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The X Spring Meeting of Young Researchers of the Italian Society of Diabetology (SID), the Italian Society of Geriatrics and Gerontology (SIGG), 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

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The X Spring Meeting of Young Researchers, jointly organized by the Italian Society of Diabetology (SID), the Italian Society of Geriatrics and Gerontology (SIGG), 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), took place in Rimini from April 6 to 8, 2025. This year's event, titled *"Spring MeeTENng – Between the PAST and FUTURE of Research, Spring is always PRESENT"*, was coordinated by young researchers from the aforementioned scientific societies, with SIGG joining for the first time. The Congress featured five thematic sessions, each addressing timely issues in the prevention and treatment of cardiometabolic diseases, offering a retrospective and forward-looking perspective spanning the past decade.

The Congress was organized by "young researchers for young researchers" from the scientific societies listed first and operating in the cardiometabolic field. The Congress hosted five different sessions, each addressing crucial issues in the prevention and treatment of cardiometabolic diseases, with a perspective that spanned the past ten years and looked toward future developments. More than 100 young researchers actively participated in oral and poster sessions, presenting and exchanging ideas on their latest findings. In the following report, we outline the core themes explored in the Meeting's lecture program.

The Meeting opened with a session addressing "non-traditional" cardiovascular risk factors. Among these, Luca D'Onofrio discussed the cardiovascular implications of autoimmune diabetes, particularly Type 1 Diabetes (T1D) and Latent Autoimmune Diabetes in Adults (LADA). It is well known that T1D is characterised by progressive β-cell destruction [1, 2], with an early onset. However, the incidence of T1D is the same before and after the age of 30 and people with T1D at the end are at increased cardiovascular mortality [3]. Life expectancy in patients with T1D is reduced by over a decade compared to the general population [3].

Subjects with T1D have a long disease duration that is one of the major risk factor for the development of cardiovascular disease (CVD) complications. Further, subjects with T1D showed several additional risk factors linked with CVD, such as poor glycemic control [4], dyslipidemia [5], hypertension [6], and heart failure [7]. D'Onofrio presented current stratification criteria for CV risk, with very high risk being defined by target organ damage or clustering of risk factors [8]. Regarding LADA, data from the UK Prospective Diabetes Study (UKPDS) [9] suggest that, although it is often misclassified as Type 2 Diabetes (T2D), individuals with LADA tend to have a lower cardiovascular risk, but the risk did not differ after adjustment for traditional cardiovascular risk factors.

The session concluded with a look toward future perspectives, emphasizing precision medicine approaches and earlier, tailored cardiovascular risk management in autoimmune diabetes [10].

The following session was dedicated to translational research in the cardiometabolic field, highlighting efforts to bridge basic science and clinical application.
Rosa Maria Bruno examined the role of vascular aging and presented the latest information on pulse wave velocity (PWV), an established biomarker for assessing cardiovascular risk and target-organ damage in individuals with hypertension. The application of PWV in clinical practice is limited due to a lack of standardization and consistency. Therefore, updated recommendations for validating devices that measure PWV were provided, along with detailed instructions for various types of devices, including their reference standards, study populations, and data analyses [11]. PWV is used to calculate vascular age, a widely recognized indicator of cardiovascular health that may correlate more closely with cardiovascular disease outcomes than chronological age [12]. The European Society of Hypertension guidelines recommend the use of carotid-femoral PWV to assess hypertension-mediated organ damage. However, its use is not widespread due to the lack of user-friendly devices. In the CARDIS Study, a novel laser Doppler vibrometer-based device for measuring carotid-femoral PWV has shown potential for development and could be used in primary healthcare settings for the early diagnosis and prevention of CVD [13].
Chiara Macchi provided an overview of the evolving role of extracellular vesicles (EVs), illustrating their transition from being regarded as mere cellular "trash bags" to being recognized as key players in translational research and promising therapeutic tools. EVs are key mediators of intercellular communication released by all cell types, from which they derive the bioactive cargo which is transported through the interstitial fluid and blood to enable communication with adjacent cells and distal tissues. Bioactive cargo encompasses a wide range of functional molecules, such as lipids, microRNAs and numerous proteins. From a technical perspective, the International Society for Extracellular Vesicles (ISEV) published the "Minimal Information for Studies of Extracellular Vesicles" (MISEV) in 2014. These guidelines have been continuously updated as a consequence of the ongoing research in this field, with the most recent version released in 2024. The goal of these new guidelines was to provide researchers with an updated snapshot of available approaches and their advantages and limitations for production, separation, and characterization of EVs from multiple sources. Overall, EVs represent an innovative tool in research for uncovering unknown molecular mechanisms. In the field of atherosclerotic burden, preclinical and clinical studies have shown that EVs can mediate the ability of proprotein convertase subtilisin kexin type 9 (PCSK9), one of the main regulator of LDL receptor, to modify their cargo, to promote a pro-inflammatory phenotype [14, 15]. Recently, EVs have gained attention for their potential as diagnostic and prognostic tools in clinical settings, since they can be used as liquid biopsies and biomarkers in cancers. The field of EVs is continuously evolving, with current research focusing on the bioengineering of EVs by loading them with exogenous cargo. This approach holds great promise for the development of engineered EVs to tailor personalized medicine.
The second day of the Meeting commenced with a session entitled "PCSK9: From Myth to Legend." The session highlighted PCSK9 as a central theme in cardiometabolic research over the past decade. Ten years ago, the inhibition of PCSK9 was proposed as a promising therapeutic strategy; today, PCSK9 inhibitors are well-established in clinical practice, and novel approaches, including epigenome editing, are under investigation. Damiano D'Ardes provided an overview of the clinical development of PCSK9-targeted therapies with his presentation "PCSK9: A star is born".

He explained as the therapies targeting PCSK9 have represented a real revolution in the field of lipidology and medicine. All the technologies connected to therapy targeting PCSK9 were discussed, in particular parenteral drugs, such as monoclonal antibodies and siRNAs [16], but also future oral treatments currently being tested [17]. The inhibition of PCSK9 not only ensures a significative reduction of LDL-cholesterol levels but also shows better clinical outcomes, reducing cardiovascular events and mortality in different categories of patients. In particular, they have radically changed the lives of many hypercholesterolemic patients, especially those with familial hypercholesterolemia (FH) [18].

Moreover, it has been underlined that PCSK9 interacts with LDLR family receptors and it is mainly produced by the liver but it is also

produced by extrahepatic tissues being involved in a great number of activities influencing many processes such as for example inflammation, response to infection and neuronal function: consequently it seems important to continue translational and clinical research on PCSK9 which could reserve further surprises and new therapeutic horizons.

Following this, emerging strategies aimed at modulating PCSK9 expression through epigenetic interventions in FH have been discussed. While genome editing can inactivate PCSK9, it involves permanent DNA modifications and potential genotoxicity.
Martino Alfredo Cappelluti discussed reversible, non-mutagenic alternative based on epigenome editing. Transcriptional repressors (ETRs) were engineered by fusing zinc-finger proteins (ZFPs) to three epigenetic effectors: KRAB, DNMT3L, and the catalytic domain of DNMT3A [19]. In vitro screening identified ZFP-based ETRs as the most potent platform for *Pcsk9* silencing. Transient delivery of ETR mRNAs via lipid nanoparticles (LNPs) to the mouse liver resulted in approximately a 50% reduction in circulating PCSK9, sustained for nearly one year. Silencing persisted even after partial hepatectomy, demonstrating the mitotic stability of the induced epigenetic marks. To simplify delivery, an all-in-one construct, EvoETR, was developed by combining all three effectors into a single ZFP fusion protein. EvoETR-8 emerged as the most effective variant, achieving approximately 75% reduction in PCSK9 levels, accompanied by enhanced DNA methylation at the *Pcsk9* promoter and minimal off-target effects, as confirmed by transcriptomic and methylomic analyses.

These results establish a "hit-and-run" epigenome editing strategy capable of inducing durable gene silencing in vivo following a single transient treatment. This platform offers a safer and reversible alternative to genome editing, holding promise for therapeutic gene regulation without permanent genetic modifications [20].
The second day concluded with Session 4, titled "Beyond Gender: Handle with Care." The session addressed the importance of considering gender/sex-related differences in both basic and clinical research. Federica Moscucci opened the session by discussing cardiovascular risk factors in the maternal-fetal dyad, highlighting how early-life exposures may influence long-term cardiometabolic health. Offspring' cardiovascular health can be affected by maternal cardiac and extracardiac environment through developmental programming, a complex mechanism consisting in the influence of maternal conditions on fetal growth [21]. Pregnancy represents a physiological stress test that can unmask underlying maternal predispositions to endothelial dysfunction, hypertension, and metabolic disorders. Conditions such as preeclampsia, gestational hypertension, and gestational diabetes are not only associated with adverse perinatal outcomes but also significantly increase the long-term risk of cardiovascular disease in the mother [22]. At the same time, the intrauterine environment profoundly influences fetal development. Exposure to maternal cardiovascular or metabolic disturbances can lead to fetal programming through epigenetic and structural adaptations, predisposing the child to hypertension, insulin resistance, and early vascular dysfunction. A prompt identification and management of cardiovascular risk is advisable, planning scheduled follow-up evaluations with a comprehensive assessment of conventional and non-conventional risk factors, promoting adequate counselling on lifestyle, cardiometabolic and mental health [23].

In addition, the implementation of structured perinatal follow-up plans and a better comprehension of the role of perinatal stress on future lifelong cardiovascular risk might allow to personalize preventive strategies and should be considered as key health objectives during pregnancy and beyond [24].
Ilaria Parrotta then focused on frailty in the elderly, presenting a comprehensive overview of sex-frailty paradox. According to the 2022 World Population Prospects, the global population aged 65 and overrepresented 10% in 2022, and is expected to rise to 12% by 2030 and 16% by 2050 [25]. Europe and North America currently have the highest proportion of older adults, with projections indicating one in four people over 65 by 2050. In Italy, as of January 2024, mortality rates declined significantly, especially among those aged >80, resulting in a life expectancy of 83.1 years. Notably, 844 people aged >105 were still alive, mostly women [26].

Aging is influenced not just by time, but by various biological, psychological, and social factors. "Successful aging" refers to maintaining good physical, cognitive, and social health, while frailty involves increased vulnerability and functional decline. A large-scale prospective study showed that frailty increases with age and is more prevalent in women, despite their longer life expectancy—a phenomenon known as the "sex-frailty paradox" [27].

Biological sex influences aging through hormones, immunity, oxidative stress and epigenetics. Estrogen offers women protective effects against cardiovascular disease and cellular aging. Men have higher testosterone, which is linked to riskier behavior and increased mortality. Metabolic and mitochondrial differences between sexes also contribute to disparities in aging and frailty [28].

Psychological and socioeconomic factors-such as stress response, social support, and healthcare access-further differentiate aging outcomes between men and women [29]. The World Health Organization advocates for a shift in focus from deficits to intrinsic capacity, a concept emphasizing individuals' physical and mental abilities throughout life. Tailored, sex-specific interventions can promote healthier, longer lives by preserving this capacity [30].
The final day of the Meeting began with Session 5, titled "Fighting Obesity on Multiple Fronts: From Adipose Tissue to Muscle." The session explored both basic and clinical research perspectives on obesity, with particular attention to its impact on muscle health and the emerging therapeutic strategies. The first lecture by Riccardo Calvani focused on a comprehensive overview of sarcopenic obesity in older adults, highlighting insights from the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) project aimed at promoting healthy aging.

Due to demographic transition and rising obesity rates, a large proportion of older adults worldwide suffer from sarcopenic obesity, which significantly increases the risk of adverse health outcomes, and affects overall quality of life [31]. The pathophysiology of sarcopenic obesity is rooted on the synergistic effects of excess adiposity with age-related neuromuscolar changes. The supraphysiological decline of muscle strength and mass that defines sarcopenia is mainly due to the loss of type II (fast-twitch) fibers, which are responsible for generating muscle strength and power [32]. In the presence of obesity, both systemic (i.e., hormonal imbalances), and local factors, such as increased intra- and intermuscular fat, exacerbate age-related muscle decay. Alterations in the biological "hallmarks of ageing", such as chronic inflammation, satellite cells depletion, mitochondrial dysfunction, dysbiosis, cellular senescence and impaired macroautophagy, may further promote fat deposition and loss of lean mass and strength [33]. Lifestyle modifications, including calorie restriction with adequate protein intake and exercise (combining resistance and aerobic routines) are the cornerstone interventions to counteract sarcopenic obesity in older adults. In the SPRINTT trial, a multicomponent intervention (combining exercise with personalized nutritional counseling) reduced the risk of developing mobility disability over a follow-up of 28 months in older adults with physical frailty and sarcopenia (mean age 79.3 years, 37% BMI>30 Kg/m^2) [34]. Participants enrolled in the multicomponent intervention group also demonstrat-

ed a significant preservation of muscle mass compared to control group. Emerging pharmacological strategies, including glucagon-like peptide-1 (GLP-1) receptor agonists and novel geroprotectors, show promise. However, the potential impact on muscle mass remains a significant concern that warrants further investigation.

The session continued with Carla Greco, who addressed new pathophysiological bases of obesity and the ongoing pharmacological revolution reshaping its management.

Obesity is a chronic relapsing progressive disease process characterised by excess adiposity that impairs health and affects about 650 million people worldwide [35, 36]. It increases the risk for multiple metabolic complications (type 2 diabetes, metabolic dysfunction associated steatotic liver disease, cardiovascular disease as well as many, osteoarthritis, obstructive sleep apnoea) and also has serious social and psychological consequences, such as low self-esteem and clinical depression [37]. Lifestyle interventions (diet, exercise and behavioural changes) are the cornerstone of obesity management resulting in up to 10% mean weight loss. Further, metabolic-bariatric surgery represents an efficacy option for treatment of obesity disease. Indeed, bariatric procedures allow a mean weight loss of 25-30%. Considering the pharmacological approach, since the beginning of the 19th century a variety of drugs have been evaluated to decrease body weight and/or to improve metabolic complications of obesity: among many others, thyroid extracts, amphetamines, serotonergics and lipase inhibitors [38]. These molecules have represented for a long time the clinician's armamentarium for weight management, but with suboptimal efficacy and high burden of adverse events [38]. Today, emerging alternatives of novel agents and combinations populate the current obesity therapeutic pipeline [39]. In particular, efforts have been directed toward developing incretin-based pharmacotherapies for treating obesity. The incretins are the peptide hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), which are secreted from the gut following nutrient intake [40] and involved in the pathophysiology of obesity [41]. Therefore, in the last decade, GLP1 receptor agonists (liraglutide and semaglutide) and GLP1/GIP dual agonist (tirzepatide) have been approved as a pharmacological weight management tool in subjects with complicated-overweight or obesity, in addition to lifestyle change. Briefly, these drugs induce anorectic effects through activation of receptors located in the central nervous system with reduction of appetite resulting in decreased energy intake [42]. Moreover, the molecules also determine effects on gastric motility which promotes satiety and, for tirzepatide a direct effect on adipose tissue has been demonstrated [43]. The efficacy of incretin-based drugs allows reaching up to 22-24% of body weight, making it competitive with bariatric surgery.

In conclusion, nowadays the US Food and Drug Administration has approved 6 agents for chronic weight management in individuals living with complicated-overweight and/or obesity, including orlistat, phentermine-topiramate, naltrexone-bupropion, liraglutide, semaglutide, and recently tirzepatide.

The Meeting, following tradition, concluded with an unconventional session that this time was dedicated to a debate about denialism, featuring interventions by Fabrizio Elia and Giovanni Talerico. Through an engaging and thought-provoking discussion, the workshop explored the cognitive, social, and emotional roots of false beliefs, scientific denialism, and conspiracy thinking. The session provided participants with critical tools to better understand—and counter—misinformation and pseudoscience.

This final session was a fitting conclusion to a Meeting that not only offered an in-depth update on cardiometabolic research but also emphasized the broader responsibility of scientists in communicating evidence-based knowledge with clarity and integrity.

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