhibitors: the future for treatment of type 2 diabetes mellitus and other chronic diseases. Diabetologia 2018; 61:2134-9.

[13] Fadini GP, Longato E, Morieri ML, et al. Long-term benefits of dapagliflozin on renal outcomes of type 2 diabetes under routine care: a comparative effectiveness study on propensity score matched cohorts at low renal risk. Lancet Reg Health Eur 2024; 38:100847.