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The XVII National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITeCS)

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CONFERENCE REPORT

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The XVII National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITeCS) was held in Milan on October 12-14, 2023. 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 a 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.

The first session focused on novel lipid-lowering therapies (LLTs) for the prevention of atherosclerotic cardiovascular diseases (ASCVD). Previous evidence has confirmed that the key initiating event in atherogenesis is the retention of low-density lipoprotein cholesterol (LDL-C) and other cholesterol-rich apolipoprotein-B (apoB)-containing lipoproteins within the arterial wall. Professor Giulia Chiesa emphasized the importance of LDL-C and thoroughly discussed the genetic disorders associated with abnormally elevated LDL-C levels, such as homozygous familial hypercholesterolaemia (HoFH). From a genetic perspective, she outlined the traits of mutations in HoFH patients and the status of treatments. Professor Alberto Corsini then presented the existing and novel LLTs and re-emphasized the importance of aggressive LDL-C lowering. Elevated levels of LDL-C remain one of the most closely related markers of ASCVD and a major modifiable risk factor. The combination of statins or bempedoic acid with ezetimibe could result in a greater reduction in LDL-C levels. Clinical trials for the following new lipid-lowering agents are currently underway: inclisiran [small interfering RNA (siRNA)] and MK-0616 (oral agent) as new inhibitors of the proprotein convertase subtilisin/kexin type 9 (PCSK9), obicetrapib as a new inhibitor of cholesterol ester transfer protein (CETP), pelacarsen and olpasiran as new treatments to lower lipoprotein(a) [Lp(a)] levels.

In the session dedicated to genetic dyslipidaemias, Professor Manuela Casula presented the pathology of familial hypercholesterolemia (FH) and described the virtuous example of LIPIGEN. LIPIGEN (LIpid transPort disorder Italian GEnetic Network) was established 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. To date, the network involves more than 50 Italian centres specialized in the management of patients affected by primary dyslipidaemias throughout the national territory, including paediatric clinics and LDL apheresis centres. The LIPIGEN Network structure is based on close interaction between clinical centres, general practitioners and patient organisations. The main objectives are to create a structured nationwide network to identify patients with genetic dyslipidaemias, facilitate molecular genetic testing and promote research in this field. This initiative also aims to raise awareness and culture of the medical community, patients and regulatory authorities in our country in the area of genetic dyslipidaemias and encourage the exchange of information and knowledge in accordance with the recommendations of scientific societies. The clinical activity of the centres is complemented by the work of specialized genetic laboratories. Based on the European Atherosclerosis Society (EAS) consensus statement on HoFH, Dr Maria Grazia Zenti explained the genetic complexity, prevalence and global registries of HoFH, presented the updated criteria for clinical diagnosis and recom-

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mended giving priority to phenotypic features over genotype. Dr Laura D'Erasmo then gave an overview of the evidence on hypertriglyceridaemia. She pointed out that severe hypertriglyceridemia is primarily multigenetic (familial chylomicronaemia syndrome [FCS]) and multifactorial (multifactorial chylomicronaemia syndrome [MCS]) and underlined the importance of genetic testing for the diagnosis, prognosis and the development of new therapies for FCS. Finally, Dr Federica Galimberti presented the current results and future perspectives of the LIPIGEN paediatric group. This group focuses on improving the detection, diagnosis and management of paediatric FH patients. To date, 1602 children and adolescents have participated in this study and 93.3% of them have undergone genetic testing. More than 200 different heterozygous LDLR variants have been identified, with a more severe phenotype in individuals with receptor-negative compared to those with receptor-detective, and large variability in LDL-C levels even among subjects with the same causative variant. Compared to adults, paediatric FH patients are less characterized in terms of physical examination (tendon xanthoma and/or arcus cornealis) and the personal history of premature coronary artery disease (CAD), whereas they could be detected by checking LDL-C levels and physical examination of their first-degree relatives. The study is still ongoing, with a focus on comparing the efficacy of nutraceuticals and LLTs and improving the screening and diagnosis of paediatric FH patients.

An increased focus on residual risk factors in the session dedicated to content beyond the guidelines. In this lecture, Professor Giovanna Liuzzo presented the contribution of inflammation in the development of ASCVD and specific groups of patients characterised by increasing systemic inflammation. She reviewed the clinical attempt to use anti-inflammatory therapies in cardiovascular (CV) prevention and discussed the recent approval of colchicine in patients with CAD and the innovative therapies related to inflammation. Professor Alberico Luigi Catapano then emphasized the fundamental tenets of LDL-lowering therapy, which should be based on the risk rather than the causes of risk, and the future challenges in reducing CV risk. Except for the principle "lower is better" in controlling LDL-C concentration, he suggested starting treatment as early as possible to reduce the lifetime CV risk and mentioned some possible improvements in future therapeutic strategies (such as controlling the levels of apoB and Lp(a)).

The congress traditionally hosts a joint symposium of the Lombardy sections of the AMD (Association of Diabetes Physicians), the SID (Italian Society of Diabetology), and SISA. This year, the presentations have focused on the management of other residual risk factors (triglycerides [TG]) and the use of polytherapy in patients with diabetes. In this session, Professor Paolo Magni discussed the epidemiological and genetic evidence for the association between TG or remnant cholesterol and CVD, and the status of TG-lowering treatments, including fibrates, omega-3 fatty acids, the antisense oligonucleotide (ASO) targeting apoC-III (volanesorsen), and the monoclonal antibody targeting angiopoietin-like protein 3 (ANGPTL3) (evinacumab). Dr Marco Mirani discussed the metabolic processes in diabetic patients and the therapies currently available for this condition. He also mentioned that tirzepatide, a dual agonist of glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), may be considered for metabolic control and weight loss. In addition, a case study was presented by Dr Laura Molteni to discuss the possibility of polytherapy for people with diabetes and other conditions.

During the last day, several hot topics related to LLTs were discussed.

Professor Alberto Zambon discussed the safety and efficacy of PCSK9 inhibitors (PCSK9i), reviewing data from clinical trials conducted in Europe and Italy, as well as data from real-life settings. Previous studies have clearly shown that PCSK9i, whether in patients with or without FH, can significantly lower LDL-C levels. Patients receiving PCSK9i treatment had higher adherence and persistence and a remarkable reduction in major adverse cardiovascular events (MACE). According to real-world data from Italy, ~79% of very-high risk patients with ASCVD did not achieve LDL-C goal according to current guidelines. Thus, the 'high-intensity statin treatment' and 'the wait and see paradigm' should be abandoned in favour of treating all very high- and extremely high-risk patients with combination therapy as the basic standard of care. Dr Andrea Baragetti gave an overview of the properties of Lp(a). Lp(a) is an LDL-like particle in which apo(a) is bound to apo(B). Epidemiological studies, meta-analyses, Mendelian randomization and genome-wide association studies have clearly shown that Lp(a) is an independent and causal risk factor for ASCVD. It has been hypothesized that there may be a linear relationship between elevated Lp(a) levels and an increased risk of developing CV events. Therefore, including Lp(a) levels in risk estimation and clinical measurement may contribute to treatment decisions, especially in patients with co-morbidities and genetic forms associated with elevated CVD risk. Currently, lipoprotein apheresis is the only option to significantly reduce Lp(a) levels, which can be considered in patients with very high Lp(a) levels and progressive CVD despite optimal management of other risk factors. Randomized clinical trials of PCSK9i and CETP inhibitors, which reduce Lp(a) levels by 20% to 25%, have consistently failed to demonstrate that lowering Lp(a) levels reduces the risk of cardiovascular events beyond what would be expected from the equivalent reduction in LDL-C and other apo B–containing lipoproteins alone. Clinical trials of novel Lp(a)-lowering therapies (antisense oligonucleotide- pelacarsen, siRNA- olpasiran and SLN360, and oral small molecule - muvalaplin) are ongoing. In the absence of specific Lp(a)-lowering therapies, early 'traditional' risk factor management is recommended for individuals with elevated Lp(a), taking into account their absolute CV risk and Lp(a) level. Dr Aldo Pietro Maggioni then briefly discussed the residual risk associated with TG and the clinical benefits of treatment with omega-3 fatty acids, particularly icosapent ethyl (a highly purified form of eicosapentaenoic acid), according to the results of the REDUCE-IT trial. Compared to placebo, icosapent ethyl 4 g/day significantly reduced first and total CV events by 25% and 30%, respectively. This treatment is safe and well tolerated but may associated with a slight increase in the incidence of atrial fibrillation.

In the last part, Professor Alberico Luigi Catapano critically evaluated the latest data on bempedoic acid. Bempedoic acid is a novel, once-daily oral lipid-lowering agent that is activated in the liver to bempedoyl-CoA, which subsequently inhibits ATP citrate lyase, an enzyme upstream of enzyme 3–hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the target of statins, in the cholesterol biosynthesis pathway. Bempedoic acid lowered plasma LDL-C and TG levels, and attenuated atherosclerosis in mice and miniature pigs. In phase 2 and 3 clinical trials, bempedoic acid treatment effectively lowers LDL-C levels as monotherapy, combined with statin or ezetimibe, and in statin-intolerant patients. This treatment provides an additional therapeutic option to lower LDL-C in high CV-risk patients. Next, Professor Stefano Carugo underlined that prescribed combination therapy has a greater and more favourable impact on prognosis, adherence and persistence. It is recommended to use combination therapy as the first-line strategy in patients with high CV risk. Finally, Professor Giuseppe Danilo Norata presented the clinical trials evaluating the safety and efficacy of a PCSK9 gene silencing approach – inclisiran. Inclisiran is an siRNA that inhibits the translation of the PCSK9 protein, leading to a reduction in LDL-C levels. Clinical trials have shown that inclisiran significantly reduces LDL-C levels, also in FH patients, but its long-term safety and clinical benefit remain to be established. He also described the use of anti-ANGPTL3 treatments (evinacumab and vupanorsen) in patients with HoFH.