



The XVI National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITECS)

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CONFERENCE REPORT



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The XVI National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITECS) was held in Milan on September 22-24, 2022. As is now customary, the Congress was organised in collaboration with the Italian Society for the Study of Atherosclerosis (SISA) Lombardy Region. The Congress included the discussion of the most recent evidence or the most topical issues in clinical and pharmacological research as well as presentations of scientific work by young researchers.

A short report of the main issues debated during the 2022 Congress lectures is offered in this issue, for the benefit of the *European Atherosclerosis Journal* readers.

The first session focused on the role of genetics and environment in susceptibility in cardiovascular diseases (CVDs). It is well known that CVDs have a complex multifactorial aetiology. Professor Gianluigi Condorelli thoroughly discussed this issue, focusing specifically on the interaction between environmental factors and genes that contributes to the complexity of CVD. Among the environmental factors, Doctor Andrea Poli showed how the evaluation of diet-related factors has proven over time to be limited, often not so robust, and strongly confounded by environmental influences. It remains a huge chal-

lenge to define the authentic cardiovascular effects of diet, largely due to the difficulty of separating the effects of each food or food component from the overall effects of dietary habits taken as a whole. On the other hand, the role of genes, which can be considered relatively fixed, must be considered. Neither genetics nor environmental agents acting independently cause the disease. Full knowledge about an individual's genetic frame or exposures to environmental factors cannot predict with certainty the onset, progression, or severity of the disease. The genes, or rather the combination of genes determining genetic predisposition, and environmental factors causing a particular multifactorial trait may vary from person to person. The disease develops as a consequence of interactions between the baseline conditions, coded in the genotype, and exposures to environmental agents indexed by time and space that are integrated at levels above the genome. Professor Condorelli also emphasised how the technologies available for genetic investigation as well as the knowledge on the interaction between genetic and environmental factors have changed rapidly over time. This enormous bulk of data in turn requires innovative analysis techniques. Artificial intelligence methods will likely respond to this need.

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In the session dedicated to the patient at high cardiovascular risk, three different case studies have been discussed. Professor Stefano Carugo described the challenges in managing patients with polyvascular disease, emphasising the importance of a comprehensive assessment of the patient. As polyvascular disease is indicative of systemic atherosclerosis, individuals with polyvascular disease are at heightened risk for cardiovascular events in all vascular districts. However, it should be considered that multiple vessel involvement is not an uncommon feature and that the use of simple measurements, such as the ankle-brachial index (ABI), may be very useful for estimating the overall cardiovascular risk. The second case, addressed by Doctor Gianluca Perseghin, concerns the diabetic patient. Since diabetes is not only a well-known cardiovascular risk factor, but is considered a CVD-equivalent, patients with diabetes are to be considered on a par with individuals in secondary prevention. Additional features that typically accompany diabetes, such as insulin resistance, vascular alterations, inflammation, and oxidative stress, together with lifestyle aspects. While the complexity of cardiovascular prevention in the diabetic patient is well recognised, it must also be acknowledged how the most recent classes of antidiabetic drugs on the market, first of all the sodium-glucose co-transporter 2 (SGLT-2) inhibitors, have revolutionised the therapeutic algorithms. Finally, Dr Paolo Fabbrini described the cardiovascular prevention approach in the chronic kidney disease (CKD) patient. He emphasized how patients with CKD have so far had few treatment options to slow down progression, and how the introduction of SGLT-2 inhibitors had a strongly positive effect in this patient population. The link between the kidney and heart is complex. Kidney disease is often secondary to diseases leading to increased cardiovascular risk. Although hypertension and diabetes explain the vast majority of renal failure incidence in the Western world, the sum of these two causes does not justify the cardiovascular risk observed in CKD patients. The development of renal disease aggravates an already complicated cardiovascular condition. From this point of view, mention must certainly be made of uremic toxins, molecules present in very small concentrations in healthy subjects but at much higher levels in the subject with impaired glomerular filtration. These toxins can also have adverse effects on the cardiovascular system. Overall, all three presentations emphasised the need for a joint effort among cardiologists, diabetologists, and nephrologists in intervening as early as possible to delay the progression of these pathological conditions and avoid organ impairment which may further increase the risk of cardiovascular events. Despite the considerable progress in the field of therapies, much work still needs to be done in these high cardiovascular risk patients.

The Congress traditionally hosts a joint symposium of the Lombardy sections of AMD (Association of Diabetes Physicians), SID (Italian Society of Diabetology), and SISA. This year, the presentations have addressed the lipid-lowering therapy in diabetic patients and discussed the most recent evidence on the efficacy and positioning of the newest anti-diabetic drugs. In his lecture, Professor Alberto Corsini reiterated the role of diabetes as CVD-equivalent in defining CV risk. The management of cholesterol levels is of paramount importance in these patients. Lipid abnormalities beyond elevated low-density lipoprotein (LDL) cholesterol contribute to increase the risk of atherosclerotic CVD in type 2 diabetes (T2D). After almost 30 years of widespread clinical use in diabetes, statin treatment remains the cornerstone of drug therapy to prevent CVD. Ezetimibe appears to be particularly beneficial as add-on for high-risk statin-treated patients with diabetes. Similarly, currently available proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors reduce CVD risk in statin-treated diabetic patients. Bempedoic acid is an interesting

new oral agent inhibiting the cholesterol biosynthetic pathway, at an earlier step than 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, namely ATP-citrate lyase. Although one might imagine that this would result in an effect equivalent in magnitude to statins, the clinical trial experience has shown that LDL reduction with bempedoic acid is about half of that observed with statin treatment. The efficacy and safety of this molecule were recently demonstrated in a randomized trial of patients at high CV risk, of whom about 30% also had diabetes. Finally, fibrates might reduce CVD risk in patients with diabetes with high triglyceride and low high-density lipoprotein cholesterol levels and may also slow the progression of diabetic retinopathy. The two subsequent presentations by Doctor Alberto Rocca and Laura Montefusco reported the most updated evidence about SGLT2 inhibitors and glucagon-like peptide 1 (GLP1) receptor agonists, respectively. SGLT2 inhibitors were originally developed as anti-diabetic agents, with clinical trials demonstrating improved CV outcomes in diabetic patients. Secondary analyses of CV outcome trials and results from kidney outcome trials consistently reported improved kidney-related outcomes independent of T2D status and across a range of kidney functions and albuminuria. SGLT2 inhibitors are generally safe and well tolerated, with clinical trials and real-world analyses demonstrating a decrease in the risk of acute kidney injury. GLP1 receptor agonists, long-acting analogues of incretin, have shown high glucose-lowering and weight-lowering efficacy when administered as once-weekly subcutaneous injection. Moreover, they have demonstrated robust and significant reductions in CV outcomes, such as hospitalizations for heart failure. This evidence has changed the landscape for the treatment of patients with T2D. Both diabetes and cardiology guidelines have responded to this paradigm shift by including strong recommendations to use SGLT2i and/or GLP-1 RA, with evidence-based benefits to reduce cardiovascular risk in high-risk individuals with T2D.

In the session dedicated to pathology registers, Doctor Manuela Casula described the virtuous example of LIPIGEN. The LIPIGEN (Lipid TransPort Disorder Italian Genetic Network) Network was created in 2009 by the Italian Atherosclerosis Society (Società Italiana per lo Studio dell'Aterosclerosi - SISA) through its Foundation (Fondazione SISA) to promote and facilitate the clinical and genetic diagnosis of familial dyslipidaemias. Until now, the network involves more than 50 Italian centres specialized in the management of patients affected by primary dyslipidemias throughout the national territory, including paediatric clinics and LDL apheresis centres. The LIPIGEN Network structure is based on a close interaction between clinical centres, general practitioners, and patient organizations. The main objectives are to create a structured nationwide network for the identification of patients with genetic dyslipidaemias, to facilitate molecular genetic testing, and to promote research in the field. This initiative also aims at raising awareness and culture of the medical community, patients, and regulatory authorities in our country in the area of genetic dyslipidaemias and encouraging the exchange of information and knowledge according to recommendations from scientific societies. The clinical activity of the centres is complemented by the work of specialized genetic laboratories. Doctor Aldo Maggioni described registries by the European Society of Cardiology (ESC) and the Italian Cardiology Society (SIC). The Europe Observational Research Programme (EORP) was launched in 2009 by ESC to assess how European cardiology centres were adhering to the ESC guidelines and highlight any gaps that could become the topics of training interventions. Another objective was to identify rare diseases, collecting data on their characteristics, management, and outcome, to gather evidence that could support the recommendations of the guidelines in a context where large clinical trials are lacking. The

different registries implemented in Italy by the National Association of Hospital Cardiologists (ANMCO) were then described. The main advantage of these experiences is the creation of a network of clinical cardiologists collecting information from the real world. This consents to improve the quality of care and clinical outcomes. An example is acute coronary syndromes: while the GISSI-1 study showed a 13% in-hospital mortality in 1987 registries show that it has now fallen to 4%.

Finally, several hot topics were discussed during the last day.

Professor Alberico Catapano and Doctor Marta Gazzotti reviewed the evidence on homozygous familial hypercholesterolemia (HoFH) and familial chylomicronemia syndrome (FCS). The different genetic causes and the presence of a heterozygous or homozygous condition influence the phenotypic presentation, but sometimes the less severe homozygous forms are at the interface with heterozygotes. Consequently, HoFH is difficult to be confirmed without genetic testing. T Within the LIPIGEN Network, the main aim of the Italian Study Group on Homozygous FH is to provide a complete molecular characterization of HoFH patients. These results are then merged in the global registry "HoFH International Clinical Collaborators (HICC)". Familial chylomicronemia syndrome (FCS) is a very rare autosomal recessive disorder of triglyceride-rich lipoproteins, characterized by severe hypertriglyceridemia, the presence of chylomicrons in fasting condition, fasting triglyceride levels higher than 885 mg/dL, and an increased risk to develop recurrent episodes of potentially lethal pancreatitis. The extension of the LIPIGEN register to FCS is expected to improve the detection of affected subjects in Italy, promoting the use of shared protocols and validating diagnostic suspicion with genetic testing. The analysis of the collected data will allow estimating the prevalence of rare forms of genetic dyslipidaemias and the identification of clusters and/or subpopulations at higher risk, as well as to evaluate response to treatments.

Another topic which is becoming of increasing interest is Lipoprotein (a) [Lp(a)]. Lp(a) consists of an LDL particle in which apolipoprotein B100 (apoB) is covalently bound to an apolipoprotein(a) unit. The first associations between Lp(a) and coronary heart disease were reported in the early 1970s. In the last decade, following large epidemiological, genome-wide association (GWAS), and Mendelian randomization studies, together with the development of more reliable immunoassays, Lp(a) has been recognized as an important CV risk factor. Given the frequency of high Lp(a) levels and the lack of effective Lp(a) lowering therapies, the potentially modifiable Lp(a) burden should be considered one of the most important risk factors to target in the coming decade. The rationale is not only to be found in genetic studies. Recently, it has been suggested that the failure to reduce Lp(a) in subjects treated with evolocumab, a PCSK9 inhibitor able of reducing LDL-cholesterol (LDL-C) levels by 60%, may explain persistent arterial wall inflammation. The same outcome trials on PCSK9 inhibitors showed a reduction in the incidence of CV events associated with the reduction of Lp(a), which was independent of the reduction in LDL-C levels. Several experimental therapies targeting Lp(a) are in development, including an antisense oligonucleotide (pelacarsen) and two small interfering ribonucleic acid (olpasiran and SLN-360).

Three lipid-lowering therapies were then discussed. Doctor Andrea Baragetti critically evaluated recent data about omega-3 fatty acids (FAs). Eicosapentaenoic acid (EPA) and docosahexaenoic acid

(DHA) have recently undergone testing for their ability to reduce residual CV risk among statin-treated subjects. The outcome trials have yielded highly inconsistent results, perhaps attributable to variations in dosage and composition. Among high-risk patients in contemporary care, mixed n3-FA formulations showed no reduction in CV events. Notably, CV trials using icosapent ethyl (IPE), a highly purified ethyl ester of EPA, reduced CV events and progression of atherosclerosis compared with mixed EPA/DHA treatments. This inconsistency justifies the lack of consensus among experts regarding the use of omega-3 fatty acids in CVD. Professor Alberto Zambon reviewed the most recent evidence from an open-label extension trial on a PCSK9 inhibitor, specifically evolocumab. These long-term data (7 years of follow-up) confirmed and even reinforced the efficacy and safety of evolocumab. The comparison between subjects treated from the start of the trial and those who only started treatment at the beginning of the open-label phase (with comparable LDL-C levels) showed that long-term treatment with evolocumab is associated with a significant reduction in clinical outcomes, including cardiovascular mortality, compared with patients who delay starting PCSK9 inhibitor therapy. Professor Marcello Arca described the characteristics and the therapeutic role of bempedoic acid, a new cholesterol-lowering drug, recently approved by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA). Bempedoic acid is a pro-drug: it is converted to its active moiety by an enzyme which is present mostly in the liver and absent in skeletal muscles, leading to a tissue-specific effect and limiting the risk of myalgia and myopathy. Clinical trials have shown that bempedoic acid is generally well-tolerated alone, or in combination with statins, ezetimibe, or PCSK9 inhibitors. Based on the data collected so far, bempedoic acid represents an additional effective and safe option to reduce LDL-C levels; it is a cost-effective therapeutic choice, to be considered in combination therapy in patients not reaching the recommended LDL-C goal, or in statin-intolerant patients, alone or in combination with ezetimibe.

Finally, Professor Maurizio Averna addressed the issue of the combination therapy in the management of hypercholesterolemia. Prof. Averna leads the European Atherosclerosis Society Task Force in working on a statement about Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients. The starting point is the recognition of the role of LDL-C and triglyceride-rich lipoproteins as primary targets for therapeutic interventions. Although many patients achieve lipid goals with high-intensity statins, certain patients do not have an optimal response because of genetic issues, intolerance, nonadherence, or therapeutic inertia. Over the past decade, clinical trials have provided strong evidence demonstrating the effectiveness and safety of non-statin medications added to statin therapy in high-risk patients. Combining statins with ezetimibe, PCSK9 inhibitors, bempedoic acid, or inclisiran has additive effects on LDL-C reduction. Moreover, fixed-dose combination tablets lower LDL-C more effectively than two separate tablets. Current clinical guidelines are shifting towards the recommendation for combination therapy, rather than the use of statin monotherapy titrated to the highest tolerated dose to reach the goals. Combination therapies increase the efficacy and reduce the side effects associated with higher doses, increasing tolerability and leading to higher adherence. Higher efficacy and adherence will result in a higher number of patients achieving recommended goals.