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

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CONFERENCE REPORT

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The XIX National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITeCS) was held in Milan on October 23-25, 2025, and, as in previous years, was organised in close collaboration with the Italian Society for the Study of Atherosclerosis (SISA), Lombardy Regional Section. In line with previous editions, the meeting brought together clinicians and researchers to discuss advances in atherosclerosis and cardiometabolic diseases, with a particular focus on translational research and innovative therapeutic strategies. In the context of the SISA Regional Meeting on October 23, 2025, the first session entitled "Beyond LDL: Ischemic cardiovascular disease", was devoted to residual risk factors beyond low-density lipoprotein cholesterol (LDL-C). The session highlighted how inflammatory activation, thrombotic pathways and genetically determined lipoprotein abnormalities contribute to plaque destabilization and ischemic complications, and how these mechanisms are increasingly being framed as causal drivers rather than simple markers of cardiovascular risk.

In the first lecture, Giuseppe Danilo Norata discussed the role of inflammation in cardiometabolic diseases and atherosclerotic cardiovascular events, highlighting atherosclerosis as a chronic inflammatory condition driven by hypercholesterolaemia and apoB-containing lipoproteins that activate innate and adaptive immune responses in the arterial wall. He focused on high-sensitivity C-reactive protein (hsCRP) as a marker of vascular inflammation and residual inflammatory risk, noting its independent association with cardiovascular events even in patients receiving lipid-lowering therapy. The lecture addressed whether cardiovascular prevention should target LDL-C, inflammation, or both, reviewing evidence that lipid-lowering therapies variably reduce hsCRP and suggesting that combined lipid and inflammatory modulation may offer added benefit in selected high-risk patients. Finally, Norata reviewed anti-inflammatory strategies targeting the IL-1β-IL-6-CRP axis and the NLRP3 inflammasome, presenting results from CANTOS, COLCOT, and LoDoCo2 and emphasized ongoing studies aimed at defining inflammation as a causal driver and therapeutic target in atherosclerotic disease.

Next, Marina Camera focused on the contribution of platelets and coagulation to cardiovascular events in patients with coronary artery disease. She highlighted that, despite optimal antiplatelet therapy, a substantial proportion of patients still experience adverse thrombotic events and that current clinical risk scores do not incorporate direct measures of platelet activation or thrombotic risk. Drawing on experimental and clinical data, she showed how platelets initiate and amplify atherothrombosis, not only by forming occlusive thrombi on disrupted plaques, but also by sustaining vascular inflammation and plaque growth through adhesion, secretion and expression of procoagulant molecules. She then discussed the search for soluble and platelet-associated biomarkers of platelet activation, with particular emphasis on tissue factor-positive platelet subsets, which in recent studies emerged as promising candidates to improve thrombotic risk stratification and may help guide more personalized antiplatelet strategies in high-risk patients. In the final talk of the morning session, Andrea Baragetti focused on lipoprotein(a) (Lp(a)) illustrating its distinctive structural and metabolic features and its strong genetic determination. He reviewed epidemiological and Mendelian randomization data showing a continuous, independent association between elevated Lp(a) levels and major cardiovascular outcomes, including myocardial infarction, stroke and aortic valve

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stenosis, and discussed how Lp(a) refines risk assessment beyond LDL-C and C-reactive protein, particularly in high-risk or genetically predisposed individuals. The lecture also covered current challenges in Lp(a) measurement, the concept of lifelong "Lp(a) burden" and the emerging pipeline of targeted Lp(a)-lowering therapies such as antisense oligonucleotides and small-interfering RNAs, which are expected to clarify whether selective Lp(a) reduction translates into additional cardiovascular benefit and to support earlier, more intensive LDL-C–lowering strategies in patients with markedly elevated Lp(a).

In the session dedicated to dyslipidaemias, Manuela Casula presented Lombardy data from the Italian LIPIGEN registry. The LIPIGEN (LIpid transPort disorder Italian GEnetic Network) was established in 2009 by the Italian Society for the Study of Atherosclerosis through its Foundation (Fondazione SISA) to promote and facilitate the clinical and genetic diagnosis of familial dyslipidaemias. She showed how regional enrolment contributes substantially to the overall cohort, providing detailed information on age at diagnosis, lipid profiles, genetic variants and treatment patterns in patients with suspected or confirmed familial hypercholesterolaemia. Emphasis was placed on the persistent diagnostic delay, the under-recognition of paediatric and young adult cases and the suboptimal achievement of LDL-C targets despite lipid-lowering therapy, underscoring the need for broader cascade screening and earlier, more intensive treatment strategies in high-risk families.

Maurizio Averna followed with an overview of current therapy for familial hypercholesterolaemia (FH) across the spectrum from heterozygous to homozygous forms and other severe LDL-C disorders. He summarised guideline-based treatment algorithms, stressing early initiation and lifelong intensification of lipid-lowering therapy using maximally tolerated statins, ezetimibe, PCSK9 inhibitors and bempedoic acid, and discussed the role of more advanced options, including lipoprotein apheresis and novel agents, in patients who remain far from LDL-C targets or present with particularly high cardiovascular risk.

Alberto Zambon then presented the recent SISA consensus document on hypertriglyceridaemias, focusing on their classification, clinical implications and management. He outlined the distinction between moderate and severe hypertriglyceridaemia, highlighting the dual concern of cardiovascular risk and acute pancreatitis, and stressed the importance of identifying secondary causes such as diabetes mellitus, obesity, alcohol intake excess and use of specific drugs. The talk summarised recommended therapeutic approaches, from lifestyle modification and optimisation of glycaemic control to the use of statins, fibrates, omega-3 fatty acids and newer agents, with an emphasis on tailoring treatment intensity to triglyceride levels and overall cardiovascular risk profile.

Next, Alberico Luigi Catapano turned to possible therapeutic approaches to reduce Lp(a) levels, framing elevated Lp(a) as a key contributor to residual cardiovascular risk in patients who are otherwise optimally treated for LDL-C. He briefly reviewed the limitations of currently available, non-specific strategies and focused on the development of targeted Lp(a)-lowering agents, in particular antisense oligonucleotides and small-interfering RNAs directed against apolipoprotein(a), which have shown profound and sustained reductions in Lp(a) levels in early-phase trials and are expected to clarify, through ongoing outcome studies, whether selective Lp(a) lowering translates into incremental cardiovascular benefit.

Chiara Pavanello then focused on lomitapide as a therapeutic option for patients with homozygous familial hypercholesterolaemia (HoFH). She described its mechanism of action as an inhibitor of microsomal triglyceride transfer protein, which reduces very-low-density lipoprotein assembly in the liver and thereby lowers LDL-C through an LDL-receptor-independent pathway, making it particularly valuable in patients with minimal or absent LDL-receptor function. The presentation reviewed efficacy data showing substantial LDL-C reductions in HoFH, as well as key safety considerations such as hepatic steatosis and gastrointestinal adverse effects, and stressed the importance of careful patient selection, monitoring and combination with other lipid-lowering strategies in specialised centres.

Marcello Arca concluded the session with a focus on evinacumab as a treatment option for patients with HoFH. He described evinacumab as a fully human monoclonal antibody targeting angiopoietin-like protein 3 (ANGPTL3), capable of producing marked LDL-C reductions through mechanisms largely independent of LDL-receptor activity and therefore particularly effective in patients with HoFH due to LDL-receptor deficiency. The lecture summarised pivotal clinical trial data demonstrating substantial and sustained LDL-C lowering and a favourable safety profile and discussed how evinacumab can be integrated with other lipid-lowering therapies and apheresis in specialised centres to improve control of extreme LDL-C elevations and cardiovascular risk in these patients.

The second day of the conference, which was the first of the XIX National Congress of the SITeCS, was opened with a session focused on proprotein convertase subtilisin/kexin type 9 (PCSK9). The opening lecture was held by Massimiliano Ruscica who has recapitulated current evidence about the main biological features and roles of PCSK9. Particularly, he has emphasized PCSK9 pivotal role in cholesterol metabolism through its control of LDLR degradation. Both genetic and pharmacological modulations of PCSK9 critically influence plasma LDL-C levels and cardiovascular (CVD) risk, establishing PCSK9 as a key biological and therapeutic target in dyslipidaemia management.

To this aim the use of anti-PCSK9 monoclonal antibodies, such as alirocumab and evolocumab, has been revealed effective in reducing circulating LDL-C levels and mitigating CVD risk as illustrated by Alessandro Maloberti. His lecture has reported an update of data obtained from clinical studies based on the application of such lipid-lowering therapies. Specifically, Alessandro Maloberti highlighted how anti-PCSK9 monoclonal antibodies can reduce the incidence of major adverse cardiovascular events (MACE) when used in appropriate patient populations, including heterozygous familial hypercholesterolemia (HeFH), atherosclerotic CVD (ASCVD) with elevated LDL-C and tolerating statin therapy, as well as in statin intolerant patients.

In addition to the use of anti-PCSK9 monoclonal antibodies, the application of small interfering RNA (siRNA) against PCSK9 has been revealed crucial to improve therapeutic adherence and long-lasting effect while reducing the injection frequency. This topic has been addressed by Gianluca Perseghin who showed some of the latest results from clinical studies about siRNA against PCSK9, namely inclisiran and solbinsiran. He has illustrated major advantages of siRNA compared to statins, as statins have to be administered to patients daily, compared to siRNA (one injection every six months), and are not supposed to be administered to statin-intolerant patients. One of the major challenges for siRNA is also to improve the long-term adherence to the treatment and cardiovascular outcomes.

A substantial resignation regarding novel drug therapies for the treatment of dyslipidaemias was thereby carried out by Alberto Corsini. Indeed, in recent years therapeutical options for the treatment of dyslipidaemias have been expanded well beyond statins. Accordingly, novel pharmacological tools are based on protein-targeting antibodies, RNA-based gene silencing, enzyme inhibitors, and emerging gene-editing technologies. While gene-editing based technologies targeting PCSK9 and ANGPTL3 are still under experimental investigation, the combination of classical lipid-lowering drugs (*i.e.* statins) with novel

pharmacological approaches, such as ezetimibe and PCSK9-based agents has allowed more precise, durable, and individualized lipid control, particularly for high-risk patients and those with inherited lipid disorders. The next frontier of therapeutic approaches for dyslipidaemias will aim at genetic risk profiling to guide therapy selection in the context of personalized medicine.

The session dedicated to PCSK9 was concluded by Marcello Arca who held a lecture on an update of the monitoring registries by AIFA (Agenzia Italiana del Farmaco). He covered updates related to real-world data collection on effectiveness, adherence, and treatment patterns for advanced lipid-lowering drugs, specifically focused on PCSK9-based agents. Accordingly, inclisiran has been recently integrated into AIFA monitoring. Moreover, AIFA has renewed the reimbursement terms for the usage of inclisiran with defined indications consistent with the registry criteria (*i.e.* primary and secondary prevention with specified LDL-C thresholds).

The following session of the SITeCS congress was dedicated to risk factors involved in CVD, specifically to ASCVD. The main lecture of this session was conducted by Stefano Bellosta and followed by an open discussion about the lecture topic. He provided a detailed panel of experimental data obtained from *in vitro* evidence showing the adverse impact of cigarette smoke and new tobacco products on the cardiovascular health. Specifically, Stefano Bellosta showed the direct effects on atherosclerosis as smoke and new tobacco products were found to induce smooth muscle cell phenotypic alteration and migration, overall contributing to the formation of the atherosclerotic plaque.

The second part of the conference day was focused on a joint symposium between AMD (Associazione Medici Diabetologi), SID (Società Italiana di Diabetologia), SISA Lombardy and SITeCS. This session was opened by the lecture of Matteo Conti, who focused his talk on the application of the novel drugs for the treatment of type 2 diabetes mellitus (T2DM) to prevent chronic kidney disease (CKD). Among this class of novel drugs sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and non-steroidal mineralocorticoid receptor antagonist (MRA) are included as they were recently approved to reduce CKD progression. Accordingly, Matteo Conti presented recently produced data from clinical trials based on the use of SGLT2 inhibitors, such as empagliflozin, dapagliflozin, and canagliflozin, which were established as first-line, disease-modifying therapies for diabetic kidney disease. Their reno-protective effects are mediated through reductions in intraglomerular pressure, albuminuria, and systemic blood pressure, and occur independently of glycaemic control. Moreover, the combination of empagliflozin with finerenone (MRA class) has shown to reduce renal and cardiac fibrosis, improving both cardiovascular and renal outcomes. On the other hand, among GLP-1RAs, semaglutide has gained approval specifically to reduce the risk of CKD progression, MACE, and albuminuria in patients with T2DM. Similarly, Conti illustrated that tirzepatide was found to exert cardio-renal protection in patients with T2DM by reducing the composite kidney endpoint (*i.e.* ≥40% decline in estimated glomerular filtration rate, renal death, progression to end-stage renal disease, or new-onset macroalbuminuria) following tirzepatide administration, as observed in the SURPASS-4 trial.

The effects of such novel drugs for the treatment of T2DM were further investigated in patients in CVD primary prevention, as illustrated by Cristina Mascadri. Her lecture provided real-world data from clinical trials based on the application of SGLT2 inhibitors and GLP-1RAs in patients in CVD primary prevention, highlighting the main cardiovascular outcomes. Specifically, Cristina Mascadri illustrated reduction of MACE and heart failure hospitalizations in patients following SGLT2 inhibitor-based therapy. Whereas GLP-1RAs were found to reduce MACE, particularly the risk of stroke, heart attack, and death compared to other agents.

This session was closed by the lecture of Paolo Magni who has focused his talk on the interconnection between T2DM, triglycerides levels and CVD risk. Accordingly, Paolo Magni has shown a detailed and updated view of the existing link connecting metabolic disorders, such as T2DM and dyslipidaemias with increased CVD risk. Indeed, from epidemiological and genetic studies it has been demonstrated that hypertriglyceridemia and remnant cholesterol are independently associated with increased cardiovascular disease risk, particularly in individuals with T2DM with heightened baseline CVD risk. As a result, elevated triglycerides in T2DM represent both a marker and mediator of residual cardiovascular risk, even when low-density lipoprotein cholesterol is optimally controlled.

The third day of the conference, that is the second of the XIX National Congress of the SITeCS, was opened by a session dedicated to current therapies for the treatment of dyslipidaemias. Alberico Luigi Catapano held a lecture on the update of the guidelines for the management of dyslipidaemias, released by the European Society of Cardiology (ESC) together with the European Atherosclerosis Society (EAS). The talk was focused on refining cardiovascular risk estimation, emphasizing earlier and more intensive LDL-C lowering, integrating newer therapies beyond statins, and highlighting risk modifiers like coronary imaging and Lp(a). The lecture was followed by an open discussion including experts like Francesco Bandera, Paolo Fabbrini, Aldo Pietro Maggioni.

This first session was closed by a lecture focused on the importance of omega-3 fatty acids in the prevention of dyslipidaemias, particularly hypertriglyceridemia. Indeed, their principal lipid-modifying effect rely on the reduction of plasma triglyceride levels (approximately 20-40% reduction), mainly through decreased hepatic very-low-density lipoprotein (VLDL) synthesis and enhanced clearance of triglyceride-rich lipoproteins, according to clinical studies illustrated by Aldo Pietro Maggioni.

The second session was dedicated on main therapeutic strategies to manage dyslipidaemias, including bempedoic acid and cholesteryl ester transfer protein (CETP) inhibitors. Particularly, Alberico Luigi Catapano held the lecture about the use of bempedoic acid, an oral lipid-lowering agent targeting LDL-C reduction by approximately 15–25% as monotherapy and providing additional LDL-C reduction when combined with statins or ezetimibe. As bempedoic acid is activated only in the liver and not in skeletal muscle, it is particularly useful in statin-intolerant patients. Moreover, clinical outcome data (CLEAR Outcomes) demonstrated a modest but significant reduction in cardiovascular events, supporting the role of bempedoic acid in primary and secondary cardiovascular prevention.

Ultimately, the session was closed by Laura Calabresi who provided an articulated lecture about CETP inhibitors, including mechanisms of action and latest updates about their effects and efficacy in preventing dyslipidaemias. Particularly, early agents failed due to safety concerns or lack of clinical benefit. However, newer compounds, such as obicetrapib, showed effective LDL-C lowering (*i.e.* by 30 -45%) with improved safety profiles. Ongoing trials are evaluating whether these lipid changes translate into meaningful cardiovascular risk reduction. The talk was followed by an open discussion among experts attending the conference.

In the end, the conference was closed by the joint symposium between SISA Lombardia and SITeCS, during which the 2025 "G. Galli" Award was presented to Clara Rossi, and young researchers, specifically Marco Bellomare, Alice Colombo, Elsa Franchi, Laura Gullà, Marta Iaia, and Arianna Moretti, were awarded for the best works presented at the conference.