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

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CONFERENCE REPORT

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The XVIII National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITeCS) was held in Milan on October 10-12, 2024. 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.

The first session on the Pre-Congress Day mainly focused on the new insights from atherosclerotic cardiovascular research. Atherosclerotic plaque formation begins with the accumulation of low-density lipoprotein (LDL) particles in the intima of large arterial blood vessels. Within the intima, LDL particles are oxidatively modified, which renders them immunogenic and triggers an early inflammatory response, including endothelial cell activation. Doctor Lorenzo Da Dalt introduced the role of lysosomes in the interaction between metabolic modulation and immune cell function. Lysosomes are membrane-enclosed organelles that function as metabolic sensors and signalling platforms in the immune-metabolic reprogramming of macrophages and other immune cells in atherosclerosis. Growing evidence indicates that lysosomal dysfunction is one of the hallmarks of lipids accumulation and macrophage activation in the atherosclerotic plaque. He presented the mechanism (restoring lysosomal acidity) and animal experimental data on the use of acidic nanoparticles to treat non-alcoholic fatty liver disease (NAFLD), the impact of lysosomes on adaptive immunity through activating mTORC1 (the mammalian target of rapamycin), as well as the novel pharmacological approaches targeting lysosomes. Next, Doctor Chiara Macchi outlined the effect of mitochondria on driving atherosclerosis. Mitochondria are multifaceted organelles that regulate various important cellular processes including metabolism and ATP generation. Mitochondrial function is required for normal vascular cell growth and function. She began by presenting the results of animal studies, and concluded that mitochondrial dysfunction leads to apoptosis and favours plaque rupture. Then, she explained the role of mitochondria in endothelial cells, macrophages, and vascular smooth muscle cells, revealed the underlying mechanisms of mitochondrial dysfunction in pro-atherosclerosis microenvironment, which could in future lead to the development of novel strategies to prevent atherosclerosis. Finally, Doctor Martino Alfredo Cappelluti presented the epigenome editing through a hit-and-run platform. Genome editing is a type of genetic engineering in which DNA is inserted, deleted, modified or replaced in the genome. He introduced the CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats) technology and its new application in transcriptional editing. In addition, the results of a case study of silencing Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) gene in vivo were presented.

In the session dedicated to genetic dyslipidemia, Professor Manuela Casula presented the pathology of familial hypercholesterolemia (FH) and its closely link to cardiovascular disease (CVD). She underlined the importance of early diagnosis and treatment initiation to prevent FH adverse outcomes. Then, she introduced the

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virtuous example of the Italian register LIPIGEN. The LIPIGEN (LIpid transPort disorder Italian GEnetic 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 60 Italian centres specialized in the management of patients affected by primary dyslipidemias throughout the national territory, including paediatric clinics. Data of more than 11,000 patients are collected; about 20% are under the age of 18. The analysis of these data allowed to outline the current gaps in FH diagnosis, as for example: the limited ability of clinical algorithms to identify affected individuals, or the presence of unknown genetic and/or environmental factors could result in a FH phenotype consistent with that observed in monogenic FH. The results from FH awareness survey addressed to both clinicians and FH patients were presented in the end of her lecture. Next, Professor Laura D'Erasmo explained the structure and content of consensus document on diagnosis and management of FH from SISA. She started with the definition, pathology, and classification of FH, followed with the novel technologies in FH diagnosis and current drug treatment strategies. FH includes disorders with a semi-dominant or recessive pattern of inheritance, which were formerly defined as Autosomal Dominant Hypercholesterolemia (ADH) and Autosomal Recessive Hypercholesterolemia (ARH). *LDLRAPOB*, *PCSK9*, *LDLRAP1* are major FH candidate genes, while apolipoprotein E (*APOE*), ATP-binding cassette sub-family G member 5 (*ABCG5*), *ABCG8*, and *LIPA* were involved in other genetic disorders of lipid metabolism mimicking the FH phenotype. She introduced the molecular analysis using next-generation sequencing (NGS), which improved the genetic analysis of FH patients allowing to analyse several genes at the same time; the imaging techniques, which could help subclassify FH patients. Finally, she concluded that the updated consensus document provided a pragmatic guidance to improve early diagnosis and to plan appropriate LDL-C lowering therapies. The information about the LIPIGEN paediatric group was presented by Doctor Cristina Pederiva. The LIPIGEN paediatric group is a subgroup of LIPIGEN network involving 39 centres, both specially dedicated to paediatric patients or adult clinics dealing with paediatric patients. The main objective is to improve the detection, diagnosis, and management of paediatric FH patients. Currently, more than 2,000 children and adolescents have been enrolled in the study. She introduced the results at the current stage and future perspective of LIPIGEN paediatric group, the investigation is still ongoing. The rational use of drugs controlling hypercholesterolemia has been in the forefront of our thoughts. Professor Alberico Corsini provided us with the novel therapeutical strategies of traditional lipid-lowering treatments (LLT). He emphasized that the addition of ezetimibe to statins or bempedoic acid reduced LDL-C levels to a greater extent than monotherapy, which was also associated with a reduced risk of CVD. Furthermore, PCSK9 monoclonal antibodies (PCSK9mAbs) – alirocumab and evolocumab, as well as small interfering RNA - inclisiran can also be considered as part of the combination. In the end, he introduced the data from ongoing clinical trials for newly developed treatments including oral PCSK9 inhibitor – MK-0616 and CETP inhibitor – obicetrapib. Based on this summary of the current therapeutical strategies, Doctor Gabriella Iannuzzo and Doctor Laura D'Erasmo focused on those drugs mainly used for homozygous FH (HoFH) patients. HoFH is a rare and life-threatening disease originally characterized by bi-allelic pathogenic variants of the genes involved in FH aetiology. In most cases, the gene involved is *LDLR*, and variants result in a defective LDLR function. Thus, HoFH patients had poor response to those therapies targeting LDLR, such as statins, ezetimibe, and PCSK9 inhibitors. Evinacumab is an inhibitor of angiopoietin-related protein 3 (ANGPTL3). Clinical trials indicated that evinacumab consistently and substantially reduced LDL-C levels regardless of LDLR function and was generally well tolerated. The efficacy and safety of evinacumab in HoFH population were also confirmed by the LIPIGEN group. Lomitapide, an inhibitor of microsomal triglyceride transfer protein (MTP), can decrease very low-density lipoprotein (VLDL) assembly and secretion in the liver, consequently, reduce LDL-C levels through a LDLR independent pathway. They finally concluded that although these two drugs were both approved for the treatment of HoFH, further investigations are required to understand their long-term efficacy and safety in the real world.

An increased focus on novel treatments targeting PCSK9 dedicated to the second day. Starting from monoclonal antibodies (mAbs), Prof Alberto Zambon overviewed the European and Italian data on lipid-lowering efficacy and therapeutical adherence of PCSK9mAbs in real-life and clinical trials. The real-life data showed that PCSK9mAbs were safe and effective in clinical practice, leading to very high adherence and persistence to therapy and achievement of recommended LDL-C target, especially when used as combination therapy. Data from clinical trials confirmed the previous findings and highlighted the safety of alirocumab in vulnerable population identified before randomization. Additionally, intensive and early lipid-lowering therapy using PCSK9mAbs in patients with acute coronary syndrome (strike early–strike strong strategy) is safe and effective in clinical practice and associated with a reduction of residual CV risk, due to its contribution to coronary plaque stability. Finally, he outlined that the combination of statins and ezetimibe, or even the addition of PCSK9 inhibitors or bempedoic acid, should be considered a first-line treatment option for patients at high risk of CVD. Next, Professor Maurizio Averna shared with us the origins, development and future of oral PCSK9 inhibitors research. MK-0616 is an orally bioavailable macrocyclic peptide that inhibits binding of PCSK9 to the LDLR. In phase 1 trials, once-daily dose of 20 mg MK-0616 provided a >93% geometric mean reduction of free plasma PCSK9, and maximum 61% geometric mean reduction of LDL-C on top of statin treatment. The results form its phase 2 trial confirmed that MK-0616 significantly reduced LDL-C by 60.9% from baseline and was well tolerated. Notably, it also reduced lipoprotein(a) [Lp(a)] levels by around 20%. All this information indicates that MK-0616 has the potential to be a novel and highly effective option for patients requiring intensive LDL-C reduction. The success of this drug promotes the development of oral PCSK9 inhibitors; several recently designed oral PCSK9 inhibitors are undergoing clinical studies. The gene silencing approach for PCSK9 was presented by Professor Giuseppe Danilo Norata. Small interfering RNAs (siRNA) selectively and catalytically silence the translation of their complementary target messenger RNAs (mRNAs) in a sequence-specific manner through the formation of effector RNA-induced silencing complexes. Inclisiran is a chemically synthesized siRNA molecule that has produced sustained hepatocyte-specific, PCSK9-specific RNA silencing. Comparing to PCSK9mAbs, inclisiran provides a long-lasting reduction in LDL-C with injections on day 1, day 90, and every 6 months. In addition, inclisiran was well tolerated, with only a small number of patients developing anti-drug antibodies in long-term studies (5.5% in the ORION-8 trial). He summarized that inclisiran could be a robust option to lower LDL-C up to 50% on top of other LLT. Finally, Professor Aldo Pietro Maggioni introduced the OMERO study. This is a multicentre study evaluating the long-term efficacy and tolerability of alirocumab in patients with severe hypercholesterolemia in an Italian real-life setting. The objective is to help maximise the proportion of

patients achieving the LDL-C target, and the follow-up duration will be about 3 years for all patients. Notably, this study has pioneered the implementation of digital tools such as electronic informed consent (eIC), with multimedia tools (such as audio, video, links) integrated with electronic trial master file (eTMF), electronic case report form, and the electronic patient-reported outcome (ePRO) app, thereby streamlining the data collection process.

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 focused on the therapeutical strategies in patients with specific disease. In this session, Doctor Stefano Ciardullo discussed the epidemiological and clinical evidence for increased CV risk in patients with metabolic dysfunction associated steatotic liver disease (MASLD). This disease is characterized by steatosis, inflammation and fibrosis of the liver, so treatment strategies focused on these three points. He presented the mechanism and clinical data of thyroid hormone receptor-beta (THR-β) agonist resmetirom, and antidiabetic medications such as incretine, semaglutide, tirzepatide, concluded that the management of MASLD should focus on both glucose-lowering/weight loss and liver-directed therapy. Doctor Silvia Cecilia Severgnini overviewed the novel technologies for patients with type 2 diabetes mellitus (T2DM). T2DM is characterized by high blood sugar, insulin resistance, and relative lack of insulin. The development of continuous glucose monitoring (CGM) had facilitated the routine care of patients with T2DM who are on basal insulin-only regimens or are managed with other medications. CGM could minimize hypoglycaemia while allowing efficient adaptation and escalation of therapies and enables target values of glycated haemoglobin A1c (HbA1c). In the Lombardy Region, guidelines for the use of glucose monitoring techniques in patients with T2DM entered into force on 1st January 2024. In the last part of this session, Professor Paolo Magni talked on the molecular mechanism between inflammation and atherosclerosis, the impact of obesity and diabetes on this progression, and possible treatment strategies. He outlined that the CV prevention should also include the assessment on inflammatory biomarkers (such as C-reactive protein) and factors released or secreted by adipose tissue (leptin, adiponectin, resistin, etc.). In terms of disease diagnosis, novel approaches such as multi-omics and nuclear magnetic resonance (NMR) should be considered.

More personalized and precise strategies of CV prevention was discussed on the final day. The different responses to LLT in women and men was presented by Professor Fabrizia Bonacina. Sex differences in human could be genetic determinate, i.e. XX or XY chromosomes, or by the gonads, which are differentiated by hormones (testosterone or estrogen). Both estrogen and X chromosome have beneficial effects on the atherosclerotic plaque and hepatic lipid metabolism. However, according to epidemiological data, mortality from CVD appears to be higher in women than in men. The evidence from randomized controlled trials indicated that statins with or without ezetimibe, bempedoic acid and PCSK9 inhibitors had similar lowering effect on lipid concentrations and major CV events in both men and women. She concluded that the higher incidence of mortality in women could be attributed to their lower adherence to treatments, a female-specific strategy is required in CV prevention. Next, Doctor Federica Galimberti explained the comparison between LDL-C, apolipoprotein B (apoB) and triglyceride (TG) levels in CV risk assessment. ApoB is the structural framework of all lipoprotein particles. Evidence from population studies showed high variability of apoB at specific levels of LDL-C and TG coupled with meaningful differences in 10-year atherosclerotic CVD rates, suggesting that the clinical benefit of lowering LDL-C and TG levels may be proportional to the absolute change in ApoB. She summarized that apoB should be routinely measured in clinical practice and considered in risk prediction, as it best recapitulates the individual CV risk. The story of bempedoic acid was recounted by Professor Alberto Corsini. Bempedoic acid is a recent, once-daily oral lipid-lowering agent that activated in the liver to bempedoyl-CoA, which subsequently inhibits ATP-citrate lyase, an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Notably, it is not activated in the skeletal muscle, thus does not result in muscular adverse effects. No dose adjustments are necessary for patients with mild or moderate renal impairment. Clinical trials had identified its efficacy regarding the LDL-C reduction and CV events, as well as its safety. An addition of bempedoic acid on top of existing LLT is recommended for intensive LDL-C lowering. In the last session, Professor Stefano Carugo explained the single-pill combination for patients with hypertension. Hypertension has persisted to be the leading cause of CV mortality. He described the types of antihypertensive drugs and the current strategy of using combination therapy with more than one drug for high-risk patients. In addition, single-pill combination therapy appeared to provide better control of blood pressure than free combination. Finally, he outlined that it is important to improve patient compliance with multiple therapies, so the next step is to develop new technologies such as antisense oligonucleotides (ASO), siRNA or mAbs for antihypertensive treatment. Next, Professor Andrea Baragetti provided the new insights into cholesterylester transfer protein (CETP) inhibitors. CETP inhibitors are known to raise high-density lipoprotein (HDL) cholesterol and reduce the CV risk. However, previous genetic studies and clinical trial evidence have not shown a causal relationship between HDL or conventional CETP inhibitors and reduced risk of CVD. He presented the data on the possible apoB-lowering effects of CETP inhibitors, as well as published and ongoing clinical trials of the novel drug obicetrapib. The pathology and treatment strategies of lysosomal acid lipase (LAL) deficiency was presented by Professor Laura Calabresi. The primary function of this lysosomal enzyme is to hydrolyse lipids such as TG and cholesterol esters and release free fatty acids and free cholesterol in the cytosol. Patients affected by LAL deficiency, an autosomic recessive disease, are characterized by lipid accumulation predominantly in liver, intestine, spleen, adrenal glands, bone marrow, and macrophages. The disease is caused by variants in the *LIPA* gene and, when early identified, can be controlled by enzyme replacement therapy, LLTs or liver transplantation. In the last session, Professor Massimiliano Ruscica summarised the evidence on Lp(a). Large epidemiological studies, Mendelian randomized studies, and genome-wide association studies confirmed that elevated Lp(a) concentration is an independent risk factor for CVD. He outlined the importance of Lp(a) measurement in CV risk assessment and introduced the ongoing clinical trials of novel Lp(a)-lowering treatments.