SPRING 2024

# Spring Meeting Giovani Ricercatori

SID SIIA SIMI SIPREC SISA

## *Research drives us crazy*

**Rimini, 25-27 Febbraio 2024**

Young investigators meeting

# SPRING 2024

Carissime Colleghe e Colleghi,

con grandissimo piacere vi invitiamo a partecipare alla IX Edizione dello Spring Meeting Nazionale dei Giovani Ricercatori 2024, che riconferma, la presenza congiunta di cinque Società Scientifiche: SID (Società Italiana di Diabetologia), SIIA (Società Italiana Ipertensione Arteriosa), SIMI (Società Italiana di Medicina Interna), SIPREC (Società Italiana per la Prevenzione Cardiovascolare) e SISA (Società Italiana per lo Studio dell'Aterosclerosi).

Il Congresso si svolgerà il 25-27 febbraio 2024 a Rimini e cercherà di essere di nuovo un momento di incontro, non solo per la discussione dei risultati della ricerca scientifica in ambito cardiometabolico promossa dai giovani soci delle cinque Società Scientifiche coinvolte, ma anche un'occasione per promuovere lo scambio di idee tra i partecipanti, incoraggiare la nascita di collaborazioni intersocietarie e più in generale favorire la crescita professionale di molti giovani ricercatori.

Dato il successo dell'ultima edizione, anche l'evento di quest'anno sarà strutturato in diverse sessioni che cercheranno di rappresentare lo stato dell'arte sia della ricerca clinica che della ricerca di base sugli aspetti più intriganti dei fattori di rischio e delle patologie in ambito cardiometabolico. Inoltre, come da tradizione, il congresso sarà una rinnovata occasione per dar voce a tutti i partecipanti attraverso il format delle comunicazioni orali e delle presentazioni poster. Non mancheranno, infine, innumerevoli opportunità di networking e di scambio di idee, che come ci auguriamo, prenderanno forma soprattutto negli spazi dedicati ai workshop su vari aspetti critici e metodologici della ricerca biomedica.

Speriamo di vedervi numerosi a condividere questa indimenticabile esperienza e fantastica opportunità di crescita collettiva!

Buon lavoro a tutti,

*Il comitato organizzatore*

Young investigators meeting

## Domenica, 25 febbraio 2024

13.00-13.45 *Light Lunch*

13.45-14.00 Arrivi e registrazione dei partecipanti

14.00-14.15 **Apertura lavori**
*Vanessa Bianconi (SISA), Damiano D'Ardes (SIMI), Luca D'Onofrio (SID), Giovanna Gallo (SIPREC), Carla Greco (SID), Rosa Lombardi (SIMI), Alessandro Maloberti (SIIA), Chiara Pavanello (SISA), Francesco Spannella (SIIA), Valeria Visco (SIIA).*

14.15-16.15 **Sessione 1 – Nutraceutici in ambito cardiovascolare: cosa ci riserva il futuro?**
*Moderatori: Alessandro Maloberti (Milano), Federica Carrieri (Chieti-Pescara)*
**Basic Research – Molecole bioattive da matrici naturali: nuove possibili frontiere terapeutiche nella prevenzione cardiovascolare**
• *Albino Carrizzo (Salerno)*
**Clinical Research - Nutraceutici e salute cardiovascolare: razionale di impiego ed efficacia clinica**
• *Federica Fogacci (Bologna)*
**Discussione congiunta**

**Comunicazioni Orali** (n.7)

16.15-18.00 **WORKSHOP – Call for Ideas: costruzione di progetti intersocietari**
*Comitato organizzatore*

18.00-18.15 **Saluto dei Presidenti:**
Angelo Avogaro (SID), Maria Lorenza Muiesan (SIIA), Giorgio Sesti (SIMI), Massimo Volpe (SIPREC), Alberico L. Catapano (SISA)

18.15-19.45 **AperiPoster - Sessioni 1-4**

**Sessione Poster 1:** *Armando Ferrera (Roma)*
**Sessione Poster 2:** *Moris Sangineto (Foggia)*
**Sessione Poster 3:** *Alessandro Mengozzi (Pisa)*
**Sessione Poster 4:** *Rosanna Villani (Foggia)*

20.30 *Cena*

## Lunedì, 26 febbraio 2024

08.30-10.30 **Sessione 2 – Dulcis in fundo: la medicina rigenerativa oltre l'ostacolo del danno cardiovascolare**
*Moderatori: Francesco Spannella (Ancona), Valeria Visco (Salerno)*
**Basic Research - Identificazione di nuovi target per la rigenerazione cardiaca**
● *Paola Cattaneo (Milano)*
**Clinical Research - Dalla rivascolarizzazione alla rigenerazione: nuove prospettive in medicina vascolare**
● *Mario D'Oria (Trieste)*
**Discussione congiunta**

**Comunicazioni Orali** (n.7)

10.30-11.00 *Coffee Break*

11.00-13.00 **Sessione 3 – In cima al cuore: sistema cardiovascolare in condizioni estreme**
*Moderatori: Andrea Baragetti (Milano), Rosa Curcio (Terni)*
**Basic Research - Cosa succede al sistema cardiovascolare in alta quota?**
● *Giovanni Vinetti (Bolzano)*
**Clinical Research - Cosa succede al paziente cardiovascolare ad alta quota?**
● *Grzegorz Bilo (Milano)*
**Discussione congiunta**
**Comunicazioni Orali** (n.7)

13.00-14.30 *Lunch*

14.30-16.30 **WORKSHOP – Call for Ideas: costruzione di progetti intersocietari**
*Comitato organizzatore*

16.30-18.30 **Sessione 4 – L'intelligenza artificiale applicata alle malattie cardiometaboliche**
*Moderatori: Chiara Pavanello (Milano), Mario Daidone (Palermo)*
**Basic Research - Ragionare è nient'altro che calcolare - T. Hobbes, Leviatano 1 cap V**
● *Luca Palazzolo (Milano)*
**Clinical Research - L'Intelligenza Artificiale nella pratica clinica, tra promesse e chimere: il caso della fibrillazione atriale**
● *Giulio Francesco Romiti* (Roma)
**Discussione congiunta**

**Comunicazioni Orali** (n.7)

18.30-19.45 **AperiPoster - Sessioni 5-8**

**Sessione Poster 5:** *Antonella Giammanco (Palermo)*
**Sessione Poster 6:** *Emiliano Fiori (Roma)*
**Sessione Poster 7:** *Arturo Cesaro (Napoli)*
**Sessione Poster 8:** *Rosa Lombardi (Milano)*

20.30 *Cena*

## Martedì, 27 febbraio 2024

08.30-10.30 **Sessione 5 (SID) – SGLT2i in prevenzione primaria**
*Moderatori: Lorenzo Nesti (Pisa), Francesco Baratta (Roma)*
**Basic Research – Evidenze precliniche: potenziali meccanismi fisiopatologici**
• *Valentina Genchi (Bari)*
**Clinical Research – Evidenze cliniche: RCT & real world data**
• *Renata Risi (Roma)*
**Discussione congiunta**

**Comunicazioni Orali** (n.7)

10.30-11.00 *Coffee Break*

11.00-12.00 **WORKSHOP – Call for Ideas: presentazione dei progetti intersocietari**
*Comitato organizzatore*

12.00-13.30 **WORKSHOP: Cognizione ed errore: quando la mente ci inganna!**
*Interviene: Fabrizio Elia (Torino)*
*Moderatore: Giovanni Talerico (Roma)*
*Discussant: Damiano D'Ardes (Chieti), Rosa Lombardi (Milano)*

13.30 ***Chiusura Lavori e Lunch***

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### Comitato organizzatore

*Vanessa Bianconi (SISA), Damiano D'Ardes (SIMI), Luca D'Onofrio (SID), Giovanna Gallo (SIPREC), Carla Greco (SID), Rosa Lombardi (SIMI), Alessandro Maloberti (SIIA), Chiara Pavanello (SISA), Francesco Spannella (SIIA), Valeria Visco (SIIA).*

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### Moderatori e relatori

*Andrea Baragetti (Milano)*
*Francesco Baratta (Roma)*
*Leonardo Bencivenga (Napoli)*
*Grzegorz Bilo (Milano)*
*Federica Carrieri (Chieti-Pescara)*
*Albino Carrizzo (Salerno)*
*Paola Cattaneo (Milano)*
*Arturo Cesaro (Napoli)*
*Rosa Curcio (Terni)*
*Mario Daidone (Palermo)*
*Damiano D'Ardes (Chieti)*
*Mario D'Oria (Trieste)*
*Fabrizio Elia (Torino)*
*Armando Ferrera (Roma)*
*Emiliano Fiori (Roma)*
*Federica Fogacci (Bologna)*
*Valentina Genchi (Bari)*
*Antonella Giammanco (Palermo)*
*Rosa Lombardi (Milano)*
*Alessandro Maloberti (Milano)*
*Alessandro Mengozzi (Pisa)*
*Lorenzo Nesti (Pisa)*
*Luca Palazzolo (Milano)*
*Chiara Pavanello (Milano)*
*Renata Risi (Roma)*
*Giulio Francesco Romiti (Roma)*
*Moris Sangineto (Foggia)*
*Francesco Spannella (Ancona)*
*Giovanni Talerico (Roma)*
*Rosanna Villani (Foggia)*
*Giovanni Vinetti (Bolzano)*
*Valeria Visco (Salerno)*

SPRING 2024

# *Abstract*

## Sessione 1 - Nutraceutici in ambito cardiovascolare: cosa ci riserva il futuro?

**Domenica 25 Febbraio 2024 ore 14.15-16.15**

*Moderatori: Alessandro Maloberti (Milano), Federica Carrieri (Chieti-Pescara)*


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Abstract n SO1_1 - Presenting author**: Fabio Troiano**

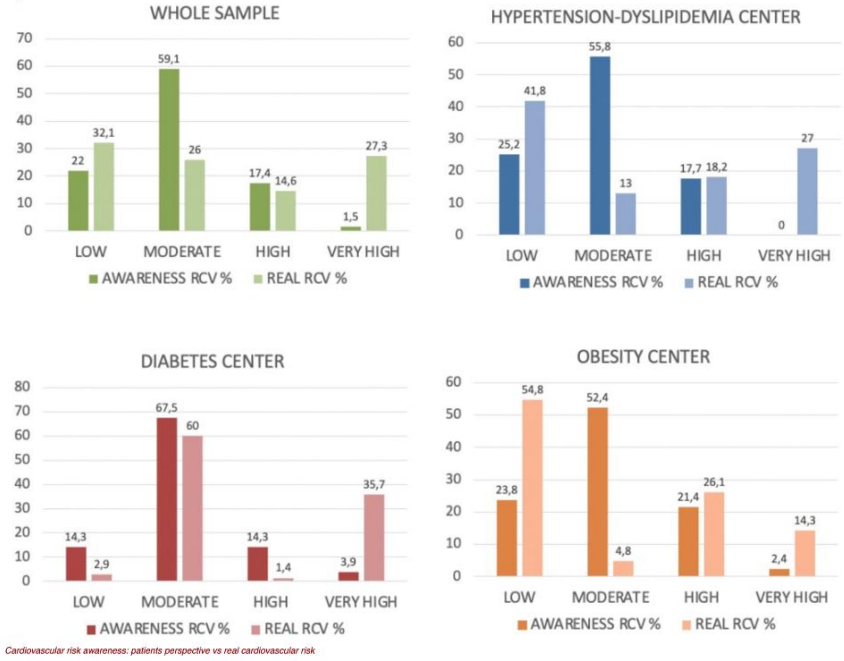
## Cardiovascular risk awareness: is the patient aware?

Fabio Troiano, Damiano D'Ardes, Paola Vizzarri, Ilaria Rossi, Francesca Santilli, Maria Teresa Guagnano, Marco Bucci, Francesco Cipollone

Department of Medicine and Aging Science, "G. D'Annunzio" University of Chieti

**Aim:** People's awareness of cardiovascular risk (CVR) factors is not fully investigated. Our aim was to evaluate CVR awareness of patients with a different cardiovascular risk.
**Methods:** A total of 284 patients were enrolled: 148 (52%) from Hypertension-Dyslipidemia Center (HDC), 92 (32.3%) from Diabetes Center (DC) and 45 (15.7%) from Obesity Center (OC). Patients completed a questionnaire to evaluate their awareness of CVR. The questionnaire was composed of 20 questions, which included demographic characteristics, personal and family history, information needed to calculate SCORE CVR. Their perception of CVR was compared with doctors' CV score evaluation.
**Results:** 32.1% of patients had low CVR, 26% moderate CVR, 14.6% high CVR and 27.3% very high CVR. Only 40% of patients had a correct perception of their CVR, among patients with incorrect CVR perception, most of patients underestimated their risk (85%) and only 15% overestimated it. CVR was underestimated by 54.7% of patients of HDC, by 49.2% of DC and by 41% of OC. A significant association was found between CVR overestimation and different Centers ($p<0.01$); OC had the highest percentage of patients overestimating CVR (33.3%).
Very-high-risk patients had no awareness of their risk condition. In fact, among patients at very high risk (27.3%), only 1.5% perceived this condition, with significant differences among the specific clinics ($p<0.01$): 0 vs 31 in HDC; 3 vs 25 in DC; 1 vs 6 in OC.
**Conclusions;** Our data showed underestimation of CVR among patients especially between very-high-risk patients underlining the need for maximize patients' risk consciousness and adherence.

Figure 1. Cardiovascular risk awareness.




Cardiovascular risk awareness: patients perspective vs real cardiovascular risk

Abstract n SO1_2 - Presenting author**: Filippini Emanuele**

## The contribution of the WHO dietary approach for reducing cardiovascular risk in patients with immune-mediated diseases

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**Aim:** Individuals grappling with immune-mediated disorders face an elevated risk of cardiovascular diseases, primarily linked to latent chronic inflammation—a contributing factor to the progression of cardiovascular ailments. This study seeks to meticulously assess the efficacy of incorporating dietary recommendations sanctioned by the World Health Organization (WHO) to mitigate cardiovascular risk factors among patients diagnosed with immune-mediated diseases. The core objective is to scrutinize changes in lipid profiles, inflammatory markers, and the holistic cardiovascular health landscape subsequent to the adoption of the WHO-endorsed dietary approach.
**Methods:** Conducting a thorough prospective cohort study, we enrolled 31 patients diagnosed with immune-mediated diseases, encompassing conditions such as rheumatoid arthritis and psoriasis. Participants received detailed dietary directives grounded in WHO recommendations, emphasizing a diet abundant in fruits, vegetables, whole grains, lean proteins, and restricted saturated fats. Over a 6-month period, we meticulously monitored compliance and adherence to the WHO-prescribed dietary approach. Baseline and post-intervention evaluations involved a comprehensive assessment of lipid profiles, HbA1c, FGB, and BMI.
**Results:** Significant reductions were observed in Body Mass Index from 29.1 to 27.2 (-6.5%), total cholesterol from 203 mg/dl to 171 mg/dl (-15.7%), calculated LDL from 96 mg/dl to 80 mg/dl (-16.6%), HbA1c from 6.35% to 6.05% (-4.7%). However, no statistically significant reductions were found in fasting blood glucose, triglycerides, and HDL cholesterol.
**Conclusion:** This investigation indicates that embracing the WHO dietary approach effectively mitigates CVR among patients with immune-mediated diseases. The observed improvements across various indicators underscore the cardiovascular advantages associated with adherence to WHO dietary recommendations. Integrating these guidelines into the management protocols of immune-mediated diseases holds promise as a substantial complement to conventional therapeutic modalities, fostering cardiovascular health and the overall well-being of individuals within this patient cohort. Prudent consideration of further extended studies is crucial to authenticate and substantiate these findings in a long-term context.

*CVR: cardiovascular risk; HbA1c: glycated hemoglobin; FGB: fasting glucose blood*

Abstract n SO1_3 - Presenting author**: Rossella Bianco**

## The role of omega-3 polyunsaturated fatty acids-rich food on the metabolic profile of patients with MASLD

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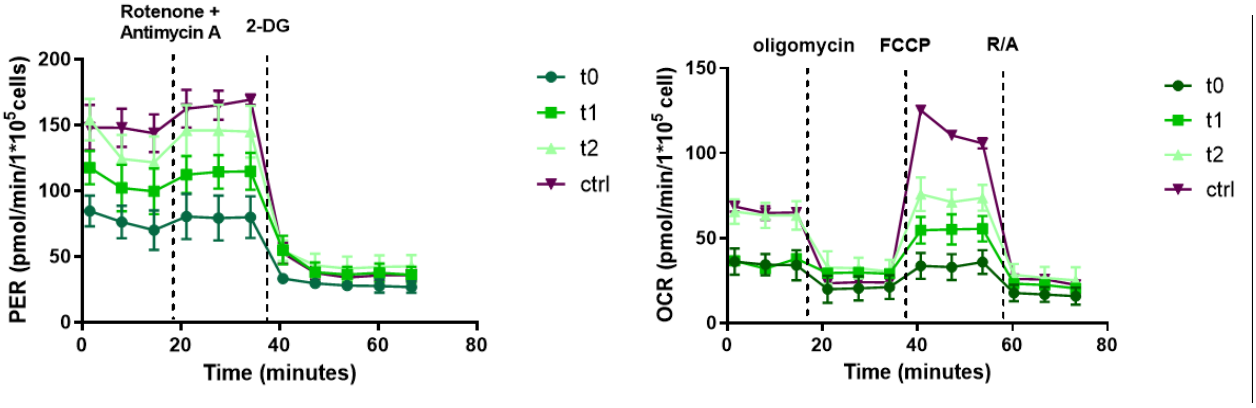
**Aim:** Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) are considered beneficial against cardiovascular disease. However, to date there are contrasting data regarding the role of ω-3 PUFAs in metabolic dysfunction-associated steatotic liver disease (MASLD). We evaluated the dietary intake of ω-3 PUFAs and the effects of ω-3 PUFA-rich food supplementation in a cohort of subjects affected by MASLD.
**Methods:** 30 patients with MASLD were enrolled, and completed a questionnaire to quantify the daily intake of foods containing ω-3-PUFAs. A dietary plan was administered, including a high intake of ω-3 (2.2-4g/die) from flaxseed and fish (10g/day of flaxseed and about 200g of fish three times/week). Only 18 patients accepted to follow nutritional advice, and 15 patients were compliant. Patients were evaluated at baseline (T0), after 3 months (T1) and after 6 months of nutritional intervention (T2) collecting anthropometric data, biochemical analysis, and peripheral blood mononuclear cells (PBMCs) for bioenergetic analysis using the Seahorse HSmini analyser (Agilent).
**Results:** The survey highlighted an average daily consumption of ω-3 of about 1.15 g/day, hence rather below the reference ranges of 2-4 g/day recommended by the LARNs (Levels of Reference Intake of Nutrients). In particular, an average EPA and DHA consumption of about 157.28 mg (below the recommended 250 mg) was found. In the patients compliant with the ω-3 diet, we observed a significant reduction of BMI at T2 (from 33,24 Kg/m$^2$ to 31,59 Kg/m$^2$ to 31,06 Kg/m$^2$, p value <0.05), and an improvement of ultrasound steatosis grade in all the patients. Moreover, at T2 blood glucose significantly reduced by an average of 14.43 mg/dl (p<0.02), and GOT and GPT reduced by 5.84 U/L (p<0.03) and 17.17 U/L (p<0.02), respectively. Finally, the PBMCs bioenergetic analysis revealed a very low metabolism at T0. Interestingly, during the diet glycolysis and mitochondrial respiration progressively increased from T0 to T2, with consequent more ATP production, and reaching levels similar to healthy subjects
**Conclusion:** The recovery of ω-3-rich food introit in MASLD patients improved their energetic and metabolic homeostasis.



Abstract n SO1_4 - Presenting author**: Beatrice Mattina**

## Dietary flavan-3-ol metabolites modulate proinflammatory human fibroblast activation in vitro: potential perspective in the prevention of CVD

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**Aim:** Consumption of food rich in flavan-3-ols, like tea, dark-chocolate, red-wine, grapes, has been associated with a protective effect against chronic diseases associated with systemic inflammation, such as CVD. Dietary flavan-3-ols are vastly metabolized to hydoxyphenyl-valerolactones (OH-PVL) by the gut microbiota. This study aims to evaluate the in vitro anti-inflammatory effect of colonic metabolites of flavan-3-ols as OH-PVL, previously identified in a metabolomics study as the most representative molecules present in plasma after the ingestion of flavan-3-ol-containing food.
**Methods:** We tested a synthetic compound, (R)-5-4'-hydroxyphenyl-γ-valerolactone (R-4-OH-PVL), purified by 2 alternative methods HPLC (5) or silica-gel flash chromatographic (6), and a commercial compound, hydroxy-phenyl-propionic acid 4-OH-PPA (7. The cytotoxicity of all compounds and the efficacy in inhibiting lipopolysaccaride LPS-induced IL-6 secretion were evaluated in human fibroblasts by MTT assay and ELISA kit, respectively. Supernatant IL-6 concentrations were normalized against the cell extract protein content, assessed by BCA assay. Statistical analysis was carried out by one-way ANOVA (significant p-value=< 0.05).
**Results:** LPS toxicity and effective concentration in increasing IL-6 secretion were preliminarily assessed. LPS resulted non-cytotoxic (IC50 >50 µM) and efficient at 1 µM (10.000pg/mL) (p=0.0087 vs untreated cells). Compounds 5-6-7 were non-cytotoxic (IC50 >50 µM) nor induced IL-6 secretion at concentrations from 0,01 µM to 10 µM, corresponding to their plasmatic levels after ingestion and metabolism of flavan-3-ols. Compounds 5 and 6 were highly effective in inhibiting LPS-induced IL-6 secretion, by 41% (p=0.0132) and 43% (p=0.0099) respectively. Conversely, compound 7 did not demonstrate any statistically significant effect (although LPS-induced IL-6 secretion was reduced by 15%).
**Conclusions:** In conclusion, the synthetic compound R-4-OH-PVL showed a significant anti-inflammatory activity on human fibroblasts in vitro, after purification by either HPLC or flash chromatography. Further studies are warranted to confirm the in vivo role of OH-PVL anti-inflammatory effects, in view of CVD prevention and/or modulation.

Abstract n SO1_5 - Presenting author**: Anna Parolini**

## The aging of neutrophils is actively involved in the metabolic consequences of high fat diet

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**Aim:** The epigenetic modifications induced by High Fat Diets (HFDs) in long-living hematopoietic cells have been well described, but whether they affect the “aging” of neutrophils, characterized by far shorter half-life, is less clear. Neutrophils "age" through a reciprocal regulation of CXCR4, promoting a "fresh" status when leaving the BM, and CXCR2, accelerating their aging in the circulation. We study whether derailed aging exacerbates the metabolic and inflammatory consequences of HFD.
**Methods:** We immunophenotyped neutrophils and characterized the metabolic responses in physiology (wild-type mice, WT) and in mice with either constitutively aged neutrophils (MRP8 driven conditional deletion of CXCR4; herein CXCR4fl/flCre+) or with constitutively fresh neutrophils (MRP8 driven conditional deletion of CXCR2; CXCR2fl/flCre+), following 20 weeks of HFD feeding (45% Kcal from fat).
**Results:** CXCR4fl/flCre+ mice display higher plasma triglycerides levels versus WT, despite comparable glucose levels, when monitored during standard feeding. This metabolic difference was exacerbated by feeding mice a HFD for 20 weeks. Indeed, despite a comparable gluco-metabolic profile between CXCR4fl/flCre+ and WT mice, liver damage was increased in CXCR4fl/flCre+, linked to the higher accumulation of CXCR4fl/flCre+ neutrophils in the liver after 20 weeks and two hours after intragastric gavage with olive oil versus fasting. As this finding was not observed after 20 weeks of standard fat diet, these results suggest that HFD feeding redirects aged neutrophil to the liver, resulting in enriched oxidative metabolism and NETosis- and inflammation-related pathways in the liver of CXCR4fl/flCre+ mice.
Conversely, CXCR2fl/flCre+ mice were protected from obesity and insulin resistance, exhibiting a proresolutive phenotype.
In humans, increased plasma levels of Cxcl1 (ligand of CXCR2) correlated with visceral obesity and metabolic syndrome.
**Conclusions:** Neutrophil aging might contribute to the cardio-metabolic consequences of HFD. This aging could represent a new therapeutic target beyond the current anti-inflammatory therapies approved for the treatment of cardiovascular diseases.

Abstract n SO1_6 - Presenting author**: Giuseppe De Girolamo**

## MASLD and muscle mass: effects of a ω3-PUFAS enriched diet

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**Aim:** Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a major health issue worldwide. There is a growing interest on the association between muscle mass (MM) and MASLD as implied in higher cardiovascular risk. Physical resistance and various nutritional strategies, including ω3 polyunsaturated fatty acid (n3-PUFA) supplementation, have been studied to prevent MM loss in the elderly, but little is known in adult steatotic patients. Here, we investigated modification of MM in MASLD patients using an n3-PUFA enriched diet.
**Methods:** We enrolled 30 patients with MASLD, referring to Centro CURE of University of Foggia. The average age was 49.7 (σ +/- 12y, 63% men, 37% women).
The diagnosis of MASLD was assessed according to the new Multisociety Delphi Consensus Statement (2023). Patients received a hypocaloric diet containing ω3-PUFAs rich foods: 1700 Kcal/day for men, 1400 Kcal/day for women, with flax seeds and walnuts (10+10g per day, corresponding to 2.8 g/day of ω3 alpha-Linolenic acid, ALA), and fish up to three times a week (about 200g at a time, corresponding to EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) intake of 1-2g/week).
Patients were evaluated at T0 and after 3 months (T1), collecting anthropometric measures and performing Total Body Bioelectrical Impedance Analysis (BIA).
**Result:** Overall, at T0, patients body composition was constituted by an average of 36% of fat mass (FM) and 64% of free fat mass (FMM) with a skeletal muscle mass (SMM) of 31.96% for men and 24.37% for women and an average BMI of 35.1Kg/m2 (σ +/- 6.2Kg/m2). Despite the high levels of FM and relatively low quantity of SMM, none of the patients encountered the criteria for sarcopenia as defined by the EGSWOP2 (SMM<20Kg for men and <15Kg for women, SMM/height2 <7Kg/m2 for men and <5Kg/m2 for women).
However, at T1, we observed a 6.55% reduction of BMI (32.8kg/m2). Moreover, there was an overall increase in SMM of 1.03% (P<0.01), + 1.96% for men (P<0.01) and + 0.44% for women (P<0.2). SMM was also adjusted for BMI and weight (SMM/BMI, SMM/W), showing a statistically significant increase (P<0.02) of respectively +0.06 and +0.02.
**Conclusion:** N3-PUFA rich food supplementation improved body composition in MASLD patients. Further studies are needed, and data at 6 months will be soon available.

Abstract n SO1_7 - Presenting author**: Elena Olmastroni**

## Higher adherence to the Mediterranean diet is associated with improved glycemic control and reduced atherogenic patterns: a sub-analysis of the Di@bet.es Study

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[9] Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina-IBIMA Plataforma BIONAND, Málaga, Spain.
[10] Department of Pharmacological and Biomolecular Sciences, Universita' degli Studi di Milano, Milan, Italy.

**Aim:** The classical Mediterranean diet (MedDiet) has been associated with a decreased occurrence of type 2 diabetes, while a potential effect on advanced lipoprotein profiles is debated. We hypothesized that greater MedDiet adherence positively impacts both glycaemic and lipoprotein profiles.
**Methods:** In this case-control study using data from the Spanish population-based survey Di@bet.es, 1540 participants with normal glycaemic profiles at baseline were involved. Over an 8-year follow-up, cases (subjects developing altered glycaemic profiles) were 1:1 matched with controls by age, sex, and body mass index. MedDiet adherence was assessed using the 14-item MEDAS tool, and lipoprotein profiles were assessed using nuclear magnetic resonance (NMR) spectroscopy. Logistic regression models analysed MedDiet adherence and altered glycaemic profile risk (odds ratios [OR], 95% confidence intervals [95% CI]).
**Results:** A total of 213 controls and 213 cases were successfully matched. Optimal adherence to the MedDiet (MEDAS score values of 9 or higher) was more frequent in controls than in cases (67.61% vs. 40.85%, p-value <0.0001). Participants with suboptimal adherence to the MedDiet had over twice the risk of developing an altered glycaemic profile (adjusted OR 2.70, 95% CI 1.77-4.12). An interaction effect revealed a more pronounced impact of the MedDiet on females. Subjects with optimal adherence to the MedDiet exhibited lower levels of very low-density lipoprotein (VLDL) cholesterol (p-value 0.006), VLDL triglycerides (p-value 0.003), and all the different VLDL subclasses (total, large, medium, and small, all p-value <0.05), and higher levels of high-density lipoprotein (HDL) cholesterol (p-value 0.005) and HDL particles (total and small, both p-value 0.007).
**Conclusions:** This study underscores the favourable impact of the MedDiet on glycaemic and lipoprotein metabolism, endorsing a less atherogenic profile, particularly affecting VLDL and HDL. Further research is essential for a comprehensive understanding of mechanisms that contribute to these benefits.

Abstract n SO2_1 - Presenting author**: Clara Rossi**

## Low-dose of simvastatin ameliorates mitochondrial disfunction in senescent vascular smooth muscle cells

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[1]Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Italy
[2]Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Italy

**Introduction and aim:** Senescence and mitochondrial dysfunction are two main indicators of aging. Mitochondria are potential drivers of aging phenotypes and dysfunctional mitochondria are associated with multiple age-related diseases. Evidence indicates that senescence induces changes in mitochondrial structure, dynamics, and function. Moreover, senescent vascular smooth muscle cells (VSMCs) are present in atherosclerotic plaques and contribute to their instability. The anti-atherosclerotic effects of simvastatin are well known, but recently other benefits, such as the promotion of mitochondrial quality, have been demonstrated.
In this study, we characterized mitochondrial dysfunction in replicative (RS) and doxorubicin-induced senescence (DIS) in VSMCs and then tested simvastatin as a therapeutic intervention.
**Methods:** To induce senescence, VSMCs at passages 5-7 (non-senescent cells) were either incubated for 48h with doxorubicin 100nM to perform DIS or serially passaged 15 to 17 times to represent RS. Then, senescent cells were treated with 0,1uM simvastatin for 48h. Next, we measured reactive oxygen species (ROS) production, mitochondrial morphology, function, and membrane potential (MMP).
**Results:** Compared to non-senescent VSMCs, RS and DIS showed decreased mitochondrial respiration and MMP, increased ROS levels, and altered mitochondria morphology with a high percentage of fragmented mitochondria. In addition, senescent VSMCs had perturbations in mitochondrial dynamics and only RS downregulated mitochondrial transcription factor A (TFAM) expression, suggesting a reduction in the number of mitochondria.
After simvastatin treatment, we observed an improvement in mitochondrial respiration and a reduction of ROS production (up to 15%) in both RS and DIS, but no changes in MMP.
**Conclusions:** Both senescent models showed an accumulation of dysfunctional mitochondria, but a down-regulation of TFAM expression was observed only in RS. Simvastatin treatment seems to be a potentially beneficial therapeutic intervention for ameliorating senescence-induced mitochondrial dysfunction. Further studies will be needed to better understand the relationship between simvastatin and mitochondrial dysfunction in senescence.

Abstract n SO2_2 - Presenting author**: Nicola Riccardo Pugliese**

## Associations of different definitions of iron deficiency with cardiac structure and function, congestion, exercise capacity and prognosis in heart failure

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[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

**Background.** It is uncertain how to best diagnose iron deficiency (ID) in patients with heart failure (HF); different ID definitions have been proposed, with discordant results.
**Objectives.** To assess the relatioship of different definitions of ID with cardiac structure and function, congestion, exercise capacity, and prognosis in outpatients with HF.
**Methods.** ID was defined according to guidelines (G-ID: ferritin <100 ng/mL or ferritin 100-299 ng/mL with transferrin saturation [TSAT] <20%) or as TSAT <20%. Alternative definitions (iron <13 $\mu$mol/L, ferritin <100 and <300 ng/mL) were explored. Relationship with rest and exercise ultrasound findings, cardiopulmonary exercise testing and a composite endpoint of cardiovascular hospitalizations or all-cause mortality were assessed.
**Results.** Of 531 patients (54% with left ventricular ejection fraction [LVEF] ≥50%), 248 (47%) had TSAT <20%, while 312 (59%) had G-ID. Compared to those without ID, patients with TSAT <20% or G-ID had greater left atrial volume and higher E/e', lower peak oxygen consumption, and were more likely to show a discontinuous renal venous flow pattern. However, only TSAT <20% was associated with dilated inferior vena cava and more B-lines at rest and peak exercise. Lower TSAT, iron and haemoglobin were associated with more effort intolerance and ultrasound signs of congestion, while ferritin and LVEF were not (Picture 1). After adjusting for age, sex, haemoglobin, NT-proBNP and LVEF, TSAT <20% and iron ≤13 $\mu$mol/L were associated with worse outcomes (hazard ratio 1.35, 95% confidence interval 1.09-2.38 and 1.54, 1.04-2.99), while G-ID or ferritin <100 or <300 ng/mL were not.
**Conclusions.** In outpatients with HF, TSAT <20% is more consistently associated with echocardiographic signs of elevated left ventricular filling pressures, intravascular and pulmonary congestion, and poorer functional capacity than other ID definitions. TSAT <20% and iron ≤13 $\mu$mol/L predict a worse prognosis but not G-ID or ferritin-based ID.

Abstract n SO2_3 - Presenting author**: Ermanno Bellizzi**

## Peripheral Blood Mononuclear Cells: A New Frontier in the Management of Patients with Diabetes and No-Option Critical Limb Ischaemia

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[1]Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy;
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**Aim:** The current study aimed to evaluate the effectiveness of peripheral blood mononuclear cell (PB-MNC) therapy as adjuvant treatment for patients with diabetic foot ulcers (DFUs) and no-option critical limb ischaemia (NO-CLI).
**Method:**The study is a prospective, noncontrolled, observational study including patients with neuro-ischaemic DFUs and NO-CLI who had unsuccessful revasculariza- tion below the ankle (BTA) and persistence of foot ischaemia defined by TcPO2 values less than 30 mmHg. All patients received three cycles of PB-MNC therapy administered through a "*below- the-ankle approach*" in the affected foot along the wound-related artery according to the angiosome theory. The primary outcome measures were healing, major amputation, and survival after 1 year of follow-up. The secondary outcome measures were the evaluation of tissue perfusion by TcPO2 and foot pain defined by the numerical rating scale (NRS).
**Results:** Fifty-five patients were included. They were aged >70 years old and the majority were male and affected by type 2 diabetes with a long diabetes duration (>20 years); the majority of DFUs were infected and nearly 90% were assessed as gangrene. Overall, 69.1% of patients healed and survived, 3.6% healed and deceased, 10.9% did not heal and deceased, and 16.4% had a major amputation. At baseline and after PB-MNC therapy, the TcPO2 values were 17 ± 11 and 41 ± 12 mmHg, respectively ($p < 0.0001$), while the pain values (NRS) were 6.8 ± 1.7 vs. 2.8 ± 1.7, respectively ($p < 0.0001$). Any adverse event was recorded during the PB-MNC therapy.
**Conclusion:** Adjuvant PB-MNC therapy seems to promote good outcomes in patients with NO-CLI and neuro-ischaemic DFUs.

Abstract n SO2_4 - Presenting author**: Vanessa Desantis**

## Methotrexate mimicry for MTHFR C677T defect inducing hyperhomocysteinemia and endothelial progenitor cell (EPCs) dysfunction in atrial fibrillation (AF) patients

Vanessa Desantis[1], Antonietta Scaringella[1], Luca Sgarra[2], Ingrid Catalina Caradonna[1], Antonio Giovanni Solimando[3], Sebastiano Cicco[3], Assunta Maria Potenza[1], Carmela Nacci[1], Angelo Vacca[3], Monica Montagnani[1]

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**Background and Aims:** Methotrexate (MTX) improved serum homocysteine levels in different diseases. Specifically, hyperhomocysteinemia have been associated with an increased risk of stroke and coronary artery disease [Homocysteine Studies Collaboration, 2002]. Folate cycle disorders are a yet underrated dysmetabolism only partly explained by methylene tetrahydrofolate reductase (MTHFR) defects and involved in the hinderance of circulating endothelial progenitor cell (EPCs) functioning [Sgarra, 2020], therefore providing one-shot explanation to both atrial stasis (increasing atrial fibrosis -AFib and generating atrial fibrillation -AF) and endothelial dysfunction. If such cardiac-bone marrow networking would be verified, a fundamental pathogenic mechanism of AF would be unraveled.
This study aims to investigate if: i) AFib would relate to folate cycle disorders inducing bone-marrow function disorders and increased homocysteine levels associated to MTHFR-C677T mutation; ii) AF patients would show dysfunctional EPCs**.**
**Methods:** We recruited 65 AF patients (General Hospital F.Miulli), and 30 hypertensive controls (Bari University) (Ethic Committee, n°6903). MTHFR-C677T genotypes (qRT-PCR), AFib (bipolar peak-to-peak voltage), RBC, RDW and homocysteinemia were measured. EPCs were isolated and functional in vitro (wound healing), and in vivo (Chick Chorioallantoic Membrane) assays performed.
**Results:** Baseline characteristics were similar in AF and controls. The percentage of AFib differs between MTHFR-C677T homozygous (n=18) vs MTHFR non-C677T homozygous (n=47) patients (P<0.01). The multivariate analysis shows RBC and RDW alteration and homocysteine increase in patients with MTHFR-C677T homozygosity (vs. non-homozygous, P<0.005). The in vitro EPCs migration and the in vivo angiogenesis ability were impaired in MTHFR-C677T homozygous AF patients (vs. non-homozygous, P< 0.05). The treatment with MTX in controls suggests the same results obtained in MTHFR-C677T homozygous patients in vitro and in vivo.
**Conclusions:** Our findings support the hypothesis that folates dysmetabolism promotes AF identifying MTHFR-C677T homozygous as a condition of increased risk in AF patients and focusing on hyperhomocysteinemia and EPCs diversion as new pharmacological targets.

Abstract n SO2_5 - Presenting author**: Sara Greco**

## Characterization of a novel dyslipidemic immunodeficient mouse model for human immune cell engraftment studies

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**Aim:** Immune response in atherosclerosis has grown of interest due to its contribution to the development and progression of the disease. Targeting of human immune cells may reveal to be a great therapeutic strategy and this prompts the necessity of adequate experimental models able to produce translatable results for testing of new approaches and to effectively mimic pathological mechanisms.
Aim of this study was the characterization of a novel immunocompromised atheroprone model.
**Methods:** Immunodeficient triple KO mice for Rag2/IL2rg/CD47 on C57BL/6J background (TKO, IMSR_JAX:025730) were crossed with LDLr-KO to generate an immunodeficient dyslipidemic TKO-LDLr KO mice. Male mice were fed a high cholesterol diet (WTD) for 8 or 12 weeks for immuno-metabolic phenotyping and comparison to immunocompetent LDLr KO mice.
**Results:** Levels of circulating total cholesterol increased with time (from 857.2±29.31 mg/dL to 1128±276.2 mg/dL). Monocytes count in LDLr KO showed a 3.7 increase at 8 weeks and of 5 times at 12, while for TKO-L at both times the increase was of 1.7 times. Neutrophils count was increased in LDLr KO of 2.1 and 5.4 times respectively, while in TKO-L was increased of 1.6 times only at 12 weeks. TKO-L showed decreased atherosclerosis compared to LDLr KO mice, despite lesions increased from 8 to 12 weeks (33289±6888 µm2 and 221412±19076 µm2 respectively).
**Conclusion:** We characterized the immuno-metabolic phenotype of dyslipidemic TKO-LDLr KO mouse model that develops atherosclerosis despite to a lower extent compared to immunocompetent LDLR KO. This model is suitable to receive human immune cells for addressing immune cell modulation in the context of atherosclerosis.

Abstract n SO2_6 - Presenting author**: Isabella Calderoni**

## Oleate prevents palmitate-induced abnormalities in insulin signaling in human cardiac progenitor cells by inhibiting p38 MAPK and c-Jun phosphorylation

Isabella Calderoni[1], Rossella D'Oria[1], Cristina Caccioppoli[1], Carmela Colabufo[1], Valentina Annamaria Genchi[1], Giuseppe Palma[1], Giuseppe Santarpino[2], Aldo Domenico Milano[1], Tomaso Bottio[1], Anna Leonardini[1], Annalisa Natalicchio1, Sebastio Perrini[1], Angelo Cignarelli[1], Francesco Giorgino[1], Luigi Laviola[1]

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**Aim:** Elevated saturated fatty acid deposition in the heart results in increased cardiovascular risk in humans. This study investigates the ability of palmitate, a saturated fatty acid, to impair insulin signaling in human cardiac progenitor cells (hCPC), and the potential protective effects of oleate, a mono-unsaturated fatty acid, on palmitate-induced abnormalities.
**Methods:** hCPC were obtained from non-obese, non-diabetic subjects undergoing elective cardiac surgery. hCPC were exposed to 0.25 mM palmitate and/or 0.1 mM oleate for 24 h, and then exposed to 100 nM insulin for the last 15 minutes. Expression of insulin receptor (IR) isoforms, A (IR-A) and B (IR-B), was evaluated by quantitative RT-PCR. IR protein levels, as well as Akt (S473), p38 MAPK (T180/Y182), and c-Jun (S63) phosphorylation levels were assessed by immunoblotting. p38 MAPK and JNK inhibition was obtained using 15 μM SB202190 and 20 μM SP600125 for 1 h, respectively.
**Results:** hCPC express both IR-A and IR-B. Exposure of hCPC to insulin induced Akt (S473) phosphorylation ($p<0.05$). Treatment with palmitate, but not with oleate, resulted in impaired insulin-induced Akt phosphorylation and downregulation of IR protein levels, increased expression of total IR mRNA, IR-A, IR-B, and increased IR-A/IR-B ratio ($p<0.05$). Palmitate, but not oleate, induced p38 MAPK (T180/Y182) and c-Jun (S63) phosphorylation ($p<0.05$). Pretreatment with SB202190 or with SP600125 inhibited the ability of palmitate to impair insulin induced Akt phosphorylation ($p<0.05$), but not downregulation of IR protein levels. Interestingly, co-incubation of palmitate with oleate prevented palmitate-induced changes in IR and inhibition of insulin-induced Akt phosphorylation ($p<0.05$). Co-incubation with oleate also abolished palmitate-induced p38 MAPK and c-Jun phosphorylation ($p<0.05$).
**Conclusions:** Oleate prevents palmitate-induced abnormalities in insulin signaling in hCPC, largely by counteracting p38 MAPK and JNK activation. Hence, oleate supplementation might limit lipotoxicity in hCPC, thus contributing to cardiac protection.

Abstract n SO2_7 - Presenting author**: Alessandro Mengozzi**

## Transcriptional regulation of Hexokinase-2 by BRD4 drives perivascular adipose tissue meta-inflammation in cardiometabolic disease

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**Aim:** To investigate BRD4-related transcriptional programmes in mouse and human models of cardiometabolic disease.
**Methods:** Small arteries (0.1-0.3 mm) dissected from visceral fat biopsies from healthy subjects (n=16) and patients with obesity and hypertension (n=16) were mounted on a pressurized myograph to assess the acute ex-vivo effects of BRD4 inhibition on vascular function. Vasorelaxation to acetylcholine and acetylcholine+L-NAME was evaluated, in the presence or in the absence of perivascular adipose tissue (PVAT), at baseline and after incubation with the BRD4 inhibitor RVX-208 and with selective anti-inflammatory and anti-metabolic drugs. A cardiometabolic mouse (high-fat diet+L-NAME supplementation) was orally administered RVX-208 (150 mg/kg) to test in vivo effect of chronic BRD4 inhibition. ROS and nitric oxide were assessed by confocal microscopy; protein and gene expression by Western blot and qPCR. Transcriptional changes upon BRD4 inhibition were investigated by a custom PCR array, confirmed by ChIP, and characterised by metabolomics, lipidomics and mitochondrial swelling.
**Results:** Endothelial-dependent vasorelaxation and vascular and perivascular TNF-alpha, IL-1beta, IL-6 were altered in cardiometabolic patients and mice. RVX-208 substantially attenuated ex-vivo vascular dysfunction, with an impact greater than anti-IL-1beta, anti-IL-6 receptor and anti-TNF-alpha. The effect was more pronounced in vessels with intact PVAT, suggesting a restoration of the PVAT anti-contractile phenotype. Gene expression profiling in PVAT unveiled hexokinase-2 (HK2) - a glycolytic enzyme implicated in mitochondrial dysfunction and inflammation - as the top downregulated gene by RVX-208 treatment. Increased binding of BRD4 to HK2 promoter in PVAT samples from cardiometabolic mice was confirmed by ChIP assays. Metabolomics assays further validated the findings by demonstrating a glycolytic shift in PVAT under disease conditions. Finally, ex vivo selective inhibition of HK2 rescued vascular dysfunction.
**Conclusion:** Targeting the deleterious BRD4-HK2 interplay restores cardiometabolic vascular dysfunction via reversal of the PVAT meta-inflammatory shift, highlighting a novel potential target to fight cardiometabolic pandemics.

Abstract n SO3_1 - Presenting author**: Federica Piani**

## Long-term cardiovascular outcomes after a pregnancy complicated by hypertensive disorders

Piani Federica[1]; Bragagni Alessio[1], Baracchi Alessandro[1]; Cromi Debora[1]; Ruscelli Federico[1]; Scarduelli Sara[1]; Vincenzi Sofia[1]; Agnoletti Davide[1]; Degli Esposti Daniela[2]; Borghi Claudio[1]

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**Objective:** The maternal vasculature undergoes significant adaptations during pregnancy to meet the increased metabolic demands of the developing fetus. These adaptations include increased cardiac output and blood volume, as well as reduced systemic vascular resistance to support the fetoplacental unit. In Hypertensive disorders of pregnancy (HDP) there is an impaired cardiovascular adaptation to pregnancy with effects extending beyond the duration of the pregnancy. In the present study we aimed to characterize long-term cardiovascular status of women who suffered from HDP.
**Design and method:** Fifty-eight women who attended at least one post-partum visit in our HDP Clinic (IRCCS Policlinico Sant'Orsola-Malpighi, Bologna, Italy) and a follow-up visit after at least 5 years from delivery were enrolled in the study. Exclusion criteria included multiple pregnancy, fetal genetic or congenital abnormalities, maternal history of organ transplantation or chronic kidney disease (CKD), and absence of a post-partum echocardiographic evaluation. In the follow-up visit participants underwent a complete cardiovascular assessment including echocardiography and multiparametric vascular function assessment.
**Results:** Two major cardiovascular events occurred, one stroke and one myocardial infarction, both in women with index-pregnancy complicated by preeclampsia (PE). While not statistically significant, women with HDP-non-PE and PE displayed a trend towards an increased risk of developing composite cardiovascular outcome, and women with PE tended to experience it sooner (**Figure 1**). Nearly half of the women with a history of HDP, whether PE or HDP-non-PE, developed chronic hypertension. Some women also developed hyperuricemia, CKD, and type 2 diabetes at follow-up, most of them with a previous history of PE. Structural and functional cardiac changes were observed in a few cases, especially among women with PE, and vascular dysfunction was more common in women with a history of HDP compared to those with normotensive pregnancies (**Figure 2**).
**Conclusions:** Results of the present study adds on literature on long-term cardiovascular impact of HDP and further emphasize the importance of a timely follow-up of women who suffered from HDP and particularly PE.


Figure 1. Kaplan-Meier estimates of years from delivery to the first event of composite cardiovascular outcome stratified by HDP diagnosis. In red women with PE, in orange HDP-non-PE, and in green NP group. Abbreviations: HDP-non-PE, hypertensive disorders of pregnancy excluding preeclampsia; NP, normotensive pregnancy; PE, preeclampsia.

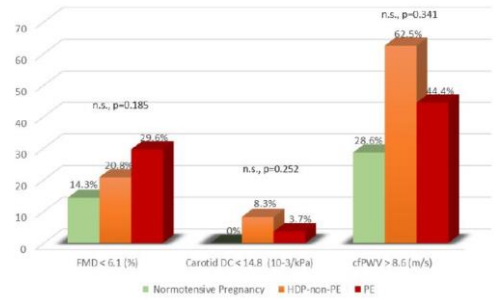


Figure 2. Histogram of vascular dysfunction prevalence across study subgroups. Normotensive pregnancy is reported in green, HDP-non-PE in orange and PE in red. P values for the trend between groups are reported over each variable. Abbreviations: cfPWV, carotid-femoral pulse wave velocity; DC, distensibility coefficient; FMD, flow-mediated dilation; HDP-non-PE, hypertensive disorders of pregnancy excluding preeclampsia; PE, preeclampsia.

Abstract n SO3_2 - Presenting author**: Emiliano Fiori**

## Association of NDUFC2 polymorphic variants with left ventricular hypertrophy and ventricular mechano-energetic efficiency reduction in human hypertension

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**Background and aims:** Previous experimental studies showed that a dysfunction of the NADH dehydrogenase (ubiquinone), the mitochondrial Complex I (CI), is associated with the development of left ventricular hypertrophy (LVH). A deficiency of Ndufc2 (a subunit of CI) impairs CI activity and causes severe mitochondrial dysfunction. The *NDUFC2*/rs11237379 polymorphic variant is associated with reduced gene expression and impaired mitochondrial function, contributing to increased susceptibility to vascular diseases. Mitochondrial dysfunction might also determine an imbalance between myocardial energetic demand and altered efficiency.
**Methods and results:** We examined the association of *NDUFC2*/rs11237379 and another *NDUFC2* polymorphic variant (rs641836) with the development of LVH and with the reduction of echo-derived mechano-energetic efficiency indexed for myocardial mass (MEEi) in hypertensive patients. Two-hundred-fourty-six hypertensive subjects (147 male, 59.7%) with a mean age of 59±15 years were studied. Seventy-nine individuals (32%) presented LVH. The association analysis for both SNPs showed that hypertensive patients carrying the TT genotype at the *NDUFC2*/rs11237379 had a significant increase of echocardiographically assessed septal thickness (p=0.001), posterior wall thickness (p=0.003), relative wall thickness (RWT) (p=0.01), LV mass/ body surface area (BSA) (p=0.012) and LV mass/height$^{2.}$(p=0.0033) compared to subjects carrying either CC or CT genotypes. To better dissect the genetic effect, a covariate ANOVA was performed for each cardiac variable, considering age, gender, body mass index (BMI), office blood pressure (BP), antihypertensive treatment with a combination of 2 or more drugs and the number of BP-lowering agents as covariates. The adjustment for covariates revealed significant differences for septal thickness (p=0.07), posterior wall thickness (p=0.008), RWT (p=0.021), LV mass/BSA (p=0.03). With regard to *NDUFC2*/rs641836, hypertensive subjects carrying the mutant A allele had a significant increase of septal thickness (p=0.001), posterior wall thickness (p=0.001), RWT (p=0.005), LV mass (p=0.001), LV mass/BSA(p=0.001), LV mass/height$^{2.7}$(p=0.002) compared to wild-type homozygotes. After adjustment for covariates, the results were significant for septal thickness (p=0.017), posterior wall thickness (p=0.011), LV mass (p=0.003), LV mass/BSA (p=0.002) and LV mass/height$^{2.7}$(p=0.010).
Patients carrying the TT genotype at the *NDUFC2*/rs11237379 had a significant decrease of MEEi compared to subjects carrying either CC or CT genotypes (p=0.011) also after adjustment for age, gender, BMI, office BP, number of BP-lowering agents and left ventricular ejection fraction (p=0.017). Consistent results were obtained for subjects carrying the mutant A allele at the *NDUFC2*/rs641836 compared to wild-type homozygotes (p=0.006; p=0.010 after adjustment for covariates).
**Conclusions:** Our results demonstrate a significant association of *NDUFC2* variants with LVH and with MEEi reduction in hypertensives and highlight a novel role of CI dependent mitochondrial dysfunction on increased susceptibility to cardiac damage in human hypertension. This study paves the way of a new pathophysiological mechanism of LVH which may lead to new clinical strategies.

Abstract n S03_3 - Presenting author**: Nicolò De Biase**

## Similarities and differences between aortic stenosis with normal left ventricular systolic function and heart failure with preserved ejection fraction

De Biase Nicolò[1], Del Punta Lavinia[1], Mazzola Matteo[2], De Carlo Marco[3], Mengozzi Alessandro[1], Nesti Lorenzo[1], Masi Stefano[1], Pugliese Nicola Riccardo[1].

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**Aims.** Degenerative aortic stenosis (AS) is highly prevalent in Western countries and displays a strong association with cardiovascular risk factors (e.g., age, arterial hypertension, diabetes mellitus, dyslipidaemia, and visceral obesity) also involved in the development of heart failure with preserved ejection fraction (HFpEF). Despite such similarities, AS with preserved left ventricular ejection fraction (ASpEF) is considered a different entity from HFpEF. With this background, we investigated the haemodynamic and metabolic features of patients with ASpEF both at rest and during physical effort and highlight similarities and differences with HFpEF.
**Methods.** We enrolled 148 patients with HFpEF, 150 with ASpEF and at least moderate aortic transvalvular gradient, and 80 age- and sex-matched healthy controls. All patients received a comprehensive laboratory evaluation, a resting echocardiographic examination, and a combined cardiopulmonary-echocardiographic stress test.
**Results.** Serum levels of N-terminal prohormone of brain natriuretic peptide were similar between HFpEF and ASpEF patients. As a marker of heightened inflammation, epicardial adipose tissue (EAT) thickness was significantly greater in ASpEF compared to HFpEF and controls. The presence of type 2 diabetes mellitus (T2DM) was associated with further increase in EAT thickness in both ASpEF and HFpEF. EAT thickness was inversely related to peak oxygen consumption (VO2) in all subgroups. All patients showed a significant impairment in peak VO2 caused by a reduction in both cardiac output (CO) and peripheral arteriovenous oxygen difference (AVO2diff). Again, the presence of T2DM was associated with more severe impairment in peak VO2 in HFpEF and ASpEF, due to reduced AVO2diff in both groups and also reduced CO in HFpEF.
**Conclusions.** ASpEF and HFpEF share important similarities. Larger studies should be designed to investigate the hypothesis that ASpEF represents a separate phenotype in the spectrum of HFpEF, and elucidate the role played by T2DM in the pathophysiology of both conditions.

Abstract n SO3_4 - Presenting author**: Anna Colomba**

## Hemodynamic Forces and their role in Multiple Myeloma patients with ventricular remodelling: a comparative study with normotensive and hypertensive patients

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**Aim:** Multiple Myeloma (MM) affects a population with high prevalence of cardiovascular morbidities, the most represented being hypertension. These patients benefit from early identification of myocardial damage before and during treatment, the latest technology being Hemodynamic Forces analysis (HDFs). This work aims to identify differences in HDFs in patients with MM, hypertension or both versus normotensive non-oncologic subjects. Comparison between HDFs analysis and standard ventricular remodelling markers may permit better understanding of their role as early markers of myocardial damage.
**Methods:** Three groups of patients were recruited by the Hypertension Unit, University of Turin: MM patients (n. 71) including hypertensive (MMHT, n. 44) and normotensive (MMNT, n. 27) patients; non-oncologic hypertensive (CoHT, n. 52) and normotensive patients (CoNT, n. 50). All three groups were evaluated by transthoracic echocardiography for HDF analysis using the QStrain Echo Prototype v.1.3 software.
**Results:** Comparing MMHT with CoHT and CoNT resulted in significantly decreased ejection fraction (EF), global longitudinal strain (GLS) and HDFs (systolic, diastolic and in the entire heartbeat) values in MMHT and CoHT vs CoNT, whereas ventricular mass (LVMi) increased in hypertensive patients (MMHT and CoHT vs CoNT). Comparing MMNT with CoNT resulted in a significant reduction of total systolic HDFs (14.0 ± 4.9 vs. 17.6 ± 5.2; p-value 0.006) and systolic ejection HDFs (14.1 ± 4.9 vs. 17.8 ± 5.1; p-value 0.008). There was no significant change in EF and LVMi between normotensive groups, emphasizing the precocity of HDFs in detecting ventricular remodelling.
**Conclusions:** MM leads to ventricular remodelling, with or without the influence of hypertension. HDFs analysis identifies this remodelling when other cardiac markers are still unvaried. HDFs analysis application in MM patients could be useful in order to detect early myocardial damage and for better stratification of cardiovascular risk, especially in candidates for cardiotoxic drugs.

Abstract n SO3_5 - Presenting author**: Giorgia Laureti**

## Unveiling heart stress, likely or very high risk of heart failure by NT-proBNP in older COPD patients eligible for triple inhaled therapy

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**Aims:** The coexistence of chronic obstructive pulmonary disease (COPD) and cardiovascular (CV) diseases, especially heart failure (HF), has several implications for the patient in terms of diagnostic challenge, optimization of pharmacological treatments and prognosis. Our study aimed to evaluate the prevalence of heart stress (HS), likely heart failure (HF), and very high risk of HF after dosing N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, as endorsed by the 2023 Clinical Consensus Statement of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), in older COPD patients eligible for triple inhalation therapy.
**Methods:** An observational cross-sectional study was conducted on 91 consecutive COPD outpatients and inpatients hospitalized for acute exacerbations of COPD (AECOPD), aged ≥ 65 years, eligible for triple inhaled therapy according to the 2023 Global Obstructive Lung Disease (GOLD) recommendations. Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) was collected before the triple inhalation therapy initiation. Patients were classified according to the age- and age/comorbidity-adjusted NT-proBNP cut-points described in the 2023 Consensus Statement of the HFA of the ESC.
**Results:** The mean age was 85±7 years, with female prevalence (52%). Outpatients were 36% (n=33), and 64% (n=58) were inpatients. The median NT-proBNP was 1150 (IQR 550-3178) pg/ml. In outpatients, NT-proBNP levels indicative of HS likely were present in 48.5% of patients, NT-proBNP levels compatible with a very high risk of HF were present in 12.1% of patients, and HF likely based on age-adjusted cut-points in 30.3% of patients. Regarding the acute setting, 22.4% of patients had NT-proBNP levels compatible with a very high risk of HF and 32.8% of patients with HF likely**.**
**Conclusions:** Our study highlights the relevance of systematic assessment of NT-proBNP dosage in the initial workup of inpatients with AECOPD and for phenotyping COPD outpatients, guiding physicians to early detect HS, likely HF and very high risk of HF comorbidity, with a potentially positive impact on the management and prognosis of COPD patients (indication to arrange for echocardiography, referral to a specialist team and appropriate individualized treatment).

Abstract n SO3_6 - Presenting author**: Lavinia Del Punta**

## Bio-humoral and non-invasive haemodynamic correlates of renal venous congestion in the heart failure spectrum

Lavinia Del Punta[1], Nicolò De Biase[1], Francesco Filidei[1], Alessio Balletti[1], Silvia Armenia[1], Valerio Di Fiore[1], Stefano Masi[1], Nicola Riccardo Pugliese[1]

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**Aim.** Doppler-derived RVF is continuous in healthy subjects and becomes discontinuous with increased fluid retention; thus, RVF evaluation allows for refined pathophysiological characterisation in HF. We sought to analyse the relationship between different RVF patterns, echocardiography-derived haemodynamic variables and bio-humoral parameters in patients at risk of or with overt HF.
**Methods.** The study enrolled 304 patients, of which 63 were at risk of developing HF, while 241 had overt HF. Among the latter, 61 patients had preserved left ventricular ejection fraction (LVEF ≥50%), and 180 had reduced LVEF (<50%). All subjects underwent a baseline echocardiographic evaluation, lung ultrasound, Doppler-derived RVF analysis, besides blood and urine sampling.
**Results.** RVF was continuous in 230 patients (76%) and discontinuous in 74 (24%; dRVF). Among the latter, 39 showed pulsatile dRVF, 18 showed biphasic dRVF (i.e., two separate phases of venous flow), and 17 showed monophasic dRVF (i.e., only during diastole). dRVF was more prevalent in patients with overt HF. Monophasic dRVF was associated with worse haemodynamic impairment and renal function, as evaluated by estimated glomerular filtration rate and urinary albumin-to-creatinine ratio. Adjusting for clinical confounders (arterial hypertension, diabetes mellitus, presence of overt HF and serum creatinine levels), worsening RVF patterns were associated with increased NT-proBNP, worse right ventricular-pulmonary arterial uncoupling, increased inferior vena cava diameter, and increased estimated pulmonary capillary wedge pressure. This trend was confirmed in the subgroup of patients with overt HF, even after adjusting for LVEF.
**Conclusion.** Doppler evaluation of RVF patterns improves the characterisation of patients within HF. The pathophysiological significance of impaired RVF is independent of common cardiovascular risk factors and LVEF. Implementing RVF analysis in clinical practice could assist physicians in gauging disease severity and trajectory, allowing for timely identification of patients at greater risk for developing or worsening HF.

Abstract n SO3_7 - Presenting author**: Alessandra Rizzuto**

## Extracellular vesicles characterization in patients with hypertrophic cardiomyopathy

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**Background:** Hypertrophic cardiomyopathy (HCM) is diagnosed according to the presence of morphological and functional traits of the heart, often in the presence of genetic mutations. A specific biomarker assessing the aetiopathology of this condition is lacking. Extracellular vesicles (EVs), small particles released by all cells into biological fluids, hold promise as diagnostic and prognostic tools for cardiac diseases. We aim at characterising plasma-derived EVs isolated from 18 consecutive HCM patients and 13 healthy volunteers (CTR).
**Methods:** HCM underwent echocardiographic assessment and genetic testing evaluating 200 genes (NGS). EVs were isolated via ultracentrifugation from platelet-free plasma. Quantitative and qualitative assessments of EVs were performed by nanoparticle tracking analysis and transmission electron microscopy. FACS analysis was used to characterize EV subpopulations. Data are expressed as median and interquartile ranges.
**Results:** Most patients were male (70.8% HCM and 54% CTR) with a median age of 61 (52.5-71) years (HCM) and 47 (44-52) (CTR). Missense mutations in the *MYH7* gene were the most found in HCM. The median maximum wall thickness in HCM was 16 mm (15-19) vs 8 mm (7-9) in CTR. No differences were found in EV concentrations between HCM and CTR, respectively, $3.6*10^9$ EV/ml/cell count ($2*10^9$-$5*10^9$) and $5*10^9$ EV/ml/cell count ($4*10^9$-$6*10^9$). However, EV concentration was positively associated with the sudden cardiac death risk score in HCM (r= 0.63). Among the EVs positive for CFSE (a specific dye for EVs), those released from platelets, progenitor endothelial cells and neutrophils were increased in HCM patients vs CTR, respectively, by 1.7-, 1.5- and 1.1-fold. A strong negative association (r= -0.74) was found between progenitor endothelial cell-derived EVs and the E/E' ratio of diastolic function, a strong predictor of first cardiac events.
**Conclusions:** HCM patients present a peculiar phenotypic pattern of EVs that associates which diastolic function and sudden cardiac death.

Abstract n SO4_1 - Presenting author**: Alfonso Ferrara**

## Using AI to identify left ventricular ejection fraction from the ECG: The SOLOMAX (SOciaL NetwOrk of MedicAl Experiences) project

Alfonso Ferrara, Valeria Visco, Antonio Robustelli, Francesco Loria, Antonella Rispoli, Andrea Martorella, Albino Carrizzo, Alessia Bramanti, Gianni D'Angelo, Carmine Vecchione, Michele Ciccarelli

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**Aim**: The interest in machine learning-based algorithms in the cardiovascular field is rapidly growing, especially for diagnostic and prognostic purposes. Recent evidence has demonstrated that certain electrocardiographic (ECG) parameters are predominantly associated with systolic function, estimated as left ventricular ejection fraction (LVEF) by echocardiography, albeit with still relatively low accuracy.
Consequently, this study aims to develop an AI-based model capable of predicting LVEF from ECG data in an Italian population.
**Methods**: Within the SOLOMAX project, we collected paired ECG-Echocardiography exams from 105 patients (64.82±16.02y;62.86%male). Precisely, we excluded patients with atrial fibrillation at the time of the ECG, PMK or electrostimulated rhythm, valve prostheses, previous cardiac surgery, O2 therapy or COPD, previous ablation or invasive electrophysiology procedures, currently hospitalized for Takotsubo or ACS, heart failure exacerbation, inotropic therapy, ACS over the last 3 months. We recorded anthropometric, clinical, biochemical, ECG, and Echocardiography parameters. The collected data was studied using AI-based techniques to create a new model to predict LVEF from ECG. Using an approach based on evolutionary algorithms, genetic programming was used. This approach solves a symbolic regression problem through genetic algorithms and provides a mathematical model of the relationship between ECG parameters and LVEF. The formula obtained was then used to build a simple explainable classifier, which provides a global interpretation of the link between ECG parameters and LVEF.
**Results**: The performance of the proposed approach and the reliability of the results were assessed using the k-fold cross-validation method and by estimating standard metrics derived from the confusion matrix associated with a binary classifier, that is, accuracy, sensitivity, specificity, precision, and F-Measure. The proposed approach consistently demonstrated its ability to distinguish patients with preserved LVEF from those with reduced LVEF. Each metric averaged across all experiments scored approximately 95%. Furthermore, in the expression generated by the AI model, the axes of the P, QRS, and T waves play a prominent role, as they are likely to provide a better interpretation of the three-dimensional cardiac geometry and, consequently, cardiac function.
**Conclusions**: AI applied to ECG data can be used to create cost-effective diagnostic and predictive tools for assessing LVEF. Indeed, the obtained formula highlights the relationship between ECG parameters and LVEF, as well as its complexity, which can aid in detecting heart diseases.

Abstract n SO4_2 - Presenting author**: Francesco Corvasce**

## PROSIT: impact of remote monitoring on patients' quality of life. A single centre study

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**Aim**: PROSIT (Patient Reported Outcomes and Smart Imaging in Telecardiology) is an innovative research initiative designed to explore the efficacy of remote patient monitoring in cardiovascular care. This project leverages wearable technology and patient-reported data to enhance the management of cardiac conditions, aiming to improve both patient outcomes and quality of life.
**Methods**: We evaluated 100 Caucasian patients, affected by hypertension, divided in three groups: groupA, with a wearable device(Hi) for continuous monitoring and an app with manual vital signs reporting, groupB with only the app, and groupC as the control group. The app for A and B group was able to suggest patient-physician interaction evaluating data inputted. All patients were assigned in different groups with a randomized approach based on factors such as age, gender, ejection fraction, presence of atrial fibrillation, and pulmonary embolism.
**Results**: Telemonitoring usage has led patients to experience safe feelings in their daily lives. In fact, patients in group B and A presented an improvement, notably significant for those in groupA ($p<0.05$), compared to groupC. In contrast, groupC did not change their responses after one month of follow-up. Despite encountering minor issues during the trial, all enrolled patients believe that the telemonitoring program and telemedicine visits are commendable. Although the patients themselves have pointed out areas for improvement in the software, this does not diminish the substantial foundation that this technology signifies. No change was found in treatment adherence or blood pressure control.
**Conclusions**: This study leads up to a future where digital support to medical practice will play a crucial role in accessing patient care and therapies, both for patients and clinicians alike. Patients are ready to embrace a new method for accessing care and being monitored by clinicians, one that integrates the old and the new, keeping pace with the times.

Abstract n SO4_3 - Presenting author**: Alessandro Gezzi**

## Validation of a novel web-based application (www.humtelemed.it) for a simple and rapid assessment of individual cardiovascular risk based on the 2021 ESC Guidelines

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**Background and aim**: Individual cardiovascular risk (CVR) assessment in primary prevention relies on the conventional consultation of the 2021 ESC Guidelines. To address this issue, we developed a multi-language and free-to-use web application (www.humtelemed.it) based on the SCORE2/SCORE2-OP model and 2021 ESC Guidelines to simplify the CVR assessment for non-expert users or busy physicians. This study assessed the agreement in CVR between the conventional method versus the multi-language web app.
**Methods**: A cross-sectional study on 1306 consecutive patients referred to our Centre. Two double-blind operators performed the CVR assessment and classified each patient into low-moderate, high, and very high-risk categories. One operator conventionally assessed CVR with SCORE2/SCORE2-OP online calculators or risk charts or, when necessary, the consultation of the 2021 ESC Guidelines. Conversely, the second operator used the web app www.humtelemed.it on the same patients. The marginal homogeneity test and the Kappa statistic were used to compare the two methods.
**Results**: Mean age was 60 ± 12 years, with male prevalence (51%). Patients in primary prevention were 82%. According to the SCORE2/SCORE2-OP and 2021 ESC Guidelines consultation, the prevalence of the individual CVR was the following: low-moderate 19% (243), high 37% (480), and very-high 45% (583). According to our web app, the prevalence of the individual CVR was the following: low-moderate 20% (255), high 35% (462), and very-high 45% (589). According to the marginal homogeneity test, the individual CVR assessed using the web app (www.humtelemed.it) was not statistically different from the one evaluated using the SCORE2/SCORE2-OP charts or calculator and guideline consultation ($p=0.907$). The two methods strongly agreed (Kappa=0.960, $p<0.001$) since they concorded in 97.5% of the cases.
**Conclusion**: We found a minor, non-statistically significant mismatch between the two methods, potentially also due to the non-infallibility of the manual CVR evaluation method.

Abstract n SO4_4 - Presenting author**: Valeria Visco**

## An Explainable Model for Diagnosing Worsening Heart Failure based on Genetic Programming

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**Aim**: The role of Artificial Intelligence-based models in cardiovascular diseases is rapidly growing, especially for diagnostic and prognostic purposes. Precisely, this study aims to develop a novel diagnostic model to predict worsening heart failure (WHF) using artificial intelligence (AI). Indeed, the development of an AI model based on clinical and instrumental parameters to identify patients at greater risk of WHF, in a phase undiagnosable for the physicians, would allow quickly diagnose and treat of such events.
**Methods**: We used retrospectively collected data from 519 patients treated at the HF Clinic of the University Hospital of Salerno. We employed Genetic Programming to construct a threshold-based binary classifier to generate a mathematical model expressing the relationship between clinical parameters and WHF.
**Results**: Experiments conducted using data from our population have demonstrated the effectiveness of our model, surpassing even the most prominent MachineLearning-based algorithms. Indeed, the proposed GP-based classifier has attained a 96% average score for all considered evaluation metrics. From the mathematical model of the proposed classifier, the WHF is closely linked to only four variables: creatinine, PAPs, CAD, and diuretics. In particular, diuretics are linked with WHF independently from other parameters. Low creatinine or PAP values seem to be associated with a lower incidence of WHF.
Finally, a 3D graphical representation of the proposed mathematical model is also provided to be used by medical staff to represent the patient's clinical situation.
**Conclusions**: Our findings support the application of GP-based models in cardiovascular diseases. AI can potentially impact the clinical practice for HF, ranging from early diagnosis to management. Specifically, ML-risk prediction models could identify patients at risk of adverse events and who may benefit from closer follow-up and post-discharge services. In conclusion, their employment could provide a set of additional benefits for both physicians and patients, such as a more rapid diagnosis, a more targeted cure, and a reduction in hospitalizations.

Abstract n SO4_5 - Presenting author**: Teresa Maria Grazia Fasciana**

## Comparison of two polygenic risk scores to identify non-monogenic primary hypocholesterolemias in a large cohort of italian hypocholesterolemic subjects

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**Aim:** Primary Hypobetalipoproteinemias (HBL) are a group of dominant and recessive monogenic genetic disorders caused by mutations in APOB, PCSK9, ANGPTL3, MTTP, Sar1b genes and characterized by plasma levels of total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and apolipoprotein B (apoB) below the 5$^{th}$ percentile of the distribution in a given population. Mutations in the candidate genes account only for a small proportion of subjects with HBL suggesting a role for a polygenic contribution to the low cholesterol phenotype.
**Methods:** To explore the complex genetic architecture of HBL we compared two polygenic risk scores in order to assess the role of the polygenic burden and the differences in the clinical phenotype between monogenic and polygenic HBL; we studied a cohort of 170 subjects with primary HBL referred over a 25-year period to 2 Italian reference centers have been studied. The genetic analyses have been based on: Sanger sequencing, in-house NGS customized panel and two scores, PRS1 and PRS2 for the polygenic burden.
**Results:** Sixty 60 (35%) and 63 (37%) subjects had a monogenic and polygenic HBL respectively. LDL-C plasma levels were significantly lower in monogenic HBL (30.87 ±3.12 mg/dl) compared with the non-monogenic HBL (42.80 ±2.18 mg/dl) ($p < 0.002$) with no differences in the percentage of fatty liver.
**Conclusions:** Only PRS1 is effective in detecting polygenic HBL while PRS2 does not improve the polygenic diagnosis.

Abstract n SO4_6 - Presenting author**: Susanna Longo**

## A metabolomic approach to unexplained syncope

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**Aim:** due to its complex etiology and the difficult interpretation of some episodes that remain unexplained, the management of syncope is often challenging and may require expensive tests without arriving at a final diagnosis. The aim of this study is to identify a metabolomic signature that facilitates the reclassification of unexplained syncope (US) and aid the risk management of syncope.
**Methods:** we evaluated the anthropometric, clinical, cardiometabolic and metabolomic profile of 85 participants with syncope, divided into: the OH group (n=23) for orthostatic syncope, the NMS group (n=26) for neuromediated syncope, the CS group (n=9) for cardiological syncope, and US group (n=27) for episodes which presentation did not fall into any ESC guidelines category. Their data were compared with a control group of healthy subjects who had not experienced syncope (CTRL group; n=10).
**Results:** to predict how to cluster US group based on the differences in metabolite levels between the five groups, we built a new sample prediction logistic regression model. From the comparison between the CS group and the NMS group, GLN/LYS were increased in the CS group (p=0.01) and C22:0-LPC in the NMS group (p=0.03). The GLN/LYS model clustered 95% of US in the NMS group and 5% in the CS group (AUC=0.829). The C22-LPC model clustered 96% of US in the NMS group and 4% in the CS group (AUC=0.84). This evidence was confirmed by the difference in plasma levels of C22-LPC and GLN/LYS which were increased in the NMS and CS groups respectively, even if statistical significance is only reached for C22-LPC (padj 0.0054).
**Conclusions:** the metabolomic approach demonstrated a good diagnostic and prognostic accuracy in the management of syncope. Based on our results, we hypothesize a possible role C22:0 LPC and GLN/LYS in reclassifying US and differentiating it from CS and NMS syncope.

Abstract n SO4_7 - Presenting author**: Giovanni Battista Vingiani**

## Single Cell RNA sequencing and Spatial Transcriptomic to profile Kupffer Cells during NASH and liver Cirrhosis

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**Background:** NASH and its subsequent progression, cirrhosis, are liver diseases that affect an increasing number of people each year. Here we present a novel approach which integrates single-cell RNA sequencing data and spatial transcriptomic data to profile changes occurring in Kupffer cells (KC) during disease progression in human and in experimental model settings.
**Methods:** The analysis of single-cell RNA sequencing and spatial transcriptomics of NASH, cirrhotic and healthy human livers was performed. The results were then compared with those obtained in C57Bl/6J mice fed a Standard Fat Diet (11% fat) or a fat and cholesterol enriched diet (58% fat, 1% cholesterol) for 24 weeks. Data processing involves normalization, SCT and Harmony transformation for batch effect removal. Differentially expressed genes (DEGs) were identified (Padj-value<0.05). Ingenuity Pathway Analysis (IPA) and NicheNet (Inference Analysis) were used to provide insights into biological pathways (FDR<0.05) and relationships between cell populations (p-value<0.05). The data used are available on GSE48452, GSE192742 and GSE156059.
**Results:** The common KC-enriched pathways between the health groups and the two disease groups, separately, show several common pathways including those involved in cholesterol metabolism, antigen processing and presentation, toll-like receptor signaling pathway, and oxidative phosphorylation. IPA analysis of the mouse dataset predicted the presence of mitochondrial dysfunction (z-score=4.89), lipid dysmetabolism (z-score=3.74) and reduced oxidative phosphorylation (z-score=-5.12). Inference analysis shows that under diseased conditions human KC can activate specific T lymphocytes and NKTs subsets, via IL-6, CD36 and IL-2. Murine inference showed a key role of TREM1 macrophages. Spatial transcriptomics showed a specific zonation of the genes emerged in the human and murine datasets.
**Conclusions:** Lipid stress metabolism impairs the transcriptome of KCs, especially regarding mitochondrial function and the activation of the Kupffer cells/T-lymphocyte axis.

Abstract n SO5_1 - Presenting author**: Alfredo Caturano**

## Effects of a Combination of Empagliflozin Plus Metformin vs. Metformin Monotherapy on NAFLD Progression in Type 2 Diabetes: The IMAGIN Pilot Study

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**Introduction:** Non-alcoholic fatty liver disease (NAFLD) encompasses a diverse range of metabolic liver disorders characterized by the presence of steatosis in at least 5% of hepatocytes. In this study, our aim was to evaluate the impact of a combination therapy involving empagliflozin + metformin in comparison to metformin monotherapy on the progression of NAFLD in patients with type 2 diabetes (T2DM).
**Methods:** A total of sixty-three T2DM patients, previously treated with metformin and without prior exposure to sodium-glucose co-transporter-2 inhibitors (SGLT2i), were included. All patients had received a diagnosis of NAFLD through ultrasound. Of these, thirty-three initiated the combination therapy, and both groups were observed over a 6-month period. Regular assessments included anthropometry, blood biochemistry, and liver evaluations using FibroScan®/CAP.
**Results:** At the 6-month follow-up, the group undergoing combination therapy exhibited significant improvements compared to the metformin monotherapy group. Specifically, the combination therapy group showed a notable reduction in body mass index (BMI) from 30.83 ± 3.5 to 28.48 ± 3.25, glycated hemoglobin levels from 8.2 (7.4–8.8) to 7.2 (6.8–7.9), alanine aminotransferase (ALT) levels from 68.5 (41.5–88.0) to 45.00 (38.00, 48.00), CAP parameter from 293.5 (270.0–319.25) to 267.00 (259.50, 283.75), and a significant improvement in the degree of steatosis ($p = 0.001$). In contrast, the control group exhibited minimal changes in these parameters over the same period.
**Conclusion:** In T2DM patients, the combination of empagliflozin + metformin demonstrated superior outcomes compared to metformin monotherapy after a 6-month follow-up. The combination therapy effectively ameliorated liver steatosis, ALT levels, body weight, and glycated hemoglobin. These findings suggest a potential benefit of the combination therapy in managing NAFLD progression in T2DM patients. Further studies and longer-term observations are warranted to validate these promising results.

Abstract n SO5_2 - Presenting author**: Salvatore Spampinato**

## Association of Triglycerides-Glucose (TyG) index with mechanical vascular impairment in subjects with Non-Alcoholic Fatty Liver Disease

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**Aim:** Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common cause of chronic liver disease. Increasing evidences showed that NAFLD is a multisystem disease strongly associated with insulin resistance, type II diabetes mellitus, dyslipidemia, chronic kidney disease and cardiovascular diseases. Recent studies showed that the Triglyceride and Glucose index (TyG) - a simple and cost-effective marker of insulin resistance – was associated with atherosclerotic cardiovascular disease (ASCVD) risk in patients with metabolic disorders. In this study we aimed to investigate the potential role of TYG on mechanical vascular impairment, evaluated by pulse wave velocity (PWV) in patients with NAFLD.
**Methods:** In this observational study we evaluated 80 middle-aged (40–70 years) NAFLD subjects without secondary causes of fatty liver or history of major adverse cardiovascular events (MACE). All subjects performed a routine medical examination from the Internal Medicine outpatient clinic of the A.R.N.A.S. Garibaldi-Nesima (Catania). Fatty liver was diagnosed by ultrasonography. PWV was measured by SphygmoCor CvMS (AtCor Medical, Sydney, Australia). The study population was divided into two groups according to the median value of TyG (high TyG group, TyG ≥ 8.58, n=40; low TyG group, TyG < 8.58, n=40). To test differences of clinical and biochemical characteristics between the two groups, we used Student's t test. Simple linear regression analysis was performed to assess the relationship between TYG and PWV.
**Results:** High TyG group exhibited a significant higher PWV compared to the low TyG group (10.11 ± 3.28 vs 8.58 ± 2.22 cm/s, $p < 0.05$). A simple linear regression analysis showed that PWV was significantly associated to TYG ($\beta=0.324$, $p < 0.01$), indicating that higher TyG values were associated with increased arterial stiffness.
**Conclusions:** In our study we observed that high TyG group exhibited a higher PWV than low TyG group; moreover, PWV was significantly associated to TyG. NAFLD patients with elevated TyG values showed an increased cardiovascular risk compared to NAFLD patient with low TyG values. In this context, TyG could be considered a useful clinical biomarker to predict the mechanical vascular impairment in patients with NAFLD.

Abstract n SO5_3 - Presenting author**: Celeste Lauriola**

## High glucose and insulin levels modulate the expression and secretion of SHBG in HepG2 cells

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**Aim:** Sex hormone binding globulin (SHBG) is a hepatic protein able to regulate the bioavailability of sex steroids. Interestingly, its reduction is associated to an increased risk of developing type 2 diabetes. Nevertheless, insulin resistance and hepatic steatosis are associated to reduced SHBG circulating levels. Nowadays, the role of glucose and insulin (HI) in regulating hepatic SHBG expression and secretion is not clear. Therefore, the aim of this study has been to investigate the effects of different concentrations of glucose in the absence or presence of HI on SHBG synthesis and secretion in HepG2 cell line.
**Methods:** HepG2 cells were exposed to different concentrations of glucose with or without 100 nM HI for 48 and 96 h. The protein expression and activation of insulin receptor (IRβ) and Akt, as well as the protein expression of SHBG and its master regulators (i.e., HNF4α and SIRT2) were assessed by immunoblotting. SHBG secreted was assessed by ELISA.
**Results:** HepG2 exposed to high glucose (30 mM) showed an increase of IRβ protein expression as compared to normal glucose (5.5 mM). Conversely, the co-incubation with HI in high glucose medium resulted in reduction of IRβ as compared to the same condition without HI. In these conditions, an impaired insulin sensitivity in terms of p-IRβ$^{Tyr1150/1151}$ and p-Akt$^{S473}$ was observed.
A dose-dependent increase in SHBG protein expression, but not in its secretion, was observed after incubation with glucose alone; however, in the presence of HI a significant reduction in SHBG protein expression and secretion at high glucose levels was observed as compared to the same condition without HI. Likewise, after 96 hours of treatment with high glucose and HI, both HNF4α and SIRT2 protein expression was significantly reduced.
**Conclusions**: Insulin resistance in hepatic cell line is associated with a down-regulation of SIRT2, HNF4α and SHBG expression and secretion.

Abstract n SO5_4 - Presenting author**: Rosanna Di Fonzo**

## The effect of dapagliflozin in a real-world population of HFrEF patients

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**Aim**: The recognition of the potential beneficial effects of SGLT2i for HF highlights how patient stratification based on LVEF is imprecise and incomplete.
In accordance with this, we introduce a hemodynamic subclassification of our real world population.
**Methods**: In this open-label, prospective, observational clinical study, we included 80 patients receiving an SGLT2i in addition to standard OMT. Parameters collected included demographic, medical history, clinical, pharmacological treatments, laboratory, electrocardiographic and echocardiographic data. At the enrollment, patients were divided according to Forrester classification in four hemodynamic profiles (A: normal flow, normal pressure; B normal flow high pressure; C low flow normal pressure; D low flow, high pressure). Patients were evaluated at 6 months from enrollment.
**Results**: from baseline to FU the following echocardiographic parameters significantly improved: LVEF (p 0.0074), E/e' ratio (p 0.0079), TAPSE (p 0.0404), RVD1 (p value 0.0476) and sPAP (p 0.0030). Precisely, LVEF significantly improved in profile B (p 0.0001), C (p< 0.00001) and D (p 0.0003). The E/e' ratio significantly improved in all the profiles; however, the E/e' ratio decreased meaningfully with a p 0.0099 for the profile A, a p < 0.0001 for the profile B and D, and a p 0.0006 for the profile C. Moreover, TAPSE improved meaningfully for the congestive profile (B and D, respectively with p 0.0004 and p<0.0001), while no significant changes were recorded for profile A and C. At the enrollment, 33 (41.25%) patients were in NYHA class II, 43 (53.75%) in NYHA III and 4 (5,00%) patients in NYHA IV. Noteworthy, patients of all the four hemodynamic profiles had a significant improvement in NYHA class up to 6 months
**Conclusions**: SGLT2i are well tolerated by the patients and improve the subjective perception of quality of life and the performance of the right ventricle. Moreover the greatest effects of SGLT2i are recorded on patients with a congestive profile, suggesting a beneficial effect on the hemodynamic balance.

Abstract n SO5_5 - Presenting author**: Cassandra Morciano**

## The Coronary Flow Reserve increase after Dapagliflozin Treatment in patients with type 2 diabetes is maintained after 4 years: a 4 Year DAPAHEART Follow-up Study

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**Introduction & Objective:** Cardiovascular (CV) outcome trials have shown that in patients with type 2 diabetes (T2D), treatment with sodium-glucose cotransporter-2 inhibitors (SGLT-2i) reduces CV mortality for heart failure. We demonstrated that 4-weeks-treatment with SGLT-2i leads to a 30% increase in coronary flow reserve (CFR) in T2D people with stable coronary artery disease (CAD) (DAPAHEART trial). The aim of this study is to evaluate the long-term effects of treatment with dapagliflozin on CFR in patients with T2D.

**Methods:** T2D patients with CAD already enrolled for a single-center, 4 weeks, prospective, randomized (1:1 dapagliflozin 10 mg or placebo), double-blind, controlled study have been followed up for 4 years. At the end of the trial all the patients in placebo group started therapy with dapagliflozin. After 4 years of treatment the CFR has been evaluated using $^{13}$N-ammonia PET-CT.

**Results:** During the follow-up, the antidiabetic treatment remained stable. The 2 groups were metabolically well balanced.

In DAPA group (n=5), the increase of 30% in CFR was sustained over 4 years (p=ns). A comparison between pre and post-4-years follow-up in DAPA group showed a 35% increase in CFR (p=0.09). The placebo group (n=4), after 4 years of dapagliflozin treatment, exhibited a 28.6% increase in CFR (p=0.07).

Overall, a 25% increase in CFR was observed across all patients after 4 years (p=0.008, n=9), along with a reduction in myocardial resting blood flow (p=0.002, n=9) as observed in the DAPAHEART trial.

**Conclusions:** This 4-years follow up trial demonstrates that the 30% increase of CFR obtained after 4 weeks treatment is maintained after 4 years, confirming the previous published results in a new population. This improvement in CFR may have important implications on the management and prognosis of patients with T2D and CAD.

Abstract n SO5_6 - Presenting author**: Emma Calzavara**

## Lean diabetic patients with metabolic dysfunction associated steatotic liver disease (MASLD) have the same progression of hepatic and cardiovascular damage of overweight ones: role for weight gain and glycemic control

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**Background and aims:** Metabolic dysfunction associated steatotic liver disease (MASLD) is characterized by hepatic fat and metabolic comorbidities, mainly Type 2 diabetes (T2DM) and obesity, however it can be present also in lean individuals. Aim: to prospectively evaluate change in hepatic and CV damage in lean versus overweight MASLD patients.
**Methods:** 237 diabetic MASLD patients (mean age 67 ±9 years, 54% male) were enrolled and re-evaluated after 5 years. Hepatic steatosis was assessed by liver ultrasonography, fibrosis by Fibroscan® (LSM>8.2kPa), CV disease by carotid doppler US (IMT>0.9 mm and carotid plaques).
**Results:** Fifty (21%) patients were lean (BMI<25 kg/m2) and 187 (79%) overweight (BMI>25 kg/m2), with no difference in baseline age, sex, duration of T2DM, glycemic control or antidiabetic therapy and prevalence of dyslipidemia, hypertension, insulin-resistance, IMT>0.9mm and carotid plaques. Conversely, lean vs overweight patients presented a lower prevalence of LSM >8.2 kPa (2% vs 11%, p=0.05). During follow-up lean patients presented a superimposable rate of fibrosis progression by Fibroscan compared to overweight ones (LSM >30% from baseline 26% vs 18%, p=0.226) as well as of new onset carotid plaques (20% vs 23%, p=0.832) or IMT>0.9 mm (26% vs 32%, p=0.783). Lean subjects vs overweight were more likely to gain weight (53.5% vs 35.5%, p=0.031) over time without any difference in worsening of glycemic control and in antidiabetic drugs at follow-up. Weight gain remained independently associated with worsening of LSM (OR 1.87, CI 95% 1.00-3.51), whereas an increase in Hb1Ac >0.5% from baseline with increase in IMT (OR 1.94; CI 95% 1.06-3.57).
**Conclusions:** Over 5-years, diabetic MASLD patients, even if lean, presented high progression of hepatic and CV damage, possibly speculating on the role of T2DM itself in this setting. Avoiding weight gain and controlling T2DM is crucial in order to prevent the worsening of both liver and CV disease.

Abstract n SO5_7 - Presenting author**: Andrea Gaido**

## Determinants of Early Subclinical Systolic Dysfunction in Patients with Type 2 Diabetes

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**Aim.** Type 2 Diabetes (DM2) is a risk factor for the development of heart failure (HF). Global longitudinal strain (GLS) is more sensitive than ejection fraction (EF) in diagnosing subclinical left ventricular systolic dysfunction (LVSD). Metabolic-associated fatty live disease has been involved in the development of subclinical LVSD-GLS. However, determinants of subclinical LVSD-GLS in DM2 remain poorly known. Our aim was to identify variables associated with altered GLS values in a cohort of DM2 individuals without heart disease and with normal EF.
**Methods.** The study was performed on DM2 patients (n=150) recruited in the TESEO cohort study with available data on GLS (Speckle Tracking Echocardiography, Epiq CVx Philips), hepatic steatosis (CAP), and liver stiffness (LS) (Fibroscan). Subjects with symptomatic HF, cardiovascular disease (CVD), other heart diseases, EF<50%, eGFR<30 ml/min/1.73m2, alcohol abuse, non-metabolic liver disease, and hepatic cirrhosis were excluded. Multiple regression and logistic regression analyses were used to identify GLS determinants and variables associated with subclinical LVSD-GLS (GLS≥-18%).
**Results.** Recruited subjects (age 61.39±7.89 years, male 57.3%) had a short DM2 duration (3.93±5.06 years) and good metabolic control (HbA1c 6.57%±1.00). Subclinical LVSD-GLS was present in 20% of subjects. Patients with LVSD-GLS had significantly higher LS values (5.77±1.75 vs 4.94±1.25, p=0.003). In multivariate regression analysis, LS values were a significant determinant of GLS, independent of age, waist circumference, diabetes duration, blood pressure, and e' lateral. In logistic regression analysis, LS was associate with a 61% (95% CI 1.15-2,25) increased OR of LVSD-GLS independent of age, gender, WC, diabetes duration, blood pressure, ACR, LVH, and e' lateral.
**Conclusions.** This study demonstrated that LS is independently associated with LVSD-GLS in DM2 patients with normal HF and without CVD. Abnormal LS values may identify a subgroup of DM2 patients at higher risk of symptomatic HF, who may benefit from closer clinical and echocardiographic monitoring.

Abstract n SP1_01 - Presenting author**: Aquilino Flavio Zarrella**

## Effect of Potassium Supplementation on Endothelial Function: A Systematic Review and Meta-Analysis of Intervention Studies

Aquilino Flavio Zarrella, Ilaria Libera Pizzulo, Angelo Forte, Alessia Attanasio, Paolo Manzi, Maria Masulli, Domenico Rendina, Ferruccio Galletti, Lanfranco D'Elia

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**Introduction:** Endothelial dysfunction is an early predictor of cardiovascular diseases. Although a large body of evidence shows an inverse association between potassium intake and cardiovascular risk, the studies on endothelial function provided contrasting results.
**Aim:** We carried out a systematic review and a meta-analysis of the available intervention studies of the potassium supplementation on endothelial function.
**Methods:** A systematic search of the online databases available (up to December 2022) was conducted including the intervention trials that reported flow-mediated dilation (FMD) changes-a non-invasive method of assessing endothelial function-after two different potassium intake regimens. For each study, the mean difference (MD) and 95% confidence intervals were pooled using a random effect model.
**Results:** Five studies met the pre-defined inclusion criteria and provided eight cohorts with 332 participants. In the pooled analysis, potassium supplementation was associated with a significant increase in FMD (MD: 0.74%), with a higher effect for a urinary potassium excretion higher than 90 mmol/day. There was a moderate heterogeneity among studies (I2 = 59%), explained by the different amount of potassium supplementation.
**Conclusions:** The results of our meta-analysis indicate that dietary potassium supplement improves endothelial function. This effect is directly associated with the amount of potassium supplement. The findings support the campaigns in favor of an increase in dietary potassium intake to reduce cardiovascular risk.

Abstract n SP1_02 - Presenting author**: Federica Carrieri**

## The effects of myoinositol on the release of extracellular vesicles

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**Background and Aims**: Recent studies suggest that treatment with Myoinositol (Myo) improves glucose metabolism and insulin resistance, both associated with inflammation and oxidative stress, common soil of the vascular damage featured in diabetes as well as Polycystic Ovary Syndrome. Aim of this study was to evaluate the effects of Myo supplementation in women affected by gestational diabetes, on the release of Extracellular Vesicles (EVs) subtypes, a direct indicator of vascular damage.
**Materials and Methods:** After 48 hours pre-incubation with Myo 0.1, 0.5 and 1 mM or alpha-lipoic acid (LA; 0.1-0.2 mM), human umbilical vein endothelial cells obtained from women with gestational diabetes (GD- HUVECs) as well as control cells (C-HUVECs) were exposed to Tumor Necrosis Factor-α (TNF-α, 1 ng/ml) for 16 hours. Then, endothelial derived vesicles (eEVs) release was determined (flow cytometry). Additionally, *in vivo* circulating levels of EVs subtypes (derived from platelet, leukocyte, and endothelial cells) were evaluated in freshly drawn whole blood from pregnant women with gestational diabetes (GDM) treated with standard of care (GD, n=13) or Myo supplementation (GD+Myo, n=17). Samples were collected at 29 ± 2.6 weeks of gestation (gw), and before delivery (36 ± 1 gw). Statistical analyses were performed using the Student's t-test and analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test for post hoc comparisons. P values less than or equal to 0.05 were considered statistically significant.
**Results:** In GD-HUVECs, pre-treatment with Myo at 1 mM or LA at 0.2 mM ($P<0.05$) significantly reduced eEVs release *in vitro*. Moreover, despite the *in vivo* supplementation with Myo (GD+Myo) was associated with an increase in total circulating EVs, it was interesting to observe that GDM women supplemented with Myo showed a lower maternal weight gain during pregnancy and a slight reduction in eEVs ($p<0.05$).
**Conclusions:** Treatment with Myo during pregnancy is associated with lower maternal weight gain and reduced markers of vascular damage, as highlighted by the lower release of endothelial derived vesicles. Accordingly, Myo might play a protective role against endothelial dysfunction typical of diabetes. Furthermore, the increase in total EVs *in vivo* after Myo supplementation might be justified by subpopulations of EVs with protective functions; this aspect will be further investigated by proteomic analysis.

Abstract n SP1_03 - Presenting author**: Tommaso Campanella**

## Qualitative and quantitative ultrasaound based characterization of carotid atherosclerosis: an analysis of clinical and laboratory predictors

Tommaso Campanella[1], Rosa Curcio[1], Maria Raffaella Martina[2], Lorenzo Chiatti[1], Marco D'Abbondanza[1], Elisabetta Bianchini[2], Vincenzo Gemignani[2], Gaetano Vaudo[1], Giacomo Pucci[1]

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**Background:** The prevalence of carotid atherosclerosis is underestimated in the general population. Its diagnosis is essential to re-classify the cardiovascular risk (CV) of affected patients. The degree of linear stenosis (SL) is traditionally accounted as the most clinically relevant morphological criterion. The clinical significance of other quantitative and qualitative parameters has not yet been fully elucidated.
**Methods:** In patients with known carotid atherosclerosis, we conducted a qualitative and quantitative plaque non-invasive analysis with ultrasound imaging equipped with a semi-automatic analyzer (QUIPU) at the level of the common carotid artery, bifurcation, internal carotid artery and external carotid artery bilaterally. SL, total plaque area (TPA), median gray scale value (GSM), skewness and kurtosis were correlated to the main CV risk factors.
**Results:** 50 patients (age 74±10 years, 52% male, 80% hypertensive) were analyzed. Total number of plaques n=180, location: internal carotid artery (39%, n=71), carotid bifurcation (26%, n=47), external carotid artery (22%, n=38), common carotid artery (13%, n=24). Plaques at the common carotid contributed more to TPA, whereas a higher degree of SL was observed for external carotid plaques. TPA was positively correlated with age, male sex, and previous CV event, and negatively with statin use and HDL cholesterol (Table). SL correlated only with history of hypertension and previous CV event. A phenotype characterized by low GSM and high skewness and kurtosis was associated with male gender, total calcium values, and no statin use.
**Conclusions:** we observed that TPA, GSM, skewness and kurtosis have significant and plausible associations with the main CV risk factors and could have a clinical importance in identifying subjects at CV risk regardless of the extent of SL, the only current clinically relevant. A non-invasive ultrasound-based study of the carotid plaques could be useful in the early identification of some plaque phenotypes potentially at high risk of complications.

| N=180 | SL, % | TPA | GSM | Skeweness | Curtosi |
|---|---|---|---|---|---|
| Age, years | 0,05 | 0,38** | 0,03 | -0,08 | -0,08 |
| Male sex, % | -0,02 | 0,21** | -0,23** | 0,15* | 0,11 |
| BMI, Kg/m$^2$ | 0,05 | -0,05 | 0,03 | 0,02 | 0,05 |
| HTN, % | 0,20** | 0,12 | 0,08 | 0,02 | -0,05 |
| DM, % | 0,06 | 0,06 | 0,08 | -0,03 | 0,02 |
| eGFR, mL/min/1,73 m$^2$ | -0,12 | -0,11 | 0,04 | -0,09 | -0,09 |
| Serum calcium, mg/dL | -0,15 | -0,04 | -0,31** | 0,21** | 0,10 |
| HDL-cholesterol, mg/dL | -0,06 | -0,21* | -0,09 | 0,05 | -0,01 |
| Statins, % | 0,05 | -0,15* | 0,06 | -0,15 | -0,16* |
| Previous CV event, % | 0,32** | 0,37** | 0,02 | 0,08 | 0,13 |

*Spearman's Rho correlation coefficent, *p<0,05, **p<0,01*

Abstract n SP1_04 - Presenting author**: Oriana De Marco**

## Changes in renal microcirculation in patients with nephrotic and nephritic syndrome: The role of resistive index

Antonietta Gigante[2], Chiara Pellicano[2], Oriana De Marco[1], Eleonora Assanto[2], Georgia Sorato[2], Alberto Palladini[2], Edoardo Rosato[2], Silvia Lai[2], Maurizio Muscaritoli[2], Rosario Cianci[2]

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**Aim:** Renal Resistive Index (RRI) is an important and non-invasive parameter of renal damage and it is associated with abnormal microcirculation or to a parenchymal injury. The aim of our study was to compare the RRI in a cohort of patients with renal diseases categorized in three groups: nephrotic syndrome (NS), acute nephritic syndrome (ANS) and patients with urinary abnormalities (UA).
**Methods:** Four hundred eighty-two patients with median age of 48 years (IQR 34-62) with indications for kidney disease were included in the study. Biochemical analyses, clinical assessment with detection of NS, ANS and UA and comorbidities were reported. Renal Doppler ultrasound with RRI was evaluated in all patients at the time of enrolment.
**Results:** NS was present in 81 (16.8 %) patients while ANS in 81 (16.8 %) and UA in 228 (47.3 %) patients. Patients with ANS showed significant higher RRI compared to both patients with NS [0.71 (IQR 0.67-0.78) vs 0.68 (0.63-0.73), $p < 0.001$] and UA [0.71 (0.67-0.78) vs 0.65 (0.61-0.71), $p < 0.001$]; RRI was higher in NS patients than in patients with UA [0.68 (0.63-0.73) vs 0.65 (0.61-0.71), $p < 0.001$]. Patients with ANS had significantly lower median estimated glomerular filtration rate (eGFR) compared respectively to NS and UA patients [19.7 ml/min vs 54.8 ml/min and vs 72.3 ml/min, $p < 0.001$], while renal length was significantly higher in patients with NS compared to both patients with ANS and UA [111.88 mm vs 101.98 mm and vs 106.15, $p < 0.001$]. Patients with ANS had more frequently hematuria and RRI ≥ 0.70 ($p < 0.001$) compared to both patients with NS and patients with UA. The multiple regression analysis, weighted for age, showed that RRI inversely correlates with eGFR (β coefficient = -0.430, $p < 0.001$).
**Conclusions:** Higher and pathological RRI were found in ANS than NS and UA. Renal resistive index in ANS reflects changes in intrarenal perfusion and microvascular dysfunction related to disease characteristics.

Abstract n SP1_05 - Presenting author**: Iolanda Veneruso**

## LncRNAs as potential biomarkers for atherosclerosis: H19 and human carotid atherosclerotic plaques

Iolanda Veneruso[1,2], Valeria D'Argenio[2,3], Vasilis F. Ntasis[4], Maria Donata Di Taranto[1,2], Giovanna Cardiero[1,2], Umberto Marcello Bracale[5], Sílvia Pérez-Lluch[4], Giuliana Fortunato[1,2], Roderic Guigó[4], Francesco Salvatore[1,2].

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**Aim.** Long non coding RNAs (lncRNAs) regulate in different ways several physiopathogenic mechanisms of an increasing number of diseases but their impact on atherogenic process is still unclear. Thus, we aimed to evaluate lncRNAs expression in human carotid atherosclerotic plaques, their adjacent intima regions with a lower grade lesions and plasma to find novel diagnostic and/or therapeutic biomarkers.
**Methods.** We collected samples from 15 patients undergoing endarterectomy. All samples were processed for RNA-Seq analysis using Next Generation Sequencing; libraries were prepared with Illumina total RNA protocol and sequenced on NextSeq550Dx. During the bioinformatic analysis, carried out in R, quality controls showed good quality results. Mapping and quantification analysis, principal component analysis (PCA), differential expression analysis, pathway enrichment analysis and network analysis were carried out. Additionally, we compared our results against data from GTEx Project database.
**Results.** Clustering analysis and PCA showed a clear separation between plaque and adjacent intima region tissue samples. Differential expression analysis highlighted 915 differentially expressed genes (DEGs) in plaques versus adjacent intima region (798 over-expressed and 117 under-expressed genes). Pathway enrichment analysis with KEGG database showed that the overexpressed genes in plaque group belong mainly to inflammation and immunity pathways. We found also 48 lncRNAs differentially expressed; among them, lncRNA H19 showed a log fold change of 4.3 (pvalue=0.000040). To strengthen our results, GTEx dataset was compared with our data highlighting about 100/200 common DEGs. Network analysis revealed an interesting relationship between H19 and LEF1 gene. Plasma analysis revealed that the lncRNA H19 levels positively correlated with the plaque-vs-adjacent region fold change, suggesting its role as circulating biomarker of atherosclerotic-related alterations.
**Conclusions.** For the first time a high lncRNA H19 expression was observed in human atherosclerotic carotid plaque tissues and also found in plasma through RNA-Seq. Our data highlighted lncRNA H19 involvement in triggering atherosclerosis by acting through different pathways.

Abstract n SP1_06 - Presenting author**: Lorenzo Da Dalt**

## Mitochondrial dynamism impact VSMCs and atherosclerotic plaque development

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**Aims:** Mitochondria are key organelles for cellular metabolism, energy generation, calcium homeostasis, sterol and bile acids (BAs) production. Mitochondria continuously undergo biogenesis, fusion, fission and mitophagy, maintaining a continuous balance between all forms. On these premises, we test the impact of OPA1, an inner mitochondria membrane fusion protein, on mitochondrial tethering on lipid metabolism in the liver and the atherosclerotic plaque.
**Methods:** OPA1HepKO and OPA1 TG on LDLR KO background were fed with a Western-type diet (WTD) respectively for 12 weeks. Inverse calorimetry, GTT, and LipidToleranceTest (LTT) were performed. Paraffin-embedded tissues were used for histological analysis, frozen tissues were used for OMICs analysis. VSMCs were isolated and cultured with VLDL (50 µg/ml).
**Results:** While OPA1HepKO mice display altered systemic metabolism with reduced body weight and reduced circulating lipid levels OPA1 overexpression on LDLR KO background showed significantly high cholesterol levels. OPA1 deficiency impair hepatic bile acid conjugation with significant accumulation of primary unconjugated bile acids in the liver. On the contrary OPA1 overexpression leads to a reduction of unconjugated bile acids and higher percentage of conjugated bile acids. OPA1 reduction leads to a reduced atherosclerotic plaque while, on the contrary, its overexpression doesn't affect atherosclerosis despite an increase in circulating lipid and lipoprotein levels. OPA1 overexpression is therefore promoting plaque stabilisation with VSMCs that are less prone to change their metabolism to synthetic.
**Conclusion:** Hepatic Opa1 deficiency alters bile acids production and therefore circulating lipid profile with a consequent reduction in atherosclerotic plaque formation. OPA1 overexpression in the aorta affects plaque stability despite the highest levels of circulating lipids.

Abstract n SP1_07 - Presenting author**: Giorgio Toscani**

## Structural and functional vascular properties after PCSK9-antibody initiation in secondary cardiovascular prevention

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**Aim:** PCSK9 inhibitors antibodies (PCSK9-i) are a valid option to reduce LDL cholesterol in patients who failed to reach therapeutic target with maximized lipid-lowering therapies or in patient with statins intolerances. These antibodies reduce the frequency of new cardiovascular events, however if this effect is due only to LDL reduction or also to an improvement in arterial function and structure is yet to be proved. Our study aim was to evaluate aortic stiffness (Pulse Wave Velocity - PWV), carotid's Intima-Media Thickness (IMT) and endothelial function (brachial Flow Mediated Dilatation - FMD) in patients treated with Alirocumab and Evolocumab.
**Methods:** This is a monocentric prospective longitudinal study on patients who received PCSK9-i administrations at the Niguarda Hospital's cardiovascular rehabilitation and prevention unit. They underwent 3 evaluations of PWV, FMD and IMT (T0 the same day of the first injection, T1 after 6 months and T2 after 12 months of therapy).
**Results:** 67 patients concluded the 12 months period. The group average age is 66,5 ± 8,6 years, most of them were male (67.2%). LDL cholesterol average levels were significantly reduced by the therapy (121,8 ± 31,7 vs 42,4 ± 28,3 mg/dL, $p<0.001$), however, there were no significant changes in PWV (10,5 ± 2,9 vs 10,8 ± 2,4 m/s, $p=0.423$), FMD (8,5 ± 7,30 vs 9,1 ± 11,0%, $p=0.966$) and IMT (714,6 ± 188,6 vs 734,4 ± 168,4 µm, $p=0.753$) values.
**Conclusions:** It was not possible to prove a significant effect of PCSK9-i on vascular properties, however, the stability of these indexes may suggest a deceleration of the atherosclerotic disease which it could have worsen in this population, especially considering the risk factors of our patients.

Abstract n SP1_08 - Presenting author**: Elisa Acitelli**

## Peripheral artery disease in Familial Hypercholesterolemia: A systematic review

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**Aim:** Familial hypercholesterolemia (FH) is a common genetic disease characterized by an increased exposure to elevated LDL-cholesterol levels, resulting in a predisposition to early atherosclerotic disease. Although the correlation between FH and coronary or carotid artery diseases is well-documented, its association with peripheral artery disease (PAD) is usually considered weaker. This systematic review aims at investigating existing evidence regarding PAD prevalence and incidence in individuals with FH.
**Methods:** Literature research of studies, published between January 2013 and December 2023, evaluating prevalence and incidence of PAD in FH patients, was conducted using MEDLINE and Embase online databases. Reviews, case reports, responses to editors and non-English language articles were excluded.
**Results:** The initial research provided 53 results, 28 articles were fully reviewed and 24 were included in the final analysis Among these, 19 studies provided data on PAD prevalence, and 5 studies on PAD incidence during a mean follow-up time of 8.7 years. PAD definition criteria were heterogeneous, resulting in a reported PAD prevalence that varied from 0.3% to 60%, with higher prevalence in studies employing less stringent criteria; PAD incidence ranged between 0.5% and 4.2%, irrespective of PAD definition criteria. PAD prevalence and incidence were lower as compared to coronary and carotid disease. Interestingly, no differences in the prevalence of other cardiovascular risk factors were noticed.
**Conclusions:** This systematic review highlights the scarcity of dedicated studies on PAD in FH patients. PAD poses a substantial health burden, leading to increased morbidity and mortality. Bridging this research gap is essential for optimal management of this genetically-predisposed population. Further investigations are necessary for a more comprehensive understanding of peripheral vascular involvement in the FH population.

Abstract n SP1_09 - Presenting author**: Domenico Tuttolomondo**

## Coronary inflammation on chest computed tomography and COVID-19 mortality

Domenico Tuttolomondo[a], Andrea Ticinesi[b,c], Damini Dey[d], Chiara Martini[e,f], Antonio Nouvenne[c], Maria Nicastro[g], Massimo De Filippo[e], Nicola Sverzellati[f], Francesco Nicolini[h], Tiziana Meschi[b,c], Nicola Gaibazzi[a]

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**Background:** The main factors associated with coronavirus disease-19 (COVID-19) mortality are age, comorbidities, pattern of inflammatory response and SARS-CoV-2 lineage involved in infection. However, the clinical course of the disease is extremely heterogeneous, and reliable biomarkers predicting adverse prognosis are lacking. Our aim was to elucidate the prognostic role of a novel marker of coronary artery disease inflammation, peri-coronary adipose tissue attenuation (PCAT), available from high-resolution chest computed tomography (HRCT), in COVID-19 patients with severe disease requiring hospitalization.
**Methods:** Two distinct groups of patients, admitted to Parma University Hospital in Italy with COVID-19 in March 2020 and March 2021 (first and third wave peaks of COVID-19 pandemic in Italy, with prevalence of wild-type and B.1.1.7 SARS-CoV-2 lineage, respectively) were retrospectively enrolled. The primary endpoint was in-hospital mortality. Demographic, clinical, laboratory, HRCT data and coronary artery HRCT features (coronary calcium score and PCAT attenuation) were collected to establish which variables were associated with mortality.
**Results:** Among the 769 patients enrolled, 555 (72%) were discharged alive and 214 (28%) died. In multivariable logistic regression analysis age ($p<0.001$), number of chronic illnesses ($p<0.001$), smoking habit ($p=0.006$), P/F ratio ($p=0.001$), platelet count ($p=0.002$), blood creatinine ($p<0.001$), non-invasive mechanical ventilation ($p<0.001$), HRCT visual score ($p<0.001$) and PCAT ($p<0.001$), but not the calcium score, were independently associated with in-hospital mortality. On stepwise multivariate logistic regression analysis, but separately performed in patients admitted during the first wave or during the third wave PCAT on chest HRCT was again independently associated with in-hospital mortality**.**
**Conclusions:** Coronary inflammation, measured with PCAT on HRCT, was independently associated with higher mortality in patients with severe COVID-19, while the pre-existent coronary atherosclerotic burden was not associated with adverse outcomes after adjustment for covariates.

Abstract n SP1_10 - Presenting author**: Giuseppe Palma**

## G-CSF counteracts the proapoptotic effects of the secretome of visceral adipose cells from obese subjects in human cardiac progenitor cells

Giuseppe Palma [1], Cristina Caccioppoli [1], Rossella D'oria [1], Valentina Annamaria Genchi [1], Isabella Calderoni [1], Tomaso Bottio[1], Antonio Braun [2], Giuseppe Santarpino [3], Angelo Cignarelli [1], Annalisa Natalicchio [1], Luigi Laviola [1], Angela Pezzolla [1], Aldo Domenico Milano[1], Angela Martinez Valverde[4], Francesco Giorgino [1], Sebastio Perrini [1]

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**Aim:** Granulocyte colony-stimulating factor (G-CSF) was reported to induce myocardial regeneration by promoting mobilization of bone marrow stem cells to the injured heart after myocardial infarction, but the precise mechanisms are not fully understood. We investigated the mechanisms of the protective action of G-CSF in human cardiac progenitor cells (hCPC) exposed to the secretome from abdominal visceral (AV) and epicardial (E) adipose stem cells (ASC) and from AV mature adipocytes from obese (Ob) subjects.
**Methods:** AV-ASC and AV mature adipocytes were isolated from 13 non-Obese (n-Ob) and 27 Ob patients. E-ASC and hCPC were isolated from 10 n-Ob and 9 Ob subjects. hCPC were isolated from n-Ob subjects undergoing elective cardiac surgery.
**Results:** The secretome of adipose cells from Ob compared to n-Ob subjects displayed a different pattern of pro-inflammatory and anti-inflammatory cytokines. The levels of RANTES, MIP1B and IFN- γ were increased in the secretome from Ob-AV-ASC and Ob-E-ASC and displayed a direct correlation with BMI ($p<0.05$). In contrast the levels of G-CSF in the CM of E-ASC was eight-fold increased in the CM of E-ASC as compared to AV-ASC from n-Ob patients ($p<0.05$) and inversely correlated with BMI ($p<0.05$). Exposure of hCPC to the secretome of adipose cells from Ob, but not from n-Ob subjects, induced apoptosis, c-Jun phosphorylation, and impairment of actin filaments, while these effects were not observed when hCPC were pretreated with G-CSF.
**Conclusions:** i) in human obesity, the secretome of AV- and E-ASC and mature adipocytes is characterized by pro-inflammatory cytokines that induce stress kinase activation and apoptosis in hCPC; ii) nOb-E-ASC secrete higher levels of G-CSF as compared to nOb-AV-ASC; iii) the ability of E-ASC to secrete high levels of G-CSF is loss in E-ASC from Ob subjects; iv) G-CSF prevents the hCPC damage induced by pro-inflammatory cytokines from Ob secretome.

Abstract n SP1_11 - Presenting author**: Chiara Tognola**

## Hypertriglyceridemia in patients with acute and chronic coronary syndrome: prevalence and their association with extreme cardiovascular risk and left ventricular function

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**Aim:** Hypertriglyceridemia prevalence in Acute and Chronic Coronary Syndrome (ACS and CCS respectively) patients in the era of very low LDL target is still unknow. The objective of our study is to evaluate the prevalence of triglyceride levels above 150 or 200 mg/dL despite statin therapy and LDL cholesterol at targets in ACS and CCS subjects enrolled in a Cardiac Rehabiliatitation (CR) program.
**Methods:** This cross-sectional observational study was conducted at the Niguarda Hospital (Milan, Italy). Patients undergoing CR after ACS/CCS from January 1, 2012, to March 28, 2023, were included. Data on demographic, clinical, laboratory, and instrumental variables were collected.
**Results:** The study population consisted of 740 patients with a mean age of 64.3±10.7 years, predominantly male (81.7%). Triglyceride levels significantly decrease during the CR period (131.1±63.8 vs 116.9±75.9 mg/dL; $p < 0.001$) similarly to LDL cholesterol (107.9 ± 38.8 mg/dL vs 69.9 ± 25.9mg/dL, $p<0.001$). 50.8% of the subjects reach the LDL cholesterol target. The percentage of patients with triglycerides >150 mg/dL at CR ends was 17.8% (15.6% when considering only patients that reach the LDL target of 55 mg/dL) while it is only 6.8% for triglycerides >200 mg/dL (5.9% when considering only patients that reach LDL target). Patients with triglycerides >150 mg/dL had higher baseline BMI, LDL cholesterol and uric acid with lower ejection fraction at CR ends. Hypertriglyceridemia significantly correlates with extreme CV risk (R= 0.08, p= 0.025). At multivariate analysis, FE (dependent variable) was significantly associated with triglycerides (beta= - 0,145, p= 0,026) and systolic BP (beta= 0,137, p= 0,032).
**Conclusions:** Despite high intensity statin therapy and lower LDL cholesterol targets, a substantial proportion of patients in cardiac rehabilitation still had elevated triglyceride levels. This study highlights the potential role of Icosapent Ethyl in managing hypertriglyceridemia in these patients.

Abstract n SP2_01 - Presenting author**: Elisa Russo**

## Predictive value of insulin resistance and GFR-adjusted uricemia on all-cause mortality: the URRAH study

Elisa Russo[1], Francesca Viazzi[1], Roberto Pontremoli[1], Carlo M. Barbagallo[2], Michele Bombelli[3], Edoardo Casiglia[4], Arrigo F.G. Cicero[5], Massimo Cirillo[6], Pietro Cirillo[7], Giovambattista Desideri[8], Lanfranco D'Elia[9], Raffaella Dell'Oro[3], Claudio Ferri[8], Ferruccio Galletti[9], Loreto Gesualdo[7], Cristina Giannattasio[10], Guido Iaccarino[11], Giovanna Leoncini[1], Francesca Mallamaci[12], Alessandro Maloberti[10], Stefano Masi[13], Alessandro Mengozzi[13], Alberto Mazza[14], Maria L. Muiesan[15], Pietro Nazzaro[16], Paolo Palatini[4], Gianfranco Parati[17], Marcello Rattazzi[18], Giulia Rivasi[19], Massimo Salvetti[15], Valérie Tikhonoff[20], Giuliano Tocci[21], Fosca A. L. Quarti Trevano[3], Andrea Ungar[19], Paolo Verdecchia[22], Agostino Virdis[13], Massimo Volpe[21], Guido Grassi[3] and Claudio Borghi[5] on behalf of the Working Group on UricAcid and Cardiovascular Risk of the Italian Society of Hypertension

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**Aim:** uric acid (UA) and insulin resistance (IR) are interlinked: UA adversely affects the insulin signaling pathway, while IR predicts the development of hyperuricemia. Both UA and IR are related to metabolic syndrome, which is nowadays one of the most prevalent risk factors for mortality. The triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio has been proved to have a high correlation with IR. The aim of the research was to explore the extent of interaction between IR and GFR-adjusted uricemia in determining mortality risk in a large population cohort study.
**Method:** data from 18,694 subjects were included from Uric acid Right foR heArt Healt (URRAH) database. We evaluated the association between TG/HDL-C ratio and GFR-adjusted uricemia, and the development of outcomes during the follow-up study period. The primary endpoint was all-cause mortality.
**Results:** after a mean follow-up of 124±64 months, there were 2,665 (14.2%) deaths for all causes. The incidence of fatal, non-fatal cardiovascular events, and all-cause mortality increased in parallel with the increase of TG/HDL-C quintiles. In both diabetic and non-diabetic patients, TG/HDL-C ratio showed a positive association with increasing of GFR-adjusted uricemia (UA/GFR ratio). TG/HDL-C ratio and GFR-adjusted uricemia significantly interact in determining all-cause mortality, even in non-diabetic patients. Subjects with higher TG/HDL-C ratio quintile had a statistically significantly higher rate of mortality than patients with lower quintiles (P <0.0001), independently by uricemia, GFR, the presence of diabetes and body mass index (BMI). Multivariate analysis showed that the TG/HDL-C ratio increase the risk for mortality even after adjustment for potential confounding factors included age, diabetes, UA/GFR, BMI and statins treatment.
**Conclusion:** TG/HDL-C ratio interacts with GFR-adjusted uricemia in predicting mortality, even in non-diabetic patients. Both IR and GFR-adjusted UA levels seems to have an important predictive role on all-cause mortality, independently of age, gender, diabetes, hypertension and statins.

Abstract n SP2_02 - Presenting author**: Armando Ferrera**

## Low perception of obesity as a pathological condition among Italian cardiologists

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**Aims** To assess perception of obesity as a modifiable pathological condition and the importance to treat it in a real-world sample of cardiologists and residents in cardiology.
**Methods** A nationwide, web-based, epidemiological survey on the perception of obesity as a disease and as a modifiable cardiovascular risk factors was conducted in 137 medical doctors (cardiologists and residents in cardiology). Participants filled with their answers a questionnaire of 31 questions about perception of obesity and strategies on cardiovascular disease prevention in clinical practice.
**Results** Of 137 individuals enrolled in our survey only 5 (3.6%) reported to measure waist circumference in their clinical practice and only 3 (2.2%) reported to measure waist-to-hip ratio. One-hundred-twenty participants (87.6%) would not pre- scribe an anti-obesity drug to a patient with grade II obesity. Sixty-eight (49.6%) participants have never read or heard of a clinical trial on obesity. On the other hand, 134 (97.8%) routinely measured blood pressure in their clinical practice, 129 (94.2%) would prescribe a statin for a hypercholesterolemic patient and 132 (96.4%) subjects have read/heard a clinical trial on type 2 diabetes in their life.
**Conclusions** Although obesity is a chronic disease and an important modifiable cardiovascular risk factor such as arterial hypertension, hypercholesterolemia, cigarette smoke and diabetes, cardiologists and residents in cardiology substantially underestimate it ignoring that it should be treated as a proper disease.

Abstract n SP2_03 - Presenting author**: Alessia Cipollone**

## Effectiveness of coronary risk score in real life

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**Aim of the study:** Genetic risk assessment is considered independent of classical clinical risk factors for CAD so should be used in addition to clinical risk assessment to provide a more accurate cardiovascular lifetime risk evaluation.
In this study we wanted to estimate if there is a substantial correspondence between the coronary score (calculated using CARDIO inCode-Score Polygenic Risk Score) and the number of cardiovascular events (CVE) in patients with high LDL-c levels enlisted in the LIPIGEN project.
**Methods:** We enrolled 113 patients with high LDL-c levels screened, on the basis of the Dutch Lipid Score criteria, for genetic forms of familial hypercholesterolemia (55 resulted positive for FH). Then we compared the results of CARDIO inCode-Score Polygenic Risk Score with each patient's clinical history to evidence a direct connection with the occurrence of CVE.
**Results:** Out of the all 113 patients 13 had a CARDIO inCode-Score <0.75 ("low risk"), 50 patients had a Score >0.75 but <1.3 ("intermediate risk"), 48 had a score >1.3 but <3 ("high risk") and 2 had a very high risk score >3.
Each class was compared with the occurrence of CVE in the patients' medical histories. In "low risk" class was registered only 1 CVE (7.7 % of the population); in the patients with "intermediate risk" score were registered 8 CVE (16% of the population); in the "high risk" population were registered 4 CVE (8.3% of the population) and in the very-high risk score patients there weren't cases of previous CV event.
**Conclusions**: Even if the Cardio InCode Score has been validated in previous studies, our data did not show a clear link between the coronary Score and the prevalence of CVE. However, our results have to be validated through more statistical analyses and an increasing sample of patients.
On the other hand, taking an individual's genetic risk into consideration can enable physicians to reclassify patients into a higher treatment category and to personalize the therapeutic approach to better prevent cardiovascular disease.

Abstract n SP2_04 - Presenting author**: Andrea Galeazzo Rigutini**

## The impAct of aTherosclerotic burden on vascular outcomEs in patieNts with stroke and atrial fibrillation "The ATHENA study"

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**Background:** Patients with a history of ischemic stroke (IS) and atrial fibrillation (AF) have an elevated risk for recurrent vascular events. The presence of atherosclerotic vascular disease in multiple vascular territories increases the overall vascular burden and is linked to poorer cardiovascular outcomes compared to disease in a single vessel.
**Aim:** This study evaluates the impact of atherosclerotic vascular disease burden across different vascular territories on the risk of vascular events in patients with recent IS and AF within 90 days.
**Methods:** We included patients with IS and AF from the International RAF network in a prospective 90-day follow-up. Atherosclerotic vascular disease was identified by at least one of the following: symptomatic ischemic heart disease, symptomatic peripheral artery disease, internal carotid stenosis ≥50%, or the presence of plaques in the aorta. The primary outcome was a composite of stroke, transient ischemic attack, systemic embolism, cerebral bleeding, and major extracranial bleeding within 90 days post-acute stroke. Patients were categorized into five groups based on the number of affected atherosclerotic vascular territories, with those with no atherosclerotic vascular disease as the reference. Kaplan-Meier curves were generated and compared using the log-rank test to determine the predictive value of the number of diseased territories for the risk of events. Data analysis was performed with SPSS/PC Win Package 25.0.
**Results:** Of the 2148 patients (mean age 77.59; 53.86% female), 744 (34.60%) had atherosclerosis. Multivariable analysis revealed that involvement of three (HR 2.80, 95% CI: 1.20-6.53) or four (HR 6.81, 95% CI: 1.02-36.24) vascular territories was significantly associated with the risk of combined events.
**Conclusions:** In individuals with recent IS and AF, atherosclerotic vascular disease is a significant prognostic marker, especially when three or four territories are affected. The degree of vascular territory involvement directly correlates with an increased risk of combined events.

Abstract n SP2_05 - Presenting author**: Filippo Egalini**

## A pilot study on dyslipidemic patients with family history of early cardiovascular events: does coronary CT scan improve CV risk stratification?

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**Aim:** A family history of early cardiovascular disease (e-CVD) [before 55 and 60 years in men and women, respectively] modifies future CVD risk, nearly doubling the probability of developing coronary artery disease. Coronary CT angiography (CCTA) is a useful, non-invasive tool for detecting coronary atherosclerotic plaques (CAPs). Based on CCTA data, we aimed to reclassify the CV risk of subjects with dyslipidemia managed in primary prevention and a family history of e-CVD.
**Methods:** Individuals with dyslipidemia and a family history of e-CVD were retrospectively enrolled in two lipid clinics in Northern Italy ("City of Health and Science" Hospital of Turin and "Azienda Ospedaliera Universitaria Integrata" of Verona). Subjects with established CVD, age ≥70 years, genetically confirmed monogenic familial hypercholesterolemia (FH), diabetes, or kidney failure were excluded. Lipid profile, smoking status, BMI, and comorbid hypertension were recorded. All subjects had undergone CCTA and subsequently an invasive coronary angiography (ICA) if a ≥50% or critical stenosis was detected.
**Results:** The study included 20 individuals (10 women) classified as high CV risk. The mean age (±SD) was 51.8±8.5 years, mean untreated LDL-c 222.7±47.3 mg/dl, and mean Lp(a) 66.4±51 mg/dl. CCTA detected at least 1 CAP and critical CAPs in 14 (70%) and 6 (30%) subjects, respectively. ICA confirmed critical CAPs in 5 patients who underwent percutaneous coronary intervention with drug-eluting stent placement, anti-platelet treatment, and lipid-lowering therapy intensification.
**Conclusions:** This retrospective pilot study suggests that a family history of e-CVD is a major CV risk per se, even in the absence of FH or high Lp(a). CCTA showed a relatively high prevalence of critical CAPs that needed stent positioning and reclassified the CV risk of most patients, leading to treatment intensification. The implications of these findings require further investigation.

Abstract n SP2_06 - Presenting author**: Valentina Bellantonio**

## Carotid-femoral pulse wave velocity progression in hypertensive patients is associated with subsequent CV outcomes

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**Aim:** arterial stiffness (Pulse Wave Velocity - PWV) is associated with CV events and mortality. However, little is known on the relationship of its progression (ΔPWV) over time with CV outcomes. The aim of our study was to evaluate the relationship between PWV progression and all-cause mortality and CV events in hypertensive subjects.
**Methods:** We enrolled 402 consecutive hypertensive outpatients. At baseline anamnestic, clinical, BP, laboratory data and PWV were assessed. We performed a PWV follow-up examination at a median time of 3.7±0.5 years. Patients were subsequently followed for a median time of 10.1 (IQR 9.5 -10.5) years recording all-cause mortality and CV events.
**Results:** At baseline the mean age was 53.2±13.0 years, SBP and DBP were 141.8±17.5 and 86.8±10.5 mmHg and PWV was 8.5±1.9 m/s. Despite an improvement in BP control (-9.2±19.5 and -8.0±12.3 for SBP and DBP respectively), at follow-up the population showed a PWV increase (ΔPWV +0.6±1.9 m/s). Progressors (ΔPWV ≥ 0.5 m/s, 204 patients, 50.7%) had a significantly lower survival probability and higher cumulative incidence of composite events, while no differences were seen for CV events (unadjusted analysis). At cox multivariable analysis neither ΔPWV ≥ 0.5 m/s (progressors) nor ΔPWV (as a spline function) were associated with CV events and with all-cause mortality. However, the association with survival probability and cumulative incidence of CV events, as a composite outcome, was significant (HR = 2.32, 95% CI: 1.33 – 4.04, p=0.003).
**Conclusions:** In conclusion, our study shows that PWV progression of at least 0.5 m/s is frequent in hypertensive patients and that it is associated with a significantly higher risk of developing CV events or dying (composite outcome).

Abstract n SP2_07 - Presenting author**: Carola Maria Gagliardo**

## Genetic heterogeneity of Familial Hypercholesterolemia by Next Generation Sequencing: a case report

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**Background:** Familiar Hypercholesterolemia (FH) is an inherited disorder of lipid metabolism characterized by high low-density lipoprotein cholesterol (LDL-C) levels and premature atherosclerotic cardiovascular disease (ASCVD). Mutations in three main genes that are responsible for this autosomal dominant disease (LDLR, APOB and PCSK9 genes) and heterogeneity of phenotype mostly depend on the underlying genotype. In addition, variants in genes causing other dyslipidaemias, showing phenotypes overlapping with FH, may also act as phenotype modifiers in patients with FH.
**Methods:** A 36-years-old woman was evaluated for hypercholesterolemia, that was known since childhood. Dyslipidaemia and atherosclerotic-based cardiovascular disease occurred at an early age (acute coronary syndrome in the father at age of 45) in many family members. The highest levels of total and LDL cholesterol (542 mg/dL and 398 mg/dL, respectively) were registered during pregnancy, when the hypolipidemic therapy was discontinued. Laboratory data showed high levels of total cholesterol (327 mg/dL) and LDL-C (255 mg/dL) despite simvastatin plus ezetimibe therapy; triglycerides and high-density lipoprotein cholesterol (HDL-C) were 46.9 mg/dL and 62.4 mg/dL, respectively. The DUTCH score 6 was suggestive of clinically probable FH. Next generation sequencing was carried out on an Ion GeneStudio S5 Plus System using the Ion 540 Chip with a custom panel including 50 candidate genes related to LDL, HDL and triglycerides metabolism.
**Results:** The proband was found to be heterozygous carrier of a previously described pathogenic non-sense mutation in LDLR with null LDL-R activity (c.1257C>G p.Tyr419Ter). Interestingly, another mutation was identified on lysosomal acid lipase (LIPA) gene (c.929G>A p.Trp310Ter) in heterozygosis. This variant has been previously identified in homozygosity in two newborns of Sicilian origin with Wolman's disease and in heterozygosity in a subject belonging to the same family (unpublished data). In addition, the determination of Polygenic Risk Score was performed (PRS: 0.652).
**Conclusion:** We report a case of heterozygous familial hypercholesterolemia (HeFH) carrying a composite genotype. The presence of a variant in modifier gene such LIPA in HeFH may further exacerbate the phenotype, partially justifying the variability among patients. Further studies are needed to evaluate how heterozygous variant c.929G>A p.Trp310Ter on the LIPA gene may modulate the lipid and cardiovascular phenotype of FH patients.

Abstract n SP2_08 - Presenting author**: Andrea Rossi**

## Attitudes and confidence to deprescribing in general practice. A focus on cardiovascular therapies

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**Aim:** General practitioners (GPs) should regularly review patients' medications and consider deprescribing interventions, when necessary, as inappropriate treatments may harm patients' health. The objective of this study was to assess the Italian GP's perceptions of deprescribing and the barriers to its implementation.
**Methods:** GPs were invited to participate in an online survey consisting of 20 questions about deprescribing process in daily clinical practice.
**Results:** We collected 598 answers in 8 months. GP sample was balanced by sex (50% female, 49.5% male, 0.5% not specified) and well distributed by years of experience (56% with <25 years of experience and 44% with >25 years of experience). Overall, less than 2% of GPs do not implement deprescribing interventions in daily practice because of insufficient experience (70%), missing specific education (60%) and no available time (40%). On the contrary, 22.6% reported to implement deprescribing often/very often, and patients over 80 years old are the most deprescribing-addressed. Regarding specific therapies, cardiovascular drugs are among the less commonly deprescribed ones (20.9% for statins and 17.6% for antihypertensives). Triggers of deprescribing process are variations of the risk-benefit balance considering comorbidities and polytherapy (74.6%), and potential adverse drug reactions linked to chronic diseases (77.9%). Specific evaluation of each patient case and personal experiences are the main adopted approaches (89.6% and 44.6%, respectively), followed by the use of guidelines and criteria (41.2% and 14.4% respectively). However, the survey highlighted issues related to poor availability of deprescribing guidelines (38.6%), difficulties in dealing with specialists (73.2%), lack of time in daily practice (35.8%), and mistrust of patient in medication interruption (53.8%).
**Conclusions:** The present study confirms that GPs' awareness of the importance of deprescribing process is growing and that the process is mainly implemented in multi-morbid elderly patients with polypharmacy. However, the need for specific education and guidelines also emerged.

Abstract n SP2_09 - Presenting author**: Marialuisa Sveva Marozzi**

## Gender disparities in hypertensive patients across the lifetime: an age-stratified analysis

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**Aim**: This study aims to explore the influence of gender on vascular and renal damage across distinct age brackets. In particular, investigates the intricate interplay between gender, aging and the onset of vascular and renal injuries. Additionally, the study incorporates an examination of the Triglyceride-Glucose (TYG) index, a surrogate indicator of insulin resistance, to discern its role in clarifying gender-specific variations in health outcomes across different life stages. This analysis aims to enhance our comprehension of age-specific vulnerabilities and contribute valuable insights to the field of gender-related health research.
**Methods**: We selected 210 Caucasian patients, all affected by hypertension, and we divided them previously in two groups, male and female, and in each group we splitted 3 clusters based on their age (under 50, 50 to 70 and over 70 years old). All patients underwent a comprehensive physical examination, with systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR). Blood samples obtained from all patients were analyzed for the complete blood count, low/high density lipoproteins and triglycerides, glycaemia and renal function, including albuminuria and proteinuria. Moreover, all patients went through ankle-brachial index (ABI) and pulse wave velocity. Lastly we calculated the TYG index of all patients.
**Results**: Regardless of the well-known correlation between TYG index and hypertension, we found that there was no gender difference between the TyG index and gender or aging. Moreover, no differences were underlined among vascular and renal injuries, neither changes in aortic stiffness were associated to gender but to age-related effects.
**Conclusions**: Despite what expected, the menopausal transition was not associated with a higher renal or vascular damage, nor to a higher risk of insulin resistance. Large-scale prospective cohort studies are needed to validate these findings, also detecting the influence of gender and aging on heart damage.

Abstract n SP2_10 - Presenting author**: Umberto Capece**

## Real-world evidence evaluation of LDL-C among hospitalized patients: a population-based observational study in the timeframe 2021-2022

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**Aims**. European registries and retrospective cohorts highlighted the lack of low-density lipoprotein-cholesterol (LDL-C) goal achievement in many very high-risk patients. Hospitalized patients are often frail, and frailty is associated with all-cause mortality and cardiovascular mortality. Aim of this study is to evaluate LDL-C levels in a Real-World setting of inpatients, identify cardiovascular risk categories and highlight treatment gaps in the implementation of LDL-C control.
**Methods.** This retrospective, observational study included all the adult patients admitted at an Italian hospital between 2021-2022 and with LDL-C values available during hospitalization. Disease-related real-world data were collected from Hospital Information Systems using automated data extraction strategies and through the implementation of a patient-centered data repository (the Dyslipidemia Data Mart). Assessment of cardiovascular risk profiles, LDL-C target achievement according to the 2019 ESC/EAS guidelines and lipid-lowering therapies (LLT) use were performed.
**Results**. 13,834 patients were included: 17.15%, 13.72%, 16.82% and 49.76% were low (L), moderate (M), high (H) and very high-risk (VH) patients, respectively. The percentage of in-target patients was progressively lower moving towards worse categories (78.79% in L, 58.38% in M, 33.3% in H and 21.37% in VH). Among LLT treated patients in VH category, in-target are 28.48%; 47.6.% in H, 69.12% in M and 68.47% in L. The impact of monotherapies and combination therapies on target achievement was also analyzed.
**Conclusions.** This study depicts LDL-C control among an entire population of inpatients, highlighting relevant gaps especially in VH category. Future efforts must aim to reduce the cardiovascular risk of these subjects.

Abstract n SP3_01 - Presenting author**: Rella Martina**

## Identification of myokine irisin receptor in pancreatic beta-cells

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**Aim***:* Irisin, a hormone secreted by skeletal muscle, is able to protects human and rodent beta-cells and pancreatic islets from lipotoxicity-induced apoptosis, to increase insulin biosynthesis and glucose-stimulated insulin secretion (GSIS), and to promote beta-cell proliferation, both in vitro and in vivo in mice. Although it has been demonstrated that irisin mediates its effects on bone and fat via αV integrin receptors, the presence of an irisin receptor in pancreatic beta-cells has not been reported.
**Methods***:* INS-1E rat insulinoma cells were treated with 30 nM αV integrin siRNA for 24 h or 1 μM RGDS (a chemical inhibitor of cellular integrins) for 10 min, and then exposed to 100 nM irisin for different times. Intracellular signalling and GSIS were evaluated by immunoblotting and insulin ELISA assay, respectively. In human pancreatic islets, irisin interactome was assessed through a pull-down assay/mass spectrometry approach.
**Results***:* In INS-1E cells, irisin activates its intracellular signalling and enhances GSIS in the presence of αV integrin knockdown or RGDS, thus excluding the involvement of integrin receptors in these effects. In human pancreatic islets, we identified 102 irisin interactors, mostly belonging to intracellular compartments (i.e., vesicles and membrane rafts), and not including canonical membrane receptors. We therefore hypothesized that irisin could be endocytosed in pancreatic beta-cells and confirmed this by immunoblotting and immunofluorescence techniques in INS-1E cells.
**Conclusions***:* These results suggest that irisin effects on pancreatic beta-cells are independent of engaging the αV integrin receptor and may instead depend on its endocytosis, thus proposing a potential new mechanism of action for peptide hormones. In addition, we highlight the possibility that the same hormone may signal through different receptors in different target tissues. These findings pave the way for the development of a new class of anti-diabetes drugs.

Abstract n SP3_02 - Presenting author**: Francesca De Vito**

## Treatment with 4-phenylbutyrate counteracts ER stress-related response in colonic mucosa of subjects with dysglycemic conditions

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**Aim:** Intestinal barrier dysfunction is a pathogenic factor in T2DM development. Activation of ER stress is involved in glucotoxicity-mediated cellular damage and it has been reported to affect gut barrier integrity in animal models. Herein, we examined whether subjects with prediabetes and T2DM display activation of ER stress in the gut along with an impaired barrier integrity and whether hyperglycemia directly induced these aberrations. Further, we tested the beneficial effects of the chemical chaperone 4-phenylbutyrate (4-PBA) on diabetes-related ER stress in the gut.
**Methods:** Levels of the ER stress and of the tight junction (TJ) proteins were evaluated in colonic mucosa fragments of 55 individuals equally subdivided in NGT, prediabetes and T2DM. Colonic mucosa samples collected from NGT subjects were cultured in presence or absence of high glucose (25mM-50mM) and those from dysglycemic subjects were cultured in presence or absence of 4-PBA 10mM.
**Results:** Subjects with dysglycemia exhibited increased colonic protein levels of the ER stress markers IRE-1α, peIF2α and of the pro-apoptotic/pro-inflammatory factors CHOP and pJNK in comparison to those with NGT along with reduced protein abundance of the TJ ZO-1 and occludin. HG exposure increased IRE-1α, peIF2α, CHOP and pJNK protein levels, with a peak at 50mM, and significantly down-regulated ZO-1 and occludin protein abundance in the colonic mucosa as compared to the untreated control. To investigate whether 4-PBA-mediated ER stress inhibition was able to counteract the observed diabetes related down-regulation of TJ proteins, colonic mucosa biopsies collected from prediabetic or T2DM subjects were cultured in absence or presence of 4-PBA. We found that 4-PBA treatment inhibited ER stress-related response in the gut and significantly increased ZO-1 and Occludin protein levels.
**Conclusion:** Hyperglycemia directly induces ER stress activation and TJ aberrations in the colonic mucosa and 4-PBA treatment is able to counteract diabetes-related cellular damage in the gut.

Abstract n SP3_03 - Presenting author**: Silvia Angelino**

## Relationship between body mass index, body composition and semen parameters in young adults with type 1 diabetes

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**Introduction**: Obesity is known to impair male fertility through alterations in the hypothalamic-pituitary-gonadal axis, disruption of testicular steroidogenesis and metabolic dysregulation. Excessive body weight has a negative impact on semen parameters, including sperm concentration, motility and morphology (a). Similarly, diabetes mellitus might negatively affect male fertility, but its impact on semen quality needs to be studied, as the available results are not conclusive (b).
**Aim**: To study the relationship between body mass index, body composition and semen parameters among young adults with T1DM.
**Methods**: This is a cross-sectional study involving men aged 18-35 years, with T1DM, in treatment with intensive insulin treatment, sexually active, excluding patients with diseases potentially affecting male fertility. All participants underwent anthropometric measurements, blood test, semen analysis, bioelectrical impedance analysis (BIA) and assessment of erectile and ejaculatory function, with IIEF-5 and PEDT questionnaires respectively. The study population was divided into two groups according to the presence of overweight or normal weight, defined by body mass index (BMI) ≥25% and BMI<25% respectively.
**Results**: Eighty-eight men with T1DM were included in the study population. Median age was 24.5 years, mean diabetes duration was 15.3 years. Mean BMI was 24.0 and thirty-two patients (36%) were overweight. Overweight patients had higher fasting plasma glucose (FPG) [BMI≥25% vs BMI<25%, median (IQR), 219 (187, 271) vs 193 (130, 211) mg/dL, P=0.008], higher $HbA_{1c}$ [8.6 (8, 9.7) vs 7.3 (7, 8) %, P<0.001] and higher insulin daily dose [55 ± 12 vs 48 ± 13 UI, P=0.019] in comparison with normal-weight men. Overweight participants showed higher semen volume [2.8 (2.5, 3.7) vs 2.5 (2.2, 2.6) mL, P=0.012], lower progressive sperm motility [26.5 (25, 33) vs 35 (25, 35) %, P=0.031], higher non progressive motility [15 (12.5, 17.5) vs 10 (10, 10) %, P<0.001], higher prevalence of erectile dysfunction [50 vs 21.4 %, P=0.011] and lower IIEF-5 score [20 (17, 25) vs 24.5 (23, 25), P=0.035] compared to normal-weight patients (Table 3). Results from univariate analysis showed that BMI was negatively associated with progressive motility (r=-0.247, P=0.021) and positively associated with semen volume (r=0.264, P=0.013) and non-progressive motility (r=0.601, P<0.001) (Table 4). Multivariable regression analysis identified lower BMI (β coefficient= -0.249, P=0.038) as independent predictor of normality of semen parameters
**Conclusions**: Young adults with T1DM and overweight showed worse semen parameters, including progressive and non-progressive motility, and worse erectile and ejaculation function, compared with patients with normal weight. BMI appears to be associated with progressive and non-progressive motility and semen volume; moreover, BMI resulted as predictor for semen quality. These results underline the need to assess and control the weight status in T1DM young adults.

Abstract n SP3_04 - Presenting author**: Anna Borrelli**

## Irisin as potential mediator of GLP-1 receptor agonists action

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**Aim**: Irisin is a hormone secreted by skeletal muscle following physical activity or excess of saturated fatty acids, able to promote energy expenditure and improve metabolic homeostasis. Serum irisin levels are reduced in type 2 diabetes (T2D), while exogenous irisin administration improves glycemic control in diabetic mice. Interestingly, irisin and GLP-1 share comparable pleiotropic effects and activate similar intracellular pathways, both at pancreatic and extra-pancreatic levels. This study investigated the potential role of irisin as mediator of GLP-1 receptor agonists (GLP-1RAs) action.
**Methods**: 190 T2D patients were enrolled and stratified by anti-diabetes therapy: diet only (30); metformin only (37); metformin plus GLP-1RAs (39); metformin plus DPP-4 inhibitors (38); metformin plus SGLT2 inhibitors (29); other therapies (17). The control group included 36 sex-, and BMI-matched subjects without diabetes. In addition, human skeletal muscle cells (HSkMC) were exposed in vitro to 1-100 nM of different GLP-1RAs (exendin-4, dulaglutide, semaglutide, and liraglutide) for different times. Irisin secretion in culture media and the activation of intracellular pathways were evaluated by ELISA assay and immunoblot, respectively.
**Results**: T2D patients showed lower irisin levels than controls. Patients treated with metformin plus GLP-1RAs showed increased serum irisin levels comparable to those of non-diabetic subjects. In addition, in vitro treatment of hSkMC with different GLP-1RAs for 24 h resulted in enhanced irisin release in the culture medium. Interestingly, despite the absence of GLP-1R on hSkMC, the treatment of these cells for 10 and 15 min with 10 nM semaglutide was able to induce AKT, CREB, and ERK 1/2 activation.
**Conclusions**: in T2D, the treatment with GLP-1-RAs significantly increased serum irisin to levels comparable to those of non-diabetic subjects. This effect could be due to a direct stimulation of skeletal muscle cells by GLP-1RAs, suggesting a role for irisin as a potential mediator of their beneficial effects.

Abstract n SP3_05 - Presenting author**: Luca Sacchetta**

## Inappropriately high leptin levels are associated with hyperinsulinemia and insulin resistance in overweight/obese youths

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**Background and aims:** Leptin is an energy-regulating adipokine and its levels are directly proportional to fat mass. Some individuals show inappropriately elevated leptin levels for their degree of adiposity. We aimed to assess the metabolic consequences of chronic hyperleptinemia in youths.
**Materials and methods:** A total of 858 overweight/obese adolescents without diabetes (age 13.2 ± 2.7 years, 58% females, BMI *z*-score 2.4 ± 0.4), underwent a 3-h 75 g OGTT with mathematical modeling of β-cell function and estimation of insulin sensitivity and clearance. Fat mass was measured by DEXA.
**Results:** Hyperleptinemic (HyperL, n=428) and normoleptinemic (NormL, n=430) individuals were identified based on the median of residuals' distribution of the sex-specific leptin vs fat mass fit. Compared with NormL, HyperL were younger (-0.9 ± 0.2 yr, p<0.0001) and had higher BMI z-score (+0.13 ± 0.02, p<0.0001) and leptin levels (+17.6 ± 0.82 ng/ml, p<0.0001), despite similar fat mass (p=0.284) and sex distribution (p=0.991). HyperL had worse glycemic control (fasting glucose +0.06 ± 0.03 mmol/L, p=0.056; 2-h glucose +0.33 ± 0.08 mmol/L, p<0.0001), increased insulin secretion rate (fasting: +16 ± 4 pmol m-2 min-1, p=0.0003; OGTT: +9 ± 2 nmol/m2, p<0.0001), and reduced insulin sensitivity (WBISI -0.4 ± 0.1 nmol/m2, p < 0.0001) and insulin clearance (fasting -0.08 ± 0.02 L min-1 m-2, p = 0.001; OGTT -0.07± 0.02 L min-1 m-2, p < 0.0001). The two groups showed similar β-cell function parameters (β-cell glucose sensitivity: p= 0.758; β-cell rate sensitivity: p = 0.627). At multivariable regression analysis, leptin levels negatively correlated with insulin clearance independently of insulin secretion and sensitivity (fasting: Std. β= -0.01, p<0.006; OGTT: Std. β= -0.07, p<0.006). Subgroup analysis did not show differences between boys and girls.
**Conclusion**: In overweight/obese adolescents, inappropriately high leptin levels are associated with a worse adiposity-related metabolic phenotype, characterized by glucose intolerance, insulin resistance, and chronic hyperinsulinemia due to enhanced glucose-stimulated insulin secretion and reduced insulin clearance.

Abstract n SP3_06 - Presenting author**: Elena Sani**

## Associations between higher plasma ferritin and hepcidin levels with liver stiffness in patients with type 2 diabetes: An exploratory study

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**Aim:** Currently, there is no information about the association between circulating levels of ferritin and hepcidin and liver fibrosis in patients with type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD).
**Methods:** We enrolled 153 patients with T2DM with no known liver diseases, who consecutively attended our diabetes outpatient service and who underwent liver ultrasonography and liver stiffness measurement (LSM) by vibration-controlled transient elastography (Fibroscan® for the non-invasive assessment of liver fibrosis). Plasma ferritin and hepcidin concentrations were measured with an electrochemiluminescence immunoassay and mass spectrometry-based assay, respectively.
**Results:** After stratification of patients by LSM tertiles [1st tertile median LSM: 3.6 (interquartile range: 3.3-4.0) kPa, 2nd tertile: 5.3 (4.9-5.9) kPa and 3rd tertile: 7.9 (6.7-9.4) kPa], we found that plasma ferritin and hepcidin concentrations increased across LSM tertiles [median ferritin: 68.7 (interquartile range: 25.1-147) vs. 85.8 (48.3-139) vs. 111 (59.3-203) µg/L, p = 0.021; median hepcidin: 2.5 (1.1-5.2) vs. 4.4 (2.5-7.3) vs. 4.1 (1.9-6.8) nmol/L, p = 0.032]. After adjustment for age, sex, diabetes duration, waist circumference, haemoglobin A1c, HOMA-insulin resistance score, triglycerides, haemoglobin, presence of hepatic steatosis on ultrasonography and patatin-like phospholipase domain-containing-3 (PNPLA3) rs738409 genetic variant, higher plasma ferritin levels were associated with greater LSM values (adjusted-odds ratio 2.10, 95% confidence interval 1.23-3.57, p = 0.005). Higher plasma hepcidin levels were also associated with greater LSM values (adjusted-odds ratio 1.90, 95% confidence interval 1.15-3.13, p = 0.013).
**Conclusions:** Higher levels of plasma ferritin and hepcidin were associated with greater NAFLD-related liver fibrosis (assessed by LSM) in patients with T2DM, even after adjustment for established cardiometabolic risk factors, diabetes-related variables and other potential confounders.

Abstract n SP3_07 - Presenting author**: Rocco Amendolara**

## No differences in kidney function decline between people with type 2 diabetes starting a SGLT2i or a GLP1-RA: a real-world retrospective comparative observational study

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**Purpose.** Diabetic nephropathy (DN) represents the leading cause of end-stage kidney disease (ESKD) in developed countries. Cardiovascular outcome trials (CVOTs) suggested that the use of glucagon-like peptide-1 receptor Agonists (GLP1RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduced the risk of incidence and progression of DN in type 2 diabetes (T2DM). In the present study, we aimed to compare the eGFR decline in people on GLP1RA or on SGLT2i in a real-world setting.
**Methods.** Data from 478 T2DM patients who initiated therapy with a GLP-1 RA (n=254) or a SGLT2i (n=224) between January 1, 2018 and December 31, 2021 were extracted. The primary outcome was any reduction ≥30% in the eGFR after the beginning of the therapy. Weight loss and drug discontinuation were also assessed.
**Findings.** Over a median follow-up of 24 months, an eGFR reduction ≥30% occurred in 34 out of 254 (13.4%) subjects starting a GLP1RA, and in 26 out of 223 (11.6%) patients starting a SGLT2i (HR [95% CI]: 0.89 [0.54; 1.49], p-value: 0.67). Median eGFR change over the whole follow-up was similar between groups (GLP1RA: -2 ml/min/1.73 $m^2$ [-13; -8]; SGLT2i: 0 ml/min/1.73 $m^2$ [-10; 7], p-value: 0.54). No worsening of kidney function was observed, even when considered the ratio eGFR mean. The value of eGFR at baseline showed a statistically significant indirect correlation with the observed absolute value of eGFR change over the follow-up (rho: -0.36, p-value: <0.001). The differences in eGFR changes over time observed by eGFR categories was statistically significant (p-value: 0.0001) in both treatment groups. No significant differences in weight loss and in drug discontinuations between groups were observed.
**Implications.** Although acting on different molecular mechanisms, both GLP1RA and SGLT2i might hold similar effects on eGFR decline in diabetes, as suggested by results of this study conducted in a real-world setting.

Abstract n SP3_08 - Presenting author**: Nicholas Cocomello**

## Incident cardiovascular events and insulin resistance markers in patients with metabolic dysfunction associated steatotic liver disease

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**Background & Aim**: Insulin Resistance (IR) is the key pathohistological process of both metabolic syndrome (MetS) and Metabolic dysfunction associated steatotic liver disease (MASLD). IR promotes visceral adiposity, atherogenic dyslipidemia and chronic low-grade inflammation leading to cardiovascular disease (CVD). Aim of the study was to investigate the predictive role of lipid-based IR markers, namely triglycerides-glycemia (TyG) index and triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-C), on CV events (CVEs) in patients with MASLD.
**Methods**: this is a post-hoc analysis of the Plinio Study, a prospective ongoing study of dysmetabolic patients affected by liver steatosis. MASLD criteria were applied according to the recent multisociety consensus. HOMA-IR, TyG index and TG/HDL-C were calculated. The optimal IR markers cut-offs for MASLD detection and CVEs prediction were calculated using receiving operative curve (ROC) analyses. Follow-up data on CVEs were prospectively collected.
**Results**: The study included 830 patients, 82.8% with MASLD. MASLD diagnosis was associated with metabolic syndrome (59.5% vs. 21.8%, p>0.001), diabetes (28.5% vs. 11.3%, p>0.001), higher HOMA-IR (3.45 [2.38-5.55] vs. 1.68 [0.91-2.48], p<0.001), TyG Index (4.77 [4.62-4.94] vs. 4.55 [4.44-4.69], p<0.001), and TG/HDL-C ratio (2.91 [2.00-4.40] vs. 1.68 [1.18-2.53], p<0.001). HOMA-IR ≥ 2.25 better detected patients with US MASLD (aOR:7.25) in comparison to TyG index ≥ 4.70 (aOR 4.39), and TG/HDL-C ≥ 2.11 (aOR 4.03). Mean time of follow-up was 47.6 months, yielding for 3,629 patients-year. Differently from HOMA-IR, TyG index ≥4.85 (aHR:2.30) and TG/HDL-C ≥2.77 (aHR:2.69) predicted CVEs, after adjusting for confounders.
**Conclusion:** While HOMA-IR is the best IR marker to identify MASLD patients, lipid-base IR markers, namely TyG index and TG/HDL-C, better predict CVEs in these patients.

Abstract n SP3_09 - Presenting author**: Miriam Longo**

## Two years with GIOIA 'Effects of gliflozins and gliptins on markers of cardiovascular damage in type 2 diabetes': A prospective, multicentre, quasi-experimental study on sodium-glucose cotransporter 2 and dipeptidyl peptidase-4 inhibitors in diabetes clinical practice

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**Aim:** To assess and compare the metabolic and vascular effectiveness of sodium-glucose cotransporter 2 inhibitors (SGLT-2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i) in the clinical practice of patients with type 2 diabetes in Italy.
**Materials and methods:** GIOIA is a 2-year prospective, multicentre, quasi-experimental study that enrolled patients with type 2 diabetes initiating SGLT-2i or DPP-4i for inadequate glycaemic control [glycated haemoglobin (HbA1c) >7%] between March 2018 and March 2021. The primary endpoints were changes in markers of organ damage [carotid intima-media thickness (CIMT), albuminuria, myocardial function] and HbA1c from baseline to year 2.
**Results:** In total, 1150 patients were enrolled in the study (SGLT-2i n = 580, DPP-4i n = 570). Patients initiated on SGLT-2i were younger (about 6 years) and heavier (about 11 kg), had higher HbA1c level (1% more), more albuminuria and cardiovascular events (16% more) than patients initiated on DPP-4i. CIMT and echocardiographic parameters were not significantly different. Propensity score matching yielded two groups, each consisting of 155 patients with diabetes with similar baseline characteristics. Despite a significant similar reduction in HbA1c levels in both groups (-0.8%), more patients on SGLT-2i had regression of CIMT and albuminuria (22% and 10%, respectively, $p < .001$ vs. DPP-4i); more patients on DPP-4i had progression of CIMT and albuminuria (23% and 28%, respectively, $p < .001$ vs. SGLT-2i). Left ventricular ejection fraction improved slightly (3%, $p = .043$) on SGLT-2i only.
**Conclusions:** In a real-world setting, both SGLT-2i and DPP-4i improve glycaemic control persisting after 2 years of treatment, with a robust effect on both CIMT and albuminuria regression for SGLT-2i as compared with DPP-4i in the propensity score matching.

Abstract n SP3_10 - Presenting author**: Antonella Al Refaie**

## Cardiovascular and Metabolic Effects of GLP-1RAs in Patients With Type 2 Diabetes Mellitus: A Preliminary Longitudinal Study

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**Aim:** Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder in the world. T2DM involves numerous cardiovascular complications, which are a cause of morbidity, mortality and increased public spending worldwide. The real challenge of new diabetes drugs is not only to reduce blood glicemia levels and glycated hemoglobin,but to prevent cardiovascular risk. The new receptor agonists for glucagon-like peptide-1 (GLP-1RAs) have been shown to play a key role in diabetes control and cardiovascular risk too.
**Methods:** We carried out a longitudinal study of 12 months evaluating the cardio-metabolic effects of GLP-1RAs on a cohort of 80 Caucasian patients with T2DM referred to the Department of Internal Medicine at the University Hospital of Siena, Italy.
**Results:** GLP-1RAs led to several positive changes in our study population, in addition to a weight loss we observed: a change in fat distribution with reduction in the percentage of visceral fat (1.21 vs 1.17, $p<0.05$); a significant reduction in the levels of LDL cholester-ol ($p<0.05$) and triglycerides.($p<0.01$); an increase in the values of adiponectin which could reflect a reduction in insulin resistance and in inflammatory state. We also ob-served a reduction in microalbuminuria and in media-intimal thickness at the epiaortic vessels ($p=0.05$).
**Conclusions:** In patients with T2DM 1-year therapy with GLP-1RAs has a positive effect on the main determinants of cardiovascular risk including body weight, visceral fat, dyslipidemia and atherosclerosis. Moreover, the increase in adiponectin may play a pivot-al role in controlling the inflammatory state and the mechanisms of vascular damage.

Abstract n SP4_01 - Presenting author**: Maria Cola**

## Homocysteine: markers of neurodegeneration in patients with alcohol dependence syndrome

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**Aim:** Alcoholism correlates with increased plasma homocysteine, leading to increased neurodegenerative risk. Caloric reduction is observed in alcoholics; in addition, the 'injurious action on the gastrointestinal canal reduces absorption and assimilation of vitamins. The metabolism of homocysteine requires vitamins B12, B6 and B9 as cofactors. Inadequate intake of these nutrients results in increased homocysteine that overcomes BBB and acts as a neurotoxin, promoting demyelination, leading to up-regulation of NMDA receptors, glutamate accumulation and neuronal lipid peroxidation, cellular modifications underlying phenomena such as learning, memory and dysesthesia. The study evaluates the association between hyperhomocysteinemia in alcohol-dependent patients and central and peripheral neuronal damage. Finally it suggests that vitamin supplementation, restoration of balanced diet and abstention from potus slow the nuerodegenerative process.
**Methods:** Psychometric instruments, MOCA and MMSE and functional, lower limb electromyography.
**Results:** 45 patients underwent blood homocysteine assay at enrollment, found to be above threshold values in 96% of cases; at T0 performed neurocognitive assessment by MOCA and MMTE, with mild to moderate impairment of cognitive abilities in 65% of cases. EMGs performed at T0 documented mild signs of senile neurogenic distress in 30% of patients. After a course of parenteral B vitamins and continuation oral vitamin supplementation for 6 months, MOCA and MMTE were repeated providing improvement in cognitive abilities in 85% of cases: moderate/light to mild. Repeat EMG at 6 months was also negative in 20% of patients with mild signs of distress. Homocysteine values at T6 were in range in 99% of patients.
**Conclusions:** The hyperhomocysteinemia observed in alcohol-dependent patients represents a risk factor for central and peripheral neurodegeneration that can potentially be modified with pharmacological strategies of vitamin replenishment and total abstention from potus.

Abstract n SP4_02 - Presenting author**: Alessandra Colantoni**

## Liver fibrosis progression and lysosomal acid lipase activity in patients with metabolic-associated steatotic liver disease

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**Aim:** Metabolic Associated Steatotic Liver Disease (MASLD) definition recently replaced Non-Alcoholic Fatty Liver Disease (NAFLD) to identify fatty liver associated with metabolic disorders. Liver fibrosis is the only MASLD severity index predicting liver and cardiovascular events in these patients. Previous studies demonstrated a reduction of Lysosomal Acid Lipase (LAL) activity in NAFLD and NAFLD-related cirrhosis. LAL is involved in lipid metabolism hydrolyzing cholesteryl esters and triglycerides from LDL-C. Aim of the study was to evaluate the association between LAL activity and liver fibrosis progression in MASLD.
**Methods:** MASLD criteria were applied to a prospective ongoing cohort (The Plinio Study) of NAFLD patients. The analyses were conducted on patients with serial FIB4 evaluations and basal LAL activity measurement. Fib4 was calculated according to guidelines. MASLD fibrosis progression was defined as changes in Fib4 values from negative to indeterminate or positive. Incident advanced liver fibrosis (ALF) was defined as changes in Fib4 from ≤2.67 to >2.67.
**Results:** The study includes 272 MASLD patients. At baseline, LAL and FIB-4 were inversely associated (rS=-0.126, p=0.038). The median follow-up time was 70.5 months. During the follow-up, 49 patients had fibrosis progression and 10 patients developed ALF. Patients with liver fibrosis worsening and those developing advanced fibrosis had lower basal LAL activity (Figure 1A-1B). When distributed according to LAL activity tertiles, the subjects with lower enzymatic activity had a higher risk of liver disease progression (Figure 1C-1D). After correction for confounders, the lower LAL activity tertile was associated with liver fibrosis worsening (aHR 2.11; [1.19-3.73]) and with ALF incidence (aHR, 5.39; [1.22-23.90]).
**Conclusions:** LAL activity was associated with liver fibrosis worsening and cirrhosis onset in MASLD patients. LAL activity might be used to identify patients at higher risk of liver fibrosis progression and who deserve a greater risk factor control to prevent liver and cardiovascular complications.

Abstract n SP4_03 - Presenting author**: Giuseppe Di Gioia**

## Association between liver cirrhosis and biochemical markers of nutritional status: age matters

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**Aim:** Malnutrition is a clinical condition caused by reduced intake or absorption of nutrients associated to impaired body composition, reduced physical and mental activity. Nutritional assessment identifies high-risk patients using Mini Nutriotional Assessment (MNA), body mass composition, arm and calf circumferences, unintened weight loss. Moreover, biochemical markers such as albumin, transferrin and lymphocytes have been used as complementary tool to assess malnutrition. Patients suffering from cirrhosis of the liver often meet malnutrition criteria, with a prevalence ranging from 20% to 60%. In those patients, malnutrition could potentially contribute to higher risk of cirrhosis-related complications. Malnutrition is also a prevalent condition in the geriatric population, ranging from 8.5% to 28% and it deeply influences morbidity and mortality. Aim of this study is to assess the validity of nutrition biochemical markers in the prediction of liver state in elderly patients according to age.
**Methods:** 115 patients aged ≥65 years admitted to Liver Unit, University of Foggia between April 2022 and June 2023 were recruited. The following exclusion criteria were considered: upper and lower limb fractures, paresis, pre-existing Immobilization Syndrome, advanced cognitive decline, hepatic encephalopathy, active neoplastic disease. Data on participants' at hospital admission including medical conditions, medical usage and laboratory tests were collected. Given the aim of this study, the values of transferrin (cutoff 200 mg/dl), albumin (cutoff 3.5g/dl) and number of lymphocytes (cutoff 1.5x10 9 /L) were considered and three groups were identified: 1) normal biomarkers; 2) 1 altered biomarker; 3)≥2 impared biomarkers. Statistical analysis was performed using logistic regression. P-value<.05 were considered statistically significant. Sex, age and BMI were considered as confounders.
**Results:** Out of the 115 patients (mean age 78.34±8.13, range 65-102 years), 61 (53%) were female and 50 (43,5 %) were affected by liver cirrhosis. In the overall population, mean levels of albumin were 3.04±0.5 g/dl, transferrin 231.08±83.84 mg/dl, lymphocyte count 1.08±0.54x10*9/l. The distribution of patients by liver condition as a function of nutritional biomarkers is reported in Figure 1. Association between liver cirrhosis and severity of alterations of serum nutritional biomarkers (OR 0.64, CI 95% 0.39-0.98, p-value<0.05) was observed. Then, logistic regression was conducted to analyse the prediction ability of nutritional biomarkers to identify liver state among age groups. In younger cohorts, there was a reduced ability to discriminate between cirrhotic and non-hepatopathic patients whereas the discriminative ability increased with advanced age.
**Conclusions:** Nutritional status assessment represents a relevant tool in terms of clinical evalutation and biochemical markers such as albumin, transferrin and lymphocytes are an integral part. Deficiency of those biomarkers could be potentially associated with malnutrition but also to liver pathology. In geriatric patients, assessment of biomarkers could support nutritional evaluation and identification of those with cirrhosis of the liver. However, the ability of those biomarkers to discriminate liver state changes with advanced age.

Abstract n SP4_04 - Presenting author**: Sabrina Scilletta**

## Cholemic Nephropathy and the Diagnostic Role of Urinary Biomarkers of Kidney Damage

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**These authors contributed equally*

**Aims:** Cholemic nephropathy is a renal disorder that causes acute kidney injury occurring in patients with elevated bilirubin values. The aim of this study was to evaluate early renal function impairment in patients with mild hyperbilirubinemia, in absence of alterations of the common parameters used in clinical practice such as serum creatinine or urea and normal renal morphology evaluated through Computed Tomography-scan. We studied urinary biomarkers of tubular damage Neutrophil gelatinase-associated lipocalin (u-NGAL), beta-2-microglobulin (u-B2M), osteopontin (u-OPN), trefoil factor 3 (u-TFF3) and Cystain C (u-Cys).
**Methods:** This is a case-control study investigating urinary biomarkers of tubular damage u-NGAL, u-B2M, u-OPN, u-TFF3 and u-Cys in patients with mild hyperbilirubinemia. 74 patients were included in this study: 36 patients with jaundice and 38 patients without jaundice.
**Results:** Subjects with jaundice (total bilirubin 12.4 ± 7.3 mg/dL) showed higher u-NGAL, u-B2M, u-TFF3, u-Cys, u-OPN compared with controls. After logistic regression analyses, including as independent variables age, estimated Glomerular Filtration Rate (eGFR), hemoglobin, diabetes, hypertension and jaundice, we observed a higher risk to have elevated values of u-NGAL (OR= 3.8,95% CI 1.07 – 13.5, p = 0.03) and u-B2M (OR= 9.4, 95% CI 2.3 – 38.9, p = 0.0018) in jaundiced subjects. Moreover, urinary biomarkers had direct correlation with alkaline phosphatase, total bilirubin and serum biliary acid.
**Conclusions:** this study demonstrated increased urinary biomarkers of tubular damage (u-NGAL, u-B2M, u-OPN, u-TFF3, u-Cys) in patients with mild hyperbilirubinemia in comparison to a control group. These findings suggest an early renal tubular damage in absence of alteration of the normal parameters used in clinical practice (eGFR, serum urea, renal morphology).

Abstract n SP4_05 - Presenting author**: Felice Cinque**

## Metabolic dysfunction-associated steatotic liver disease in people with HIV is associated with lower BMI and more liver fibrosis compared to the uninfected population

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**Aim:** People with HIV (PWH) are at high risk of metabolic dysfunction-associated steatotic liver disease (MASLD), defined by the presence of hepatic steatosis plus any among overweight, diabetes, hypertension, or dyslipidemia. There are limited data whether MASLD in PWH differs in clinical presentation from MASLD in the uninfected population. Aim: to compare the severity of metabolic and hepatic dysfunction between MASLD patients with and without HIV.
**Methods:** 212 consecutive HIV mono-infected patients with MASLD at McGill University in Montreal were compared to a sex and age matched MASLD HIV negative control group at Policlinico Hospital in Milan. Fibroscan with controlled attenuation parameter (CAP) was used to define MASLD (CAP≥248 dB/m), severe MASLD (CAP>280 dB/m), and significant liver fibrosis (liver stiffness measurement>7.0 kPa).
**Results:** PWH with MASLD presented lower median BMI (28[25-31] vs 29[27-32] Kg/m2, p=0.002) and lower prevalence of obesity (26% vs 44%, p<0.001) compared to MASLD uninfected patients, along with a lower prevalence of hypertension (21% vs 38%, p<0.001). The prevalence of dyslipidemia (41% vs 26%, p<0.001), hypertriglyceridemia (26% vs 9%, p<0.001) and low HDL cholesterol (34% vs 15%, p<0.001) was higher in MASLD patients with vs without HIV. No difference in cardiovascular events and diabetes prevalence was observed between the two groups. Regarding liver disease, PWH with MASLD had lower prevalence of severe MASLD (54% vs 74% p<0.001) but higher prevalence of significant liver fibrosis (15 vs 7%, p=0.03) compared to MASLD uninfected patients. After adjustment, HIV positivity was an independent factor associated with significant liver fibrosis (figure).
**Conclusions:** Despite having lower BMI, PWH with MASLD have a more severe hepatic presentation and atherogenic lipid profile than MASLD uninfected patients. HIV positivity seems to be independently associated with significant liver fibrosis. Screening and follow-up for MASLD and liver fibrosis is recommended in PWH, even if they are lean.

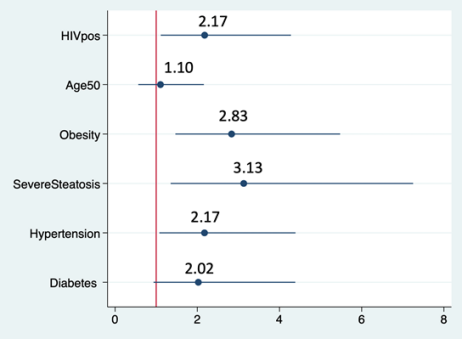


**Figure:** Multivariable regression analysis of factors associated with significant liver fibrosis (adjusted OR with 95% CI).

Abstract n SP4_06 - Presenting author**: Daniele Pilotto**

## Elderly people experience a less severe metabolic dysfunction associated steatotic liver disease: a survivorship bias?

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**Aim:** Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly non-alcoholic fatty liver disease (NAFLD), is a disease characterized by liver accumulation of lipids because of metabolic disorders. Little data exists on MASLD characteristics in elderly patients. Previous data showed that MASLD is less prevalent in elderly and that it associates with a less severe liver disease and metabolic burden. Aim of the study was to evaluate MASLD prevalence and its characteristics across age groups, in a large population of metabolic patients.
**Methods:** according to the recent consensus definition, MASLD prevalence across varying age was assessed in the Plinio Study cohort. To minimize possible confounders, after propensity score matching (PSM) for sex and specific therapeutic interventions (antidiabetic, antihypertensive, antiplatelet and statins), MASLD characteristics were evaluated in patients aged below and above 65 years. N-terminal propeptide of type III collagen (PRO-C3) was measured as marker of collagen III deposition during liver fibrogenesis.
**Results:** in the study were included 1080 patients and 78.6% of them had MASLD. MASLD prevalence progressively decrease from 81.1% in patients with <65 years to 58.8% in those ≥80 years. After PSM, a subset of 374 patients were selected. Patients aged ≥ 65 years had a more favorable lipid profile (HDL-C: 48.5 [42.0-61.0] vs. 46 [39.0-56.7], p=0.022; LDL-C: 108.0 [81.2-132.0] vs. 118.0 [96.4-141.7], p=0.005), lower HOMA-IR (2.9 [0.6-4.9] vs. 3.7 [2.5-5.6], p=0.001) and pro-C3 (6.1 [5.2-7.8] vs. 6.8 [5.7-8.3], p=0.022). No significant difference in albumin concentration was observed between the groups, excluding malnutrition as a confounding factor.
**Conclusions:** Our data, from a large population of dysmetabolic patients, confirm that MASLD prevalence decrease by age and that elderly patients experienced a less severe MASLD condition characterized by a reduced metabolic burden and lower liver collagen deposition. Further studies are needed to explore a potential survivorship bias for MASLD in elderly patients.

Abstract n SP4_07 - Presenting author**: Federica Cetti**

## PPAR-mediated reduction of lipid accumulation in hepatocytes relies on the autophagy-lysosome-mitochondrion axis

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**Aim:** Lysosomal acid lipase (LAL) catalyzes the hydrolysis of cholesteryl esters and triglycerides in the lysosomal compartment. Recently, it was shown that NAFLD patients can develop an acquired LAL deficiency which is rescued by PPAR-alpha activation. The aim of the study was to investigate the effect of other isoform-specific and dual PPAR agonists on lipid accumulation in an *in vitro* model of steatosis, and to characterize the underlying mechanisms, including the role of LAL.
**Methods:** To induce lipid accumulation, HepG2 cells were incubated oleate and palmitate (FA) in the presence or absence of selective agonists of PPAR alpha (fenofibric acid), gamma (pioglitazone) and delta (seladelpar) receptors, or of a dual alpha/gamma agonist (saroglitazar). Experiments were replicated in the presence of specific inhibitors of LAL (lalistat), cpt-1 (etomoxir) and autophagy (CA-5f).
Lipid accumulation was assessed by Oil Red O staining, LAL activity was measured by fluorescence, the activation of autophagy was monitored through the expression of p62 and LC3. Mitochondrial beta-oxidation was assessed by gene expression.
**Results:** All PPAR agonists significantly reduced lipid accumulation in FA-loaded HepG2 cells. PPAR agonists promoted TFEB expression, with the consequent activation of autophagy, lysosomal biogenesis and increased LAL activity. All agonists increased mitochondrial mass and stimulated beta-oxidation, as shown by the increased expression of genes involved in mitochondrial fission, fusion, fatty-acids uptake and catabolism. Moreover, PPAR agonists decreased ROS production and the expression of pro-inflammatory mediators. The reduction of lipid accumulation was completely lost when autophagy, LAL activity and mitochondrial lipid transport were blocked by specific inhibitors.
**Conclusions:** Our results demonstrate that PPAR agonists reduce lipid accumulation in hepatocytes by promoting autophagy, lipid hydrolysis in the lysosomes and FA oxidation in the mitochondria. These effects are independent from the PPAR isoform activated, and LAL activation plays a key role in PPAR-mediated hydrolysis of intracellular lipids. These data indicate that the pharmacological modulation of LAL should be explored in the management of steatosis.

Abstract n SP4_08 - Presenting author**: Francesca Fantini**

## Modulation of mitochondrial dynamism in Kupffer Cells impacts systemic metabolism

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**Background and Aim:** Kupffer Cells are hepatic resident macrophages that are essential for liver physiology and contribute to the development of Non-Alcoholic Fatty Liver Disease (NAFLD). OPA1 is a mitochondrial-shaping protein whose activity promotes mitochondrial fusion and positive modulation of oxidative phosphorylation. Since mitochondria are critical for the energy requirements of Kupffer Cells, this project aims to study how OPA1-driven alteration of mitochondrial dynamism might impact systemic lipid metabolism and immune-metabolic response.
**Methods:** Mice with selective OPA1 deficiency in Kupffer Cells were fed either a low-fat diet (chow diet) or a high-fat diet. The metabolic phenotype was assessed by in vivo indirect calorimetry, measurement of plasma and tissue lipid profile, glucose and insulin sensitivity assays, and immunophenotype characterization. Single cell RNA sequencing was also performed to profile with higher resolution the impact of OPA1 deficiency on Kupffer Cell function and cross talk with other liver cells.
**Results:** Under Standard diet conditions mice selectively lacking OPA1 in KC show a significant reduction in the KC1 pro-inflammatory subset, while the pro-resolutive KC2 increases. In addition, mice lacking OPA1 in KC show a metabolic preference towards carbohydrates, despite comparable energy expenditure and oxygen consumption. The systemic immune profile was comparable between the two groups, with an expected reduction in KC total number under High-fat diet conditions, where a reduction in liver fibrosis was observed.
**Conclusions:** These preliminary data suggest that OPA1-mediated mitochondrial function in Kupffer Cells affects the systemic metabolic response differently under low- or high-fat diet conditions, where systemic metabolism is comparable, but the loss of OPA1 appears to influence the progression of NAFLD through a reduction in liver fibrosis. Ongoing studies aim to understand the molecular mechanisms underlying these different immune-metabolic responses.

Abstract n SP4_09 - Presenting author**: Laura Gullà**

## Apolipoprotein E and immuno-metabolic response: characterization of the role of the protein produced by hepatocytes vs Kupffer cells

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**Aim:** Apolipoprotein E is one of the main proteins associated with lipoproteins, which are responsible for packaging cholesterol and triglycerides and carrying them through the bloodstream. The role of ApoE in cardio-vascular disease has been extensively studied but the cellular source responsible for these effects is still debated.
Therefore, we investigated whether the difference source of hepatic ApoE produced either by hepatocytes or Kupffer cells, would affect systemic lipid metabolism and immune response.
**Methods:** Hepatocytes and Kupffer cells selective ApoE-KO mice were generated by crossing ApoE fox/flox mice respectively with Albumin-Cre (ApoE Hep-KO) and Clec4f-Cre (ApoE KC-KO) mice. Mice were fed a high cholesterol diet (WTD) or a normal chow diet for 12 weeks. FPLC and Western blot were performed on total plasma, poloxamer test for VLDL production together with histological and immunophenotype by flow cytometry were performed.
**Results:** ApoE Hep-KO presented a complete absence of plasmatic ApoE regardless of diet, while ApoE KC-KO only presented a reduction on chowD (-59%). In both models, a reduction of ApoE in HDL was detected. Despite no differences in total cholesterol levels, only ApoE Hep-KO presented VLDL and LDL cholesterol peak by FPLC analysis. Interestingly, ApoE Hep-KO, but not ApoE KC-KO, showed a reduced VLDL synthesis similar to ApoE KO mice (-46%). No differences were detected in liver steatosis and in the immuno-phenotype for both models.
**Conclusion:** We confirmed the important role of ApoE produced by hepatocytes in lipid metabolism, especially in the production and clearance of VLDL. In contrast, no role for ApoE derived from hepatocytes and KC in the modulation of immune response was observed, but both contribute to apoE present on HDL. Therefore, both ApoE produced by hepatocytes and ApoE produced by Kupffer cells have a role in lipid and lipoprotein metabolism which, however, appears to be different.

Abstract n SP5_01 - Presenting author**: Antonio Concistrè**

## Primary Aldosteronism: A Rare yet Critical Contributor to Severe Gestational Hypertension – A Case Report

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Gestational hypertension and preeclampsia, affecting 6-8% of pregnancies, typically resolve postpartum. However, persistent hypertension after delivery poses a unique challenge. This case report focuses on a 37-year-old woman with a one-year history of hypertension, initially exhibiting normal aldosterone/renin ratio. During pregnancy, she received alpha-methyldopa with limited effectiveness. Emergency cesarean section at 36 weeks was necessitated by uncontrolled hypertension. Postpartum, the patient experienced headaches and muscle cramps, with a mean ABPM24h of 140/100 mmHg on nifedipine and alpha-methyldopa. Further evaluation revealed elevated plasma aldosterone (31.7 ng/dl), suppressed renin (0.9 IUI/ml), an elevated aldosterone-to-renin ratio (35.22), and low serum potassium (2.4 mEq/l). Adrenal imaging identified a 1 cm left adrenal nodule suggestive of adenoma. Effective blood pressure and potassium control were achieved with spironolactone, and the patient is slated for adrenal venous sampling to subtype primary aldosteronism (PA).
PA, a significant cause of secondary hypertension, affects less than 1% of pregnant women, often resulting from idiopathic bilateral adrenal hyperplasia or aldosterone-producing adenoma. This case underscores the rarity of PA in pregnancy, with fewer than 40 cases reported in the literature. Given the pivotal role of the renin–angiotensin–aldosterone system in maternal and fetal well-being during pregnancy, early PA diagnosis is imperative to mitigate severe complications associated with gestosis.

Abstract n SP5_02 - Presenting author**: Soraya Puglisi**

## Do patients with adrenal incidentaloma develop different cardiometabolic comorbidities according to sex? Results from a multicenter longitudinal study

Soraya Puglisi[1], Anja Barač Nekić[2], Valentina Morelli[3], Ylenia Alessi[4], Michele Fosci[5], Angelo Pani[5], Karin Zibar Tomsic[2], Serena Palmieri[6], Francesco Ferraù[4], Anna Pia[1], Giuseppe Reimondo[1], Iacopo Chiodini[7], Darko Kastelan[2], Massimo Terzolo[1].

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**Aim:** Recent evidence on sex-related differences in cardiometabolic comorbidities in patients with adrenal incidentaloma (AI) is available. However, longitudinal studies are scarce. This study aimed to analyze the association of sex with development of comorbidities during follow-up.
**Methods:** After excluding who underwent adrenalectomy during follow-up, we retrospectively evaluated 189 patients (120 females, 69 males) with AI, from four expert centers. Clinical characteristics and hormonal data were collected at baseline and at last follow-up visit (LFUV).
**Results:** Median follow-up was 52 (IQR 25-86) months. At LFUV, arterial hypertension was more frequently reported than at baseline in both sexes (females: 77.8% *versus* 65.8%, p=0.002; males: 69.1% *versus* 58.0%, p=0.035), as well as hyperglycemia (females: 39.6% *versus* 28.8%, p<0.001; males: 54.0% *versus* 36.2%, p<0.001).
By using the 1-mg dexamethasone suppression test, patients were stratified in two groups (non-functional adrenal incidentaloma [NFAI] and mild autonomous cortisol secretion [MACS]) with similar sex distribution: 99 (62.6% females) and 89 (64.0% females), respectively. In the NFAI group, frequency of hyperglycemia was higher in males than in females (57.6% *versus* 33.9%, *p*=0.03) at LFUV. In the MACS group, females were younger (66, IQR 61-73 *versus* 73.5, IQR 65-78, years; *p*=0.02) and presented more frequently bone impairment (88.9% *versus* 58.8%, *p*=0.01) than males, at LFUV.
**Conclusions:** Patients with AI frequently develop arterial hypertension and hyperglycemia and they should be periodically checked for these comorbidities, regardless of sex. Bone impairment was more frequently reported in females with MACS, suggesting a sex-specific effect of cortisol.

Abstract n SP5_03 - Presenting author**: Barbara Pala**

## Ponderal index and body fat percentage are increased in adult outpatients with masked hypertension

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**Aim.** Essential hypertension is frequently associated with obesity. The correlation between body mass index (BMI) and other indexes of obesity in different hypertension phenotypes has been partially assessed. We aimed to evaluate obesity indexes in adult outpatients with different hypertension phenotypes.
**Methods.** A single-centre, cross-sectional study was conducted in treated and untreated adult outpatients with essential hypertension, aged 20 years or more, who consecutively underwent full blood pressure (BP) assessment. All BP measurements were performed and BP thresholds were set according to European guidelines: white-coat hypertension (WCHT), clinic BP >=140/90 and 24-hour BP <130/80 mmHg; masked hypertension (MHT) clinic BP <140/90 and 24-hour BP >=130/80 mmHg; sustained hypertension (SHT), >140/90 and 24-hour BP >130/80 mmHg. The following parameters of obesity were evaluated: body mass index (BMI), ponderal index (PI), body fat percentage (BFP).
**Results.** We analysed an overall sample of 1,089 adult outpatients, among whom 26.1% ha NT, 11.4% WCHT, 20.9% MHT and 41.5% SHT. No significant difference was found among groups for the BMI. Patients with MHT showed significantly higher PI (16.2±3.0) compared to both WHT (16.0±3.0) and SHT (15.9±2.9; P=0.032); similarly, MHT patients had significantly higher BFP than that of other groups (33.4±8.3% vs. 32.2±8.4% vs. 31.6±8.2%; P<0.001). Significant positive correlations were observed between night-time systolic BP and BMI (r=0.101; P<0.001), PI (r=0.075; P<0.001), and BFP (r=0.046; P<0.001). Similar correlation was observed between night-time diastolic BP and BMI (r=0.036; P<0.001); however, both PI (r=-0.044; P<0.001) and BFP (r=-0.171; P<0.001) resulted significantly and inversely related with night-time diastolic BP. All these obesity indexes also resulted significantly and inversely related with night-time systolic and diastolic BP dipping.
**Conclusions.** MHT patients exhibited elevated obesity indices, placing them at an increased risk of cardiovascular events compared to individuals with other hypertension phenotypes.

Abstract n SP5_04 - Presenting author**: Fabrizio Buffolo**

## Long-term follow-up of patients with high aldosterone-to-renin ratio but negative confirmatory test for primary aldosteronism.

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**Aim:** A total of 10% of patients with hypertension has a positive screening test for primary aldosteronism (PA) and 50-70% of them have a negative confirmatory test for PA. However, the appropriate follow-up of these patients is unknown. We investigated the incidence of PA in patients with previous negative confirmatory testing for PA, with a follow-up comprised between 2 and 8 years.
**Methods:** A total of 184 patients with a previously positive screening test for PA followed by a negative confirmatory test were enrolled in two hypertension centres: Torino and Munich. We repeated the screening test for PA and, if positive, the confirmatory test (seated saline infusion test or captopril challenge test).
**Results:** After a mean follow-up of 5 years, 20% of patients had confirmed PA diagnosis: 16% in Torino and 24% in Munich. When subtype diagnosis was offered systematically, 31% of patients displayed a unilateral form of PA. Patients with new onset of PA had higher systolic blood pressure (142±17 versus 133±12 mmHg, P=0.005), diastolic blood pressure (89±8 versus 85±9 mmHg, P=0.007) and a higher prevalence of cardiac organ damage (60.9% versus 35.8%, P=0.031) than patients without PA, despite similar intensity of anti-hypertensive therapy. A mild progression of autonomous aldosterone secretion was evidents even in patients without confirmed PA, with increase of aldosterone post-saline infusion test (3.3 [2.3-4.3] versus 4.5 [3.5-5.4] ng/dL; P<0.001), but with relatively stable blood pressure levels. Among patients without PA, aldosterone post-saline infusion test at follow-up was positively associated with the follow-up time (β 0.262 [0.005; 0.520]; P=0.046).
**Conclusions:** About 20% of patients with a negative confirmatory test for PA develop overt PA over time. A clinical follow-up of patients with a negative confirmatory test is advisable, along with the repetition of PA investigation, especially in patients with worsening of blood pressure control.

Abstract n SP5_05 - Presenting author**: Carmine De Luca**

## Acute hypertensive disorders, University of Naples Hypertension Centre's experience

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**Aims:** The study proposed a follow-up system to understand short-, mid- and long-term prognosis and the progression of subclinical hypertension-mediated organ damage (HMOD) of these patients. The secondary aim was to identify patients affected by secondary hypertension.
**Materials and methods**: Patients admitted to the ED with symptomatic blood pressure (BP)≥180/110 mmHg were enrolled and managed according to their clinical presentations. After 3 days, they underwent clinical evaluation and subclinical HMOD assessment at a Hypertension Centre; second and third evaluations were scheduled after 3 and 12 months. HMOD was determined by blood tests and echocardiography.
**Results**: 35 patients were included in this report, 15 (42,9%) of them attended the whole follow-up.
19 (54,3%) out of 35 were women. Mean age was 60±16 years. 3 (8,6%) patients were diagnosed with HE, 32 with HU. After 72 h, blood pressure was well controlled in 11 (31,4%) patients, while hypertension grade 1, 2, and 3 was found, respectively in 10 (28,6%), 10 (28,6%) and 4 (11,4%) cases. Systolic BP mean was 138,9±23,8mmHg, while Diastolic BP was 77,4±12,7mmHg. After 3 months, BP was well controlled in 16 (45,7%) patients, while after 12 months BP was well controlled in 10 out 15 that underwent the three medical examinations. In 4 (11,4%) cases, the HU occurred in patients affected by secondary hypertension. The report includes University of Naples' results.
**Conclusion**: The study shows that after the discharge from the ED, the follow-up system proposed by our protocol (72h, 3 and 12 months) allows the correct management of hypertension in patients with acute hypertensive disorders, avoiding additional hospitalizations.

Abstract n SP5_06 - Presenting author**: Mirko Parasiliti-Caprino**

## Association of mineralocorticoid function with cardiometabolic abnormalities in patients with resistant hypertension

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**Aim.** To evaluate the association of mineralocorticoid function with the presence of cardiometabolic alterations in patients with resistant hypertension (RH).
**Methods.** Patients in primary prevention with RH underwent full biochemical assessment for primary aldosteronism (PA), with basal ARR and saline infusion test (SIT). In patients without a known history of diabetes mellitus (DM), plasma glucose and insulin levels were measured in the fasting state and after a 75 g oral glucose tolerance test (OGTT) to assess insulin resistance, β-cell function, and insulin sensitivity according to HOMA2-IR, HOMA2-β%, and ISI-Composite.
**Results.** PA was confirmed in 23 out of 88 patients (26.1%). In the multivariate analysis PA was an independent predictor of left ventricular hypertrophy (OR 7.82, p=0.016), microalbuminuria (OR 4.14, p=0.039), and presence of at least two types of OD (OR 3.58, p=0.036). PAC after SIT remained an independent predictors of left ventricular hypertrophy (OR 1.21 per 10 pg/mL increase in PAC after SIT, p=0.004), microalbuminuria (OR 1.12 per 10 pg/mL increase in PAC after SIT, p=0.025), and the presence of at least two types of OD (OR 1.13 per 10 pg/mL increase in PAC, p=0.019) in multivariate analysis. Overall, no significant difference was observed between patients with PA and essential RH (eRH) in the prevalence of glycemic alterations and metabolic syndrome. In patients without a known history of DM (n=74), no difference was found between PA and eRH in insulin resistance, insulin sensitivity, and β-cell function indices.
**Conclusions.** We confirmed that patients with PA exhibit a higher prevalence of OD, compared to patients with eRH. PAC after SIT emerged as an independent predictor of OD in patients with RH, suggesting that an impaired modulability of aldosterone secretion in response to alterations of sodium and water homeostasis may be involved in the pathogenesis of OD in this population.

Abstract n SP5_07 - Presenting author**: Rosa Curcio**

## Relationship between heart rate and central-to-peripheral pulse pressure amplification measured invasively

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**Introduction:** Central-to-peripheral pulse pressure amplification (PPA) is a measure of vascular aging, reflects the extent of the arterial stiffness gradient between the center and the periphery, and it is inversely related to cardiovascular prognosis. Some authors described heart rate (HR) as a direct determinant of PPA.
**Aim:** The objective of the study is to evaluate whether such relationship exists for measures of arterial pressure (BP) and HR determined invasively during cardiac catheterization.
**Methods:** 111 subjects undergoing diagnostic coronary angiography and enrolled in a pilot study were evaluated at the end of the invasive examination. Invasive aortic BP (aSBP/aDBP) was determined at the level of the aortic bulb. The brachial invasive BP (bSBP/bDBP) was determined at the medial point of the brachial artery with a sequential pull-back technique. Patients in whom the time interval between the 2 measurements exceeded 30 seconds (n=13) and patients in whom the HR difference between the two sites was greater than 5 bpm (n=20) were excluded.
**Results:** 78 patients, 87% gender M, age 73±9 years. aSBP/aDBP 137±27/64±12 mmHg, bSBP/bDBP 148±25/63±11 mmHg. Average heart rate 71±12 bpm. aSBP and bSBP showed no significant relationship with HR, while aDBP and bDBP showed positive correlation with HR (R=0.35 and R=0.36 respectively, both $p<0.001$). Slope=3.6 mmHg/10 bpm for aDBP and 3.4 mmHg/10 bpm for bDBP (difference between slope=ns). In a multivariate model including age, gender, and HR as predictors of PPA (expressed as the bPP/aPP ratio), adding the difference between bSBP and aSBP eliminated the dependence of HR on PPA.
**Conclusions:** the dependency of PPA from HR is observable only if PPA is expressed as a bPP/aPP ratio. It is determined both by the dependency of DBP from heart rate and by the extent of central-peripheral pressure amplification. It is therefore not necessary to normalize the degree of PPA for FC but simply to represent this latter measure in absolute terms, as the difference between bPP and aPP, rather than as the ratio.

Abstract n SP5_08 - Presenting author**: Maddalena Tesone**

## Sex differences in the usefulness of unattended blood pressure measurement in patients with hypertension

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**Introduction**: Unattended blood pressure measurement was recently introduced following the results of the Spring study. Conflicting results are present in literature in relation to the concordance between values in unattended mode (AOBP), conventional outpatient monitoring (OBP) and 24-hour ambulatory monitoring (ABPM).
**Aim**: To evaluate the concordance between the measurement of blood pressure values in unattended, OBP and ABPM modes.
**Methods**: 232 patients were recruited in 6 hypertension centers belonging to the Italian society of hypertension, as part of a research coordinated by the SIIA youth group. Patients underwent blood pressure measurement in AOBP and OBP modes before and after ABPM. AOBP and OBP measurements were performed in alternating mode before and after ABPM and the mean values were calculated. Blood pressure was defined controlled if the 24-hour average blood pressure was <130/80 mmHg on the ABPM.
**Results**: The average age of the patients was 59±13.6 years, with a female prevalence of 49% and a duration of hypertensive disease of 11.6±8.4 years. The AOBP and OBP blood pressure values were 137.1±17.3/ 78.5±12.4 mmHg and 139.8±19.5/ 83.1±12.8 mmHg, respectively ($p<0.01$) . In ROC curve analysis, the AOBP measurement mode showed an accuracy in correctly identifying patients with controlled hypertension equal to 0.77, higher than that shown by the OBP measurement equal to 0.73 ($p<0.05$). This difference in a sex-specific analysis was larger for females where the AOBP measurement showed an AUC of 0.78 versus an AUC of 0.72 for the OBP mode.
**Conclusions**: Our data suggest that AOBP may be particularly useful in identifying patients with controlled blood pressure, more accurately than OBP. This advantage, due to a virtual elimination of the white coat effect, is more marked in females.

Abstract n SP5_09 - Presenting author**: Giulia Nardoianni**

## Correlation between arterial stiffness and hyperglycemia in adult outpatients with essential hypertension

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**Aim.** Increased pulse wave velocity (PWV) is now recognized as marker of vascular hypertension-mediated organ damage (HMOD). Glucose abnormalities are frequently associated with hypertension, though their correlation with PWV has not been fully clarified. We aimed to investigate clinic and 24-hour ambulatory PWV in a large cohort of adult outpatients with essential hypertension, according to glucose profile.
**Methods.** A single-centre, cross-sectional study was conducted in treated and untreated adult hypertensive outpatients of both sexes, aged more than 20 years, who consecutively underwent full BP assessment and evaluation of vascular HMOD. Clinic and 24-hour PWV were measured by using an automated, oscillometric device (Mobil-O-Graph PWA Monitor, I.E.M. GmbH, Stolberg, Germany). Patients were stratified into 3 groups: 1) normal glucose profile (NGP); 2) Hyperglycaemia (HYG), defined as fasting glucose levels between 100-126 mg/dl without glucose lowering therapies; 3) Diabetes mellitus (DM), defined as fasting glucose levels above 126 mg/dl and/or glucose lowering therapies.
**Results**. We analyzed an overall sample of 2,686 adult outpatients (42.6% female, mean age 61.1±14.3 years, BMI 27.4±4.7 kg/m2), among whom 1385 (51.6%) had NGP, 608 (22.6%) had HYG and 693 (25.8%) DM. Clinic PWV showed a positive and progressive increase from NGP to HYP and DM (9.0±2.3 vs. 9.4±2.1 vs. 10.1±1.9 m/sec; P<0.001); the same findings were observed when considering PWV measured during the 24-hour (6.9±1.6 vs. 7.6±1.6 vs. 8.4±1.2 m/sec; P<0.001), day-time (7.0±1.6 vs. 7.7±1.6 vs. 8.5±1.4 m/sec; P<0.001) and night-time (6.6±1.7 vs. 7.3±1.6 vs. 8.2±1.4 m/sec; P<0.001) periods. Fasting glucose levels were positively associated with clinic (r: 0.154; P<0.001), 24-hour (r: 0.224; P<0.001), day-time (r: 0.224; P=0.005), and night-time (r: 0.228; P=0.005) PWV.
**Conclusions.** Our findings showed a trend toward significant increase and strong correlation between clinic and 24-hour ambulatory PWV and glucose profile in adult outpatients with essential hypertension.

Abstract n SP5_10 - Presenting author**: Pugnaloni Simone**

## Non-HDL cholesterol and apolipoprotein B in a hypertensive population: role of adiposity and insulin resistance

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**Aim**: evaluate how adiposity and IR affect non-HDLc and ApoB levels in essential hypertensive patients.
**Methods**: We performed a cross-sectional study on 272 consecutive patients referred to our Hypertension Centre and not taking lipid-lowering drugs. Body mass index (BMI) and waist circumference (WC), measured to the nearest 0.1 cm at the midpoint between the lowest rib and the iliac crest, were used to assess adiposity. IR was evaluated with HOMA-IR index, calculated according to the formula: HOMA-IR = [glucose] (mmol/l) × [insulin] (µU/ml)/22.5.
**Results**: Mean age: 50.2±14.5 years; male prevalence: 65.1%; mean BMI: 27.9±4.8 Kg/m$^2$; mean WC: 99.1±13.1 cm; mean Non-HDLc: 156.2±48.6 mg/dl; mean ApoB100: 113.8±36.4 mg/dl; median HOMA-IR index: 2.4 (1.7-4.0). The prevalence of overweight/obesity and IR was 76.0% and 48.6%, respectively. We found a fair correlation between non-HDLc and ApoB ($r=0.588$; $p<0.001$). Overweight/obese patients showed higher prevalence of IR (57.4% of overweight/obese). We found no linear association of both BMI and WC neither with ApoB nor with non-HDLc (all $p>0.05$), while a negative correlation was found with HDLc ($r=-0.295$; $p<0.001$ for BMI and $r=-0.224$; $p=0.009$ for WC) and a positive correlation with triglycerides ($r=0.222$; $p=0.004$ for BMI). A significant correlation emerged between HOMA-IR index and ApoB100 ($r=0.280$; $p=0.016$), independently of BMI.
**Conclusions**: In our study, the excess adiposity is directly linked to HDLc and triglycerides, while IR is directly linked to ApoB levels. Although there is a close association between IR and obesity, not all overweight/obese patients had IR, IR that probably plays a major role in atherogenic lipoprotein levels than just obesity.

Abstract n SP5_11 - Presenting author**: Lorenzo Airale**

## Unsupervised clustering for the phenotyping of left-ventricular function in non-ischemic left ventricular cardiomyopathy

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**Aim:** Non-invasive hemodynamic forces(HDF) analysis as a tissue-tracking-based myocardial wall analysis is a novel approach to estimate the time-resolved energy exchange in the blood-chamber interaction. Extending beyond previous studies that focused solely on the longitudinal component and peak/mean values, this study incorporates both longitudinal and transverse HDF and their comprehensive waveforms to stratify cardiovascular risk in non-ischemic left ventricular cardiomyopathy through unsupervised clustering.
**Methods:** A retrospective cohort of 304 patients with non-ischemic left ventricular cardiomyopathy, who underwent cardiac MRI at Vall d'Hebron Hospital, Barcelona, was examined. Patients were grouped solely based on time-resolved HDF curves using Dynamic Time Warping distances as similarity measures and the Partitioning Around Medoids algorithm for unsupervised clustering. Follow-up data were sourced from integrated digital medical records in Catalonia.
**Results:** Median age was 64±13years, with females comprising 26% of the cohort. A subset of 59.3% had left ventricular dilation, with an indexed end-diastolic volume of 115±35.8 ml/m², and 38.8% demonstrated late gadolinium enhancement(LGE). We identified 3 different HDF-based clusters. No significant differences in age and sex distribution were found between clusters, but they delineated risk groups with worsening left atrial (LA) and ventricular(LV) strains, indicating a stepwise increase in cardiovascular risk(LV-GLS, LVGCS, LA-Reservoir, and LA-Booster, all $p<0.001$). No differences were found in left ventricular ejection fraction(LVEF). Over a 38-month median follow-up, a trend towards an increased risk of major adverse cardiac events(MACEs) was observed across clusters. In the multivariate Cox regression, cluster classification was a significant predictor of MACEs, after adjusting for age, LVEF, LV-GLS, and LGE.
**Conclusion:** Integrating the assessment of HDF's multidimensional components offers a refined approach to cardiovascular risk stratification and MACE prediction in non-ischemic left ventricular cardiomyopathy. This study advances the understanding of HDF analysis, moving beyond traditional singular value assessments and highlighting the importance of a comprehensive examination of HDF patterns.

Abstract n SP6_01 - Presenting author**: Daniele Tramontano**

## A Noninvasive Evaluation of Liver Fibrosis Risk in subject with severe Hypertriglyceridemia: a single center comparison between MCS and FCS

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**Background and aim**: Lipoprotein lipase (LPL) is the crucial enzyme responsible for (TG) hydrolysis in chylomicrons and very-low density lipoproteins (VLDL). In patients with metabolic features, the dysfunction of this pathway can lead to the development of chylomicronemia (TGs>1000 mg/dl , known as multifactorial chylomicronemia or MCS). Non-alcoholic fatty liver disease (NAFLD) is frequent in patients with features of the metabolic syndrome (MetS), obesity, or type 2 diabetes and associates with an increased risk of liver fibrosis. Rarely, chylomicronemia is characterized by LPL deficiency (LPLD), an autosomal recessive disease called familial chylomicronemia syndrome (FCS), which is associated with an increased risk of recurrent pancreatitis and hepatosplenomegaly. The hepatic consequences of FCS and MCS has been only partially investigated. This study aims to compare liver stiffness and the risk of liver fibrosis between FCS and MCS.
**Methods**: To this aim, 83 patients with chylomicronemia were consecutively enrolled in the LIPIGEN study from the lipid clinic of the Policlinic Umberto I, Sapienza University of Rome. All patients underwent molecular diagnosis of FCS or MCS. Demographic, clinical and biochemical data were retrospectively revised by revising medical charts from enrollment (last visit) backward to baseline (first visit in the lipid clinic). Biochemical parameters collected were used to non-invasively estimate liver fibrosis by using FIB-4 index. At last visit all participants underwent routine liver ultrasonography and stiffness measurement after at least 4-h fast using transient elastography (Fibroscan and/or acoustic radiation force impulse (ARFI)).
**Results**: In this cohort 22 patients were classified as FCS and 61 as MCS. The median age at enrolment was 50.5 years (IQR 40.5-66.5) in FCS and 47.2 years (IQR 37.0– 57.0) in MCS (P=0,33). The two cohort were equally distributed between sexes and no differences were found in the baseline triglycerides levels. The median follow-up during in FCS was significantly longer than in MCS respectively 7.7 (IQR 3,37 – 11,33). years vs 4.0 (IQR 0,91- 6,91). As expected, MCS were showing a greater prevalence of metabolic features and a better response to triglycerides lowering therapies; in fact, the median on treatment TG levels was significantly higher in FCS than in MCS (1293 mg/dl vs 818 mg/dl; p=0.002). At last visit no difference were found in the prevalence of NAFLD between the two cohorts (84.8% of MCS and 90.5% of FCS patients, P=NS). Despite being within the normal range, results showed that FCS patients were showing a greater hepatic stiffness when compared to MCS group (5.73 kPa vs 3.89 kPa, respectively, P=0.03). The estimation of Fib-4 at last visit showed similar results with FCS showing an higher values as compared to MCS (1.84 vs 1.0, respectively, P=0.004).
**Conclusion**: In this study, NAFLD was commonly observed in both FCS and MCS subject. Nevertheless, our results showed that liver fibrosis might be more severe in FCS than MCS; this observation may be the results of the liver exposure to very high triglyceride levels since birth in the monogenic chylomicronemia and potentially suggest the need of a more careful assessment of liver disease in these patients independently from BMI and other metabolic parameters. Further study in larger cohort are needed to definite clarify if liver fibrosis might be considered another hallmark of FCS.

Abstract n SP6_02 - Presenting author**: Simone Mattivi**

## Familiar chylomicronemia syndrome (FCS) and multifactorial chylomicronemia syndrome (MCS): two different diseases or an overlapping syndrome?

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**Aim:** Familial chylomicronemia syndrome (FCS) and multifactorial chylomicronemia syndrome (MCS) are metabolic conditions underlying genetically based severe hypertriglyceridemia. These conditions have been only partially investigated, expecially comparing the genetic profiles and clinical outcomes in FCS and MCS.
Aim of our study was to investigate the genetic profile of three different patients with severe hypertygliceridemia (TG) and recurrent pancreatitis.
**Methods:** We performed an NGS test in three different patients all with TG above 1000 mg/dL, severe pancreatitis and abdominal recurrent pain.
**Results:** A 51-year-old man with triglycerides levels above 1000 mg/dL (with or without therapy). Lipigen's score was 17 pt and Moulin's score was 11 pt (high suspicion for FCS)
The genetic analysis allowed us to find:

- c.166G>C (p.Gly56Arg) in homozygosity in the GPIHBP1 gene and
- c.42C>A (p.Cys14Ter) in homozygosity in the GPIHBP1 gene

A 21-year-old woman, current smoker (5/6 cigarettes/die) with hepatic steatosis and high triglycerides levels with multiple episodes of pancreatitis requiring hospitalization.; Lipigen's score (13 pt) and Moulin's score (10 pt).
The genetic analysis allowed us to find:
- c.835C>G with consequent replacement of the leucine with valine in position 279, present in heterozygosity in the LPL gene and c.998G>A with consequent replacement of the arginine with isoleucine in position 333, present in heterozygosity in the LPL gene
A 53 years man with recurrent pancreatitis and tryglicerydes above 1500 mg/dL.
The genetic analysis allowed us to find:

- c.427>of (p.Arg143fs) in heterozygosity in the APOA5 gene and
- c.886G>A (p.Ala296Thr) in heterozygosity in the LPL gene

The double heterozygosity allowed us to diagnose a MCS syndrome, but eligible for therapy with volasorsen in accordance with AIFA
**Conclusion:** Our data confirm that FCS is more related to a biallelic mutations in genes involved in triglycerides metabolism. Heterozygosity for APOA5 variants is confirmed as the most frequent genotype of MCS. But the clinical overlap between the two syndromes remains a clinical challenge, due to the need of an aggressive lipid lowering therapy.

Abstract n SP6_03 - Presenting author**: Sining Xie**

## Network meta-analysis of randomized controlled trials comparing the effect of lipid-lowering therapies and colchicine on C-reactive protein concentration

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**Aim:** Recently low-dose colchicine had been approved for adult patients with established cardiovascular diseases. Additionally, our earlier meta-analysis demonstrated that several lipid-lowering therapies (LLTs) had anti-inflammatory effects. This study aimed to compare the effect of some LLTs and colchicine on C-reactive protein (CRP) levels.
**Methods:** We conducted a network meta-analysis according to the PRISMA guidelines; databases were searched from inception to November 2023. Inclusion criteria were: (1) randomized controlled trials (RCTs) in human, parallel design, phase II, III or IV; (2) English language; (3) using statins, statins plus ezetimibe, bempedoic acid, or colchicine as intervention; (4) reporting the effect on CRP levels; (5) an intervention duration of more than 3 weeks. Pooled estimates were assessed by a random-effects model within a Bayesian hierarchical setting and presented in mean (95%CI).
**Results:** A total of 77,292 subjects from 55 RCTs were included. The CRP-lowering effect was ranked highest for patients treated with statins plus ezetimibe compared to placebo (-1.10 mg/L [-1.40 to -0.82]). Similarly, CRP concentration decreased by -0.66 mg/L (-0.86 to -0.47) with statins and -0.69 mg/L (-1.10 to -0.32) with colchicine, showing no significant differences in their direct comparison (0.03 mg/L [-0.38 to 0.44]). On CRP levels, bempedoic acid showed the least effect in absolute values, even if the percentage reduction was higher, due to the low baseline CRP levels (-22.20% vs -15.64% for statins plus ezetimibe, -17.73% for statins, and -15.78% for colchicine). There was a slight but non-significant difference (0.24 mg/L [-0.22 to 0.70]) comparing to colchicine.
**Conclusions:** In conclusion, the anti-inflammatory effects of statins and colchicine seem to be comparable in short-term use. It becomes crucial to explore the comparative medium- to long-term effects of colchicine, statins, as well as of statins plus ezetimibe, to determine whether and in which patients the combination of colchicine with hypolipidemic drugs is appropriate.

Abstract n SP6_04 - Presenting author**: Marina Lanza**

## Molecular characterization of patients with and without coronary artery disease with "extreme'' levels of HDL-C

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**Aim:** Observational studies have highlighted the opposite association between LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) and the risk of developing coronary artery disease (CAD). Results of all large scale-randomized trials have demonstrated the causal relationship of LDL-C, while mendelian randomization studies on HDL-C are inconsistent and ambiguous. Targeted Next Generation Sequencing (NGS) analysis in recent years have been developed to study the coding regions and intron/exon boundaries of genes affecting the main pathways of HDL-C synthesis and metabolism in patients with hypo and hyper-alphalipoproteinemia.
**Methods:** The study sample includes patients enrolled in the Verona Heart Study (VHS) with angiographically documented CAD (positive CAD) and subjects without CAD who underwent coronary angiography for other clinical indication (negative CAD). We selected patients with extreme HDL-C phenotype (<2° percentile - 29 mg/dl and >98° percentile - 99 mg/dl). For genetic analysis, a large-scale targeted sequencing analysis was performed on Ion Torrent technology. We selected, for each patient, variants in candidate genes known to be associated to regulate HDL levels.
**Results:** Among subjects with high HDL-C phenotype (>98° percentile - 99 mg/dl) were available samples for 5 patients (5 negative CAD). No pathogenic variants in candidate genes were identified. Among subjects with low HDL-C (<2° percentile - 29 mg/dl) were available samples of 38 patients (31 positive CAD and 7 negative CAD). In this patients we identified an ABCA1 gene mutation c.5398A>C (p.Asn1800His) in heterozygosity in one positive CAD patient. Two variants in ABCA1 (c.103A>G, p.Ile35Val) and CUBN (c.10759G>A, p.Gly3587Arg) of uncertain clinical significance were identified in heterozygosity in one positive CAD patient. Another one (positive CAD) was found to be carrier of the ABCA1 variant c. 2328G>C, p.Lys776Asn in heterozygosity.
**Conclusions:** In most cases the phenotype cannot be correlated to the presence of variants in the candidate genes.

Abstract n SP6_05 - Presenting author**: Stefano Scotti**

## Factors influencing statin treatment in hospitalized patients after a cardiovascular event: a retrospective cohort study

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Guidelines recommend lipid-lowering therapy following atherosclerotic cardiovascular or cerebrovascular events (CVE). We aimed to evaluate potential factors influencing statin initiation among discharged patients following a CVE.
Using administrative data from Bergamo Local Health Unit in Lombardy, we identified individuals aged ≥40 years who experienced a CVE in 2016 and were not previously treated with statins. We assessed whether these individuals received a statin (ATC 4th level: C10AA) within 90 days post-discharge or received no statin. The 1-year Proportion of Days Covered (PDC) was calculated for all patients who received a statin prescription post-discharge, with optimal adherence defined for PDC≥0.80. A multivariate logistic regression model was applied to estimate odds ratios (OR) and 95% confidence intervals [95%CI] to assess the impact of several factors on the likelihood of initiating statin treatment following a CVE. A more recent analysis of data pertaining to the period 2017-2022 is currently underway.
Within our cohort of 3041 patients (39.2% female), 49.8% did not receive a statin after discharge (48.1% female, mean age±SD: 75.45±11.87; vs patients who received a statin: 30.3% female, mean age±SD: 66.94±11.72; p<0.001). Among patients with a statin therapy, 81.90% exhibited optimal adherence and 68.80% were also treated with aspirin. The likelihood of receiving statin treatment after a CVE was higher for patients aged 50-60 years (OR 1.44, 95%CI 1.86-1.12 vs 60-70 years), for females (OR 1.42, 95%CI 1.20–1.68), and for patients taking anticoagulants (OR 1.60, 95%CI 1.31-1.95). Conversely, age 70-80 years (OR 0.78, 95%CI 0.96-0-63), age 80-90 years (OR 0.35, 95%CI 0.44-0.27), and exposure to antidiabetics (OR 0.74, 95%CI 0.57-0.95) were associated with a lower likelihood of statin initiation.
This study highlights the sub-optimal rate of statin initiation in patients discharged after a CVE. Understanding influencing factors could inform tailored interventions for improving adherence in secondary prevention patients.

Abstract n SP6_06 - Presenting author**: Vincenzina Palermo**

## Use of bempedoic acid to treat hypercholesterolemia in patients affected by neuromuscular diseases

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**Background:** Statin treatment is often associated to development of muscular side effects with different spectrum of severity (e.g. myalgia, myositis or rhabdomyolysis). Lipid lowering treatment could be challenging in patients affected by neuromuscolar diseases. Bempedoic acid (BA) is an ATP-citrate-lyase inhibitor that targets cholesterol synthesis upstream of HMGcoAR, but it is activated in the liver and not in most peripheral tissues, including skeletal muscle.
**Methods:** We evaluated efficacy and safety of BA in patients with rare neuromuscular disease clinical to assess efficacy and safety of BA. We evaluated lipid profile, liver, muscular enzyme and biochemical parameters at baseline and after 4 weeks of BA treatment.
**Results:** We enrolled 4 patients (3 carriers of Charcot–Marie-Tooth disease and 1 affected by mitochondrial myopathy with cox deficiency), the mean age was 47± 18,69 years,3/4 patients had NAFLD, 2/4 were hypertensive, 1/4 was diabetic, no patient reported cardiovascular event or carotid atherosclerosis. Although patients were on maximally tolerated hypolipidemic therapy with Ezetimibe, they have not achieved the desired LDL-C target. After 4 weeks treatment with BA, we observed a significant reduction in LDL-C levels (from 120,75± 29,02 mg/dl to 80±19,97 mg/dl p<0,001), with an average reduction of 49,21%. We observed also significant changes in lipid profile (TC from 185,75± 29,63 mg/dl to 147±27,21 mg/dl, TG from 155,75±58,87 mg/dl to 165,5±50,73, HDL from 36,5±6,75 mg/dl to 34±6.93None reported any adverse event such us elevation of liver and muscular enzymes (creatinine from 0.78±0.58 to 0,74±0.48, uric acid from 7±2,21 to 7,27±1,44, AST from 28,25±6,02 to 33,25± 9,07 U/l, ALT from 37,5±20,47 to 35,75±15,08 U/l).
**Conclusion:** Although we reported data in a small population, BA has been shown to be promising for patients affected by neuromuscular disease in which statin treatment could be difficult to manage.

Abstract n SP6_07 - Presenting author**: Michela Algeri**

## Multidrug resistant dyslipidemia: A case report

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**Introduction:** Recently introduced lipid-lowering agents (PCSK9-i, bempedoic acid) can efficiently treat statin-intolerant patients, who couldn't reach LDL target before. Nonetheless, there are still cases where the pharmacological management may have strong limitations.
**Case report:** A 71 year-old woman, with multiple cardiovascular risk factors (diabetes, hypertension and familial dylipidemia, LDL-C 276) underwent heart transplantation for a hypertrophic cardiomyopathy with an evolution towards a dilated phenotype in 2005. Before the transplant, she was on low-dose statin treatment (pravastatin 10 mg/die) that was suspended years later owing to hyper-CKemia (600 U/L), despite her being totally asymptomatic.
A second attempt with simvastatin/ezetimibe 40/10 mg resulted again in elevation of CK levels, associated with significant muscular pain. Thus, just ezetimibe was continued.
In 2020, 15 years after the transplant, the patient underwent a coronary angiography showing a moderate coronary allograft vasculopathy (ISHLT CAV2). Specifically, a sub occlusive ostial left main coronary artery lesion was treated by percutaneous angioplasty and stent implantation.
Since a lower LDL target was needed (LDL-C 55 mg/dL), Alirocumab was introduced.
However, 6 months later, no significant LDL levels reduction had been observed. The shift to evolocumab led to the same result, although the patient reported full therapeutic compliance.
In the suspicion of anti-drug antibodies development, we opted for Inclisiran without achieving a significant decrease in LDL-C levels.
In parallel with the search for genetic mutations in the PCSK9 gene and other genes involved in cholesterol metabolism (including LDLR, APOB, and LDLRAP1 and resulting positive only for common variants in LDLR receptor), therapy with bempedoic acid was initiated, again without substantial benefit (LDL-C 118 mg/dL).
**Conclusion:** Despite cholesterol management has been simplified by the introduction of new drugs, it may still be complex in patients requiring very low LDL-C levels in some specific cases. Drugs with a LDL receptor-independent mechanism of action (e.g., evinacumab) may allow the achievement of therapeutic goals suggested by clinical guidelines.

Abstract n SP6_08 - Presenting author**: Federica Fogacci**

## Effect of Coenzyme Q10 on physical performance in elderly patients with statin-associated asthenia: a double-blind, randomized, placebo-controlled clinical trial

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**Aim:** The effect of coenzyme Q10 (CoQ10) supplementation on physical performance and statin-associated asthenia has never been investigated before. This double-blind, randomized, placebo-controlled clinical study aimed to investigate the effect of chronic dietary supplementation with CoQ10 phytosome on physical performance in older adults with statin-associated asthenia.
**Methods:** Eligible patients were 65-80 years old individuals free from atherosclerotic cardiovascular diseases, who had been for at least 6 months on statin monotherapy (i.e. on the same statin at the same dosage) and who have claimed statin-associated asthenia for at least 3 months at the study entry. Participants were randomized to receive daily either 2 indistinguishable pills of placebo or 150 mg CoQ10 phytosome (i.e. 300 mg CoQ10 phytosome per day, equivalent to 60 mg CoQ10; Ubiqsome®). Asthenia and handgrip strength (HGs), 1-minute sit-to-stand (STS) repetitions and 2-minute steps (2MST) were performed at baseline and at 8-week follow-up.
**Results:** At baseline, the study groups were well matched for all relevant clinical and demographic data. After the first 4 weeks of dietary supplementation, CoQ10 phytosome supplementation correlates with more significant improvement in asthenia compared placebo ($p< 0.05$). At 8-week follow-up, patients undergoing CoQ10 dietary supplementation experienced significant improvements in asthenia (-30.0±20.0%), HGs (+29.8±3.6%), 1-min STS repetitions (+36.4±3.9%), and 2MST (11.1±1.8%) ($p <0.05$ versus baseline and versus placebo).
**Conclusions:** Chronic dietary supplementation with CoQ10 phytosome is able to effectively improve physical performance in older adults with statin-associated asthenia. Of course, this could have a relevant implication to improve the compliance of older adults to statin-treatment.

Abstract n SP6_09 - Presenting author**: Fabrizia Bonacina**

## Impact of immune system humanization on atherosclerosis in dyslipidemic immunocompromised mice

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**Background and aim:** Given the key role of immune response during atherosclerosis and the therapeutic interest on biologics targeting human immune cells, the need of experimental models to translate molecular mechanisms and test therapeutic approaches for atherosclerosis is continuously increasing.
Here we provide an immune and metabolic characterization of an innovative immunodeficient mouse humanized with human hematopoietic cells on an atheroprone background.
**Methods:** LDLR-KO mice were crossed with the immunodeficient C57BL/6J strain Rag2-KO/IL2rg-KO/CD47-KO (TKO, IMSR_JAX:025730) to generate an immunocompromised dyslipidemic mouse (TKO-LDLR KO mice) recipient of human hematopoietic stem cells (hCD34+).
**Results:** TKO-LDLR KO were first characterized for their immune and metabolic profile. TKO mice are deficient in mature lymphocytes and NK cells and this profile was conserved in TKO-LDLR KO mice. Under high cholesterol diet, TKO-LDLR KO develop marked dyslipidemia, steatosis and atherosclerosis. This profile confirms the suitability of TKO-LDLR KO mice for atherosclerosis studies. Next we tested the impact of immune system humanization on atherosclerosis. TKO-LDLR KO pups received a low-dose irradiation (200 cGy) and thereafter 2 x 10^5 hCD34+ were injected in the liver. Engraftment of human leukocytes (hCD45+) was evaluated after two months by flow cytometry analysis from tail blood. This approach allows to reconstitute between 10-30% of hCD45+, mainly B and T cells. hCD45 were detected also in the thymus (95%), spleen (20%) and liver (25%). The humanization with hCD34+ cells did not affect cholesterol levels (939,8±94,41 vs 987,4±48,82 mg/dL), but worsen atherosclerosis development by en face analysis and lesion area at the aortic valve, compared to non-humanized TKO-LDLR KO mice.
**Conclusion:** We have generated and characterized the humanized dyslipidemic TKO-LDLR KO mouse. This mouse model presents human B and T cells and represents an important toll to investigate the impact of human adaptive immune cell pharmacological modulation in the context of atherosclerosis.

Abstract n SP6_10 - Presenting author**: Rosario Mare**

## Effects of plant sterols, β-glucans and chitosan, combined in nano-sized liposomal formulation, on lipid metabolism and hepatic fat accumulation

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**Aim:** Numerous natural bioactive molecules can help reduce circulating LDL cholesterol, notoriously linked to cardiovascular diseases, but their dietary intake at therapeutic dosages can be difficult.
Previously, research demonstrated that daily phytosterols intake reduces LDL levels and hepatic steatosis. Chitosan and β-glucans also lower circulating LDL, but their effects on the liver lack thorough investigation. Additionally, no studies have assessed the impact of all these elements combined.
Liposomes are vesicular nano-sized formulations able to host and deliver different biomolecules, beyond protecting them from degradative phenomena.
The aim of this project was to realize an innovate nano-carrier containing phytosterols, chitosan, β-glucans as one, finally testing and comparing its effect on lipid metabolism in comparison with single-molecule formulations.
**Methods:** Liposomes were obtained by the thin-layer evaporation technique followed by the extrusion process. All formulations were characterized by dynamic light scattering. The obtained samples were tested on Hep-G2 cell line. Cell viability and intracellular lipids content were respectively assessed by MTT-test and Oil Red-O staining technique. In addition, pathways and genes implied in lipid metabolism were evaluated by the Western blotting and rt-PCR.
**Results:** The multi-drug liposomes (MDL) had mean size almost double compared to the empty formulation (303.3±3.8 vs 159.3±1.2 nm) and opposite surface charge (3.77±0.52 vs -13.2±1.1 mV), while preserving homogeneity of formulation (PDI 0.222±0.015 vs 0.170±0.009). Phytosterols, for the first time in a liposomal carrier, demonstrated to reduce intracellular lipid content on Hep-G2 hepatic cell line, while chitosan and β-glucans didn't exert any effect.
Compared to empty liposomes, MDL reduced intracellular lipid content at both doses ($p<0.0001$ and $p=0.04$ respectively) and decreased the expression of SREBP-2 and SREBP-1c, that are genes involved in lipogenesis ($p<0.0001$ and $p=0.014$ respectively). Remarkably, the MDL formulation had greater efficacy in reducing intracellular lipid content (-47.9%) compared to liposomes loaded with only phytosterols (-16.34%).
**Conclusions:** Vesicular carriers are effective in delivery multiple biomolecules in a single formulation. Our results, for first time, suggest that the combined delivery of phytosterols, chitosan and β-glucans in liposomal carrier reduces lipid accumulation in liver and modulates lipid metabolism.

Abstract n SP6_11 - Presenting author**: Gaia Fabris**

## Improving effects of sacubitril/valsartan on hepatic fibrosis in MASLD patients with heart failure.

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**Introduction:** Metabolic associated steatosic liver disease (MASLD) is associated with cardiovascular events and increased mortality. Liver fibrosis is a major determinant for chronic liver disease (CLD) progression, and is associated with previous history of coronary heart disease, atrial fibrillation, heart failure correlating with poor prognosis. Liver fibrosis has no current approved drugs and its identification by non-invasive tests (NIT) (such as Fib-4, NFS, NAFLD Fibrosis Score, FAST, Agile 4) or non-invasive imaging (Fibroscan or T1-mapping MRI) is still a matter of controversy.
Sacubitril/valsartan is a new drug for the heart failure treatment, improving myocardial function and reducing myocardial fibrosis. In this setting, our study aims to evaluate in patients with MASLD with mild-reduced ejection fraction (HF r or m EF), the effects on liver fibrosis assessed by liver stiffness measurement (LSM) with Fibroscan.
**Material and methods:** In this prospective cohort, data were collected from subjects attending the clinical cardiology (either ward or outpatients setting) of the Azienda Ospedaliera Universitaria Integrata di Verona –AOUI -, Veneto region, Italy, enrolled in the Heart Failure registry of AOUI Verona, with a chronic HF r o m EF. Echocardiography and Fibroscan were performed before and 6-month after sacubitril/valsartan administration, following optimization of all the other HF therapies. No signs of clinical or ultrasound congestion were documented.
**Results:** Twenty-seven patients were enrolled (male 89%, median age 61). Median HF was 30%. Six month therapy with sacubitril/valsartan led to an HF improvement from 30 to 38%. In 9 patients (33.3%) with hepatic fibrosis (LSM at the baseline > 8kPa, F1), we found a significant decrease in LSM from 9.8 to 7.8 kPa (p=0.008), whereas Fib score did not show any significant difference.
**Conclusions:** Though in a small sample, we reported the beneficial effects of sacubitril/valsartan on hepatic fibrosis of MASLD patients. This finding paves the way to analysis of larger series of patients.

Abstract n SP7_01 - Presenting author**: Marco Di Lorenzo**

## Identification of CREB3L3 mutations in patients with hypertriglyceridemia

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**Aim:** Hypertriglyceridemia (HTG) is a common form of dyslipidemia associated with an increased risk of cardiovascular disease and pancreatitis. According to recent guidelines fasting TG plasma levels < 1,7 mmol/l (150 mg/dl) can be considered normal while TG levels between 2 to 10 mmol/l (175 mg/dl - 885 mg/dl) and > 10 mmol/l (885 mg/dl) identify subjects with mild to moderate and severe hypertriglyceridemia respectively. Very severe HTG, defined at TG >20mmol/L (>1770mg/dL) is much more rare (prevalence 0.014%). Monogenic autosomal recessive forms are characterized by homozygous or compound heterozygous loss-of-function mutations in canonical genes involved in triglyceride metabolism: *LPL, APOC2, APOA5, GPIHBP1, and LMF1*. Mutations in CRE-binding protein 3–like 3 (CREB3L3) and glucokinase regulator (GCKR) have been associated to dominant forms of familial hypertriglyceridemia.
**Methods:** We performed targeted Next Generation Sequencing (NGS) analysis to study the coding regions and intron/exon boundaries of genes affecting the main pathways of triglyceride synthesis and metabolism in 19 patients with moderate, severe and very severe hypertriglyceridemia.
**Results:** A total of five patients were found to be carriers of variants in *CREB3L3* gene in heterozygosity. Three patients with heterogenous phenotype (moderate, severe and very severe HTG) were found to be carriers of a nonsense variant (c.610C>T - p.Arg204Ter). A patient with severe HTG was carrier of a previously reported pathogenic mutation (c.718G>A p.Glu240Lys). Another one with moderate HTG was found to be carrier of a loss of function mutation (c.732_733insG - p.Lys245GlufsTer130).
**Conclusion:** Our results indicate that *CREB3L3* gene does not appear to be associated only with moderate HTG phenotype typically seen in autosomal dominant hypertriglyceridemia. Further studies are needed for elucidate the genotype-phenotype correlation in these patients.

Abstract n SP7_02 - Presenting author**: Stella Covino**

## Functional characterization of uncertain significance variants (VUS) in patients with Familial Hypercholesterolemia (FH) through the application of flow cytometry

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**Background:** Familial hypercholesterolemia (FH) is an autosomal disorder of lipid metabolism presenting with increased cardiovascular risk. LDLR mutations are the cause of disease in 90% of the cases but many variants lack functional evidence to evaluate their pathogenicity and are classified as variant of uncertain significance (VUS). This generates uncertain results making the definitive diagnosis of FH difficult.
**Aim:** We aim to assess the functionality of VUS LDLR variants identified in FH patients by using flow-cytometry technique.
**Methods:** Peripheral blood mononuclear cells (PBMCs) isolated from blood samples of 15 FH-VUS patients using a density gradient method were stimulated with CD3/CD28 beads in a medium containing a lipoprotein deficient serum. The LDLR activity (expression on cell surface, LDL binding and uptake) was measured through flow cytometry. PBMCs from wild-type normocholesterolemic subjects (HD) and FH carriers positive to one known pathogenic variant were used as negative and positive controls. Results were expressed, in percentage, as ratio between geometric mean fluorescence of patients and negative controls cells'.
**Results:** Of the 10 VUS variants tested (n=15 FH carriers), the c.1860G>T and c.1171G>A showed a reduced binding (HD:100%, c.1860G>T: 50%, c.1171G>A: 64%), uptake (HD:100%, c.1860G>T: 64%, c.1171G>A: 35%) and expression of LDL receptor (HD:100%, c.1860G>T: 52%, c.1171G>A: 77%). Conversely, the c.(-97)G>A presented reduced binding (HD:100%, c.(-97)G>A: 65%) while the c.1945C>T reduced binding (HD:100%, c.1945C>T: 43%) and expression (HD:100%, c.1945C>T: 46%) compared to HD cells. The c.1530_1532del and c.367T>C had, respectively, reduced LDLR expression (HD:100%, c.1530_1532del: 83%) and reduced uptake (HD:100%, c.367T>C: 69%). Finally, 4 of the 10 VUS variants tested (c.2282C>T, c.817+5G>C, c.929T>A and c.941-20C>T) did not change the LDLR activity compared to wild-type.
**Conclusions:** We have functionally profile 10 VUS variants in the LDLR gene. These results suggest the importance to conduct functional tests to improve the molecular diagnosis of FH.

Abstract n SP7_03 - Presenting author**: Martina Ferrandino**

## Different HDL subfractions distribution in patients with Familial Hypercholesterolemia with and without pathogenic variants

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**Aim.** Familial Hypercholesterolemia (FH) is an inherited disease associated with increased risk of coronary artery disease (CAD) and mainly due to pathogenic variants in the LDLR, APOB and PCSK9 genes. It is characterized by high level of LDL-cholesterol (LDL-c), although sometime also low HDL-cholesterol (HDL-c) levels were observed. We aim to evaluate the distribution of cholesterol in HDL subfractions to further refine the biochemical characterization of patients with (FH/V+) and without (FH/V-) pathogenic variants.
**Methods.** HDL subfractions analysis was performed in plasma from 99 patients (72 FH/V+ and 27 FH/V-) using the Quantimetrix Lipoprint system. This method allows to separate 10 subfractions of HDL that are grouped into 3 categories: Large, Intermediate and Small. The lipid profile of each patient also included total cholesterol, LDL-c, HDL-c and triglycerides.
**Results.** FH/V+ patients showed lower levels of HDL Small (13.6±5.2%) than FH/V- patients (15.9±4.8%; p=0.042). The reduction of HDL Small in FH/V+ patients was more evident analysing the ratio between Small and Large HDLs (HDL S/L): 0.45 (0.33-0.68) in FH/V- and 0.32 (0.21-0.52) in FH/V+ patients (p=0.030). The HDL S/L ratio was correlated with triglycerides (Spearman coefficient=0.617; p<0.001), HDL-c (Spearman coefficient= -0.432; p<0.001) and with the LDL- c/HDL-c ratio (Spearman coefficient=0.338; p=0.001). At the multivariate linear regression, the HDL S/L ratio remain associated with the triglycerides levels (beta-coefficient=0.369; p<0.001) and with HDL-c levels (beta-coefficient= -0.340; p=0.009), independently from age, sex and presence of pathogenic variants.
**Conclusions.** Patients with pathogenic variants showed a decreased proportion of HDL Small reflecting in a lower HDL S/L ratio, this partially explain the phenotypic variability of FH patients in relation to the genetic confirmation. A different HDL distribution could explain the different predisposition to cardiovascular disease due to the presence of pathogenic variants.

Abstract n SP7_04 - Presenting author**: Federica Galimberti**

## Heterogeneity of the genetic profile of Familial Hypercholesterolaemia in two cohorts from Italy and Russia

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Here we aimed to evaluate the genotype-phenotype relationship by comparing data from Familial Hypercholesterolemia (FH) patients, in two cohorts from Italy and Russia.
223 clinically diagnosed FH patients were studied: 144 from our centre of the Italian LIPIGEN Network and 79 from the centre of the EAS Russian Lipid Clinics Network in Saint Petersburg. Demographic, clinical characteristics and results from a standardised genetic test were collected. Patients were divided according to genetic diagnosis, in: positive (with one causative variant), inconclusive (with only variants of uncertain clinical significance [VUS]), and negative (with likely benign/benign variants, heterozygous variants in LDLRAP1 gene, or without causative variants).
The mean age at baseline was comparable (Italy: 47.5±12.5years, Russia: 45.1±12.4years; p=0.15); the Russian cohort presented with higher levels of pre-treatment LDL-cholesterol (pre-LDL-C) compared to the Italian cohort (324.1±91.6mg/dL vs 296.0±51.8mg/dL; p=0.01). The genetic test was positive in 76.4% of the Italian cohort and in 49.4% of the Russian cohort, while the presence of only VUS was detected in 7.6% and 19.0% (p<0.001), respectively. After stratifying the two cohorts by DLCN score, the same trend was observed. Among subjects with positive FH diagnosis, pre-LDL-C levels were higher in the Russian cohort (353.5±111.3mg/dL vs 302.4±52.1mg/dL; p=0.009), as well as the percentage of treated patients (53.8% vs 14.5%; p<0.001) and the prevalence of premature coronary heart disease (12.8% vs 3.6%; p=0.039). Among subjects with inconclusive FH diagnosis, the Russians were about 12 years younger compared to Italians (42.7±12.1years vs 54.5±10.5years; p=0.013), while the mean pre-LDL-C levels were similar (299.5±68.1mg/dL vs 299.0±46.4mg/dL; p=0.982). Among pathogenic/likely pathogenic variants and VUS, only 5% and 4% was shared between the two cohorts, respectively.
Our results highlighted a high variability in the genetic profile of patients diagnosed with FH from two different countries. A better understanding of the causes of variability in the phenotype-genotype relationship is a fundamental task of a personalized approach in managing FH patients.

Abstract n SP7_05 - Presenting author**: Ilaria Rossi**

## Deciphering ANGPTL3's Influence on Hepatic Lipid Storage: A PCSK9-Independent De Novo Lipogenesis Mechanism

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**Aim**: ANGPTL3 is an hepatokine, negative regulator of lipoprotein lipase. Vupanorsen, anti-ANGPTL3 antisense oligonucleotide, was discontinued from clinical trial due to increased liver fat fraction. Here, we investigated the molecular mechanism underlying this side effect and studied the potential involvement of PCSK9 whose levels have been correlated to triglycerides plasma concentration and its expression was induced after in vitro ANGPTL3 gene silencing.
**Methods**: We utilized hepatocarcinoma Huh7 cells treated with siRNA-ANGPTL3, siRNA-PCSK9, or the combination of the two siRNA. Western blot, Oil red-O, RTqPCR, biochemical and ELISA assays were performed to assess changes in lipid metabolism.
**Results**: Oil red-O analysis demonstrated that lipid content increased significantly after ANGPTL3 or PCSK9 silencing as well as the combination of both (respectively 3.5, 0.45, 1.40 fold) compared to basal. When ANGPTL3 gene expression was reduced by 99.5% we observed an increase in main genes involved in de novo lipogenesis (FAS +36%, ACC1 +54%, ACLY +18%, SCD1 +89%) and in SREBP1 (+49%), SREBP2 (+27%) and PCSK9 (+163%). We also found a significant increase in FAS and SCD1 proteins (2,81 and 3,16 fold vs basal, respectively) after siRNA-ANGPTL3. Moreover, PCSK9 silencing increases ANGPTL3 expression (by 1,58 fold) and vice versa (2,63 fold) but no significant changes were found between siRNA-ANGPTL3 vs siRNA-ANGPTL3 combined with siRNA-PCSK9.
**Conclusions**: efficient lipid accumulation following gene silencing emerged, mirroring what was seen in vupanorsen-treated patients. Our data indicates that siRNA-ANGPTL3 stimulated de novo lipogenesis via the activation of SREBP1 pathway. This activation could be due to a change in the ratio of free and esterified cholesterol, reducing free cholesterol and activating SREBP pathway. Moreover, a second relevant finding is a mutual regulation between PCSK9 and ANGPTL3 which could be the result of SREBP1 activation. Finally, the lipid accumulation in response to ANGPTL3 silencing is independent from the presence of PCSK9.

Abstract n SP7_06 - Presenting author**: Simone Bini**

## ANGPTL3 and PCSK9 determine a shift in the activted metabolic pathways in a HEPG2 cellular model.

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**Background and Aims:** ANGPTL3 and PCSK9 are known regulators of lipoprotein metabolism. Patients affected by familial hypobetalipoproteinemia type 2, due to homozygous loss of function in the ANGPTL3 gene, show reduced levels of circulating PCSK9 indicating a possible coordinate regulation of these two proteins. Our research aims to establish whether the two proteins show intracellular or extracellular interaction and if they are able to determine a metabolic shift in a liver cellular model.
**Methods:** Co-immunoprecipitation (Co-IP) was performed both intracellularly and in the culture medium to detect direct interaction of ANGPTL3 and PCSK9 within or outside cells. Then we generated ANGPTL3 and PCSK9 over-expressing (OE) cells and we used a phospho-proteome profiler to study intracellular activated pathways.
**Results:** ANGPTL3 and PCSK9 co-localize and co-precipitate in the intracellular compartment. At the proteome profiler, ANGPTL3 OE cells show an activation of the IGF-1 receptor and PLC-gamma and STAT3. PCSK9 OE cells show the activation of different TRK receptors and the intracellular activation of STAT1. Double OE cells re-establish intracellular signaling similar to control cells.
**Conclusions:** ANGPTL3 activates the IGF1R-PLC-γ-STAT3 axis associated with increase in lipolysis. Conversely, PCSK9 activates the STAT1 pathway associated with increased mitochondrial beta-oxidation.

Abstract n SP7_07 - Presenting author**: Sara Matteucci**

## Structure and trafficking of PCSK9 in LDL binding

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**Introduction:** Circulating PCSK9 is known to interact with the LDL-R thus promoting its degradation and blunting the uptake of LDL from the circulation. In this context, anti-PCSK9 mAbs and siRNAs are approved for the treatment of hypercholesterolemia. Previous studies have demonstrated that a significant proportion of circulating PCSK9 associates to LDL. The purpose of our research is to better understand the basis of the PCSK9-lipoprotein interaction and whether it has a physiological impact.
**Methods:** A three-layered iodixanol gradient was used to isolate lipoproteins fractions from patients' plasma before and after treatments. Lipoproteins components were studied by spectrophotometric, lipidomic and proteomic approaches.
**Results:** The LDL-C levels decreased from 94±41 to 41±17 mg/dL after siRNA treatment and from 125±52 to 62±40 mg/dL after mAbs therapy. Circulating PCSK9 decreased 70-80% after siRNA, while plasma PCSK9 levels increased 10-fold after mAbs (n=18 and 30 respectively; $p<0.05$). Independent of the therapy, PCSK9-bound to LDL was on average 10% (n=30; $p<0.01$). Immunoblotting analysis demonstrated that PCSK9 circulates also as acetylated protein and is bound to LDL. By lipidomic analysis, PCSK9 associates to a LDL subfraction that has a lower density than average LDL, due to its composition: 17.16% proteins, 28.62% phospholipids, 14.41% triglycerides and 34.81% cholesterol. By LC-MS, this subfraction showed a higher amount of ApoE, ApoCI, ApoCII, ApoCIII than LDL fraction (89±10 and 11±1; 64±8 and 6±1; 76±10 and 15±2; 53±5 and 6±1 attomoles/femtomoles ApoB respectively; $p<0.05$).
**Conclusions:** Our study identified a LDL subfraction more buoyant than the classical LDL (IDL-like lipoprotein) involved in PCSK9 binding. Although the therapies significantly modify the total amount of circulating LDL and PCSK9, the percent of PCSK9-bound to LDL remains constant. The acetylated form of PCSK9 seems to be involved in the LDL binding; whether the rate of acetylation contributes to the total PCSK9 bound remains to be addressed.

Abstract n SP7_08 - Presenting author**: Giorgia Marodin**

## An in vitro study on the pharmacological modulation of LDLR by small interfering RNA and antibodies anti-PCSK9

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**Aim.** After acute coronary syndrome ESC/EAS dyslipidemia guidelines recommend high-intensity statin therapy within the first 1-4 days of hospitalization. In the same clinical setting, the efficacy of mAbs anti-PCSK9, is under investigation. A recently discovered means of decreasing PCSK9 levels is the administration of siRNA anti-PCSK9, inclisiran. In this scenario, appropriate pharmacodynamic and pharmacokinetic characteristics of anti-PCSK9 therapies are essential for an effective pharmacological action.
In this study, we investigated the pharmacological modulation of LDLR by siRNA and mAbs anti-PCSK9.
**Methods.** Hepatocarcinoma Huh7 cells were incubated at different time-point with siRNA anti-PCSK9 or evolocumab. LDLR and PCSK9 expression were determined by western blot. ApoB and PCSK9 were measured with ELISA kits. LDL-DyLightTM550 uptake were determined by cytofluorimetry.
**Results.** siRNA anti-PCSK9 reduced intracellular PCSK9 from 4 to 8h (-30 and -35%, respectively). The reduction on secreted PCSK9 was observed from 8h (-37%) onwards. Longer time-course experiments revealed that siRNA reduced PCSK9 protein expression after 24 and 48h (-46 and -68%, respectively), while the extracellular levels showed a stronger effect after 48 and 72h (-60%). No effect was observed on apoB secretion. Surprisingly, the reduction in PCSK9 levels only marginally, but not significantly, reduced LDLR expression.
Evolocumab itself didn't show any modulation on LDLR, while incubation with recombinant-humanPCSK9 (recPCSK9) for 24h induced the receptor's complete degradation, rescued by the co-incubation with evolocumab. In line with LDLR expression, recPCSK9 strongly reduced the LDL-DyLightTM550 uptake in Huh7, while the combination with evolocumab increased the uptake.
Using HepG2 overexpressing-PCSK9, siRNA anti-PCSK9 increased LDLR expression by 2-fold.
**Conclusions.** Both siRNA and mAbs anti-PCSK9 didn't significantly affected the LDLR expression most likely due to the low concentration of PCSK9 in Huh7. Instead, in the presence of exogenous recPCSK9, LDLR undergoes degradation, effect reversed by evolocumab. A different in vitro model, using HepG2 overexpressing-PCSK9, seems to better modulate LDLR.

Abstract n SP7_09 - Presenting author**: Ottavia Terenghi**

## Definition of the metabolic pattern of ANGPTL3 deficient mice on a chow diet and under dysmetabolic conditions

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**Aim:** ANGPTL3 controls lipid and lipoprotein metabolism through lipoprotein lipase and endothelial lipase inhibition and the prevention of lipoprotein-derived triglycerides hydrolyzation.
Here we present the metabolic profile of ANGPTL3 deficient mice in physiology and during the development of metabolic disorders.
**Methods:** Angptl3 KO mice (C57BL6/J background) and their littermate controls (wild-type, WT) were fed a chow and a High Fat Diet (HFD, 60%kcal from lipids) for 16 weeks.
During the diet protocol, changes in lipids and lipoprotein profile, under fast, fed, and fast-refeed setting were assessed. The metabolic phenotype was assessed, with a Glucose Tolerance Test (GTT) and an Insulin Tolerance Test (ITT); the lipids absorption profile was assessed with an Oral Lipid Tolerance Test (OLTT).
**Results:** ANGPTL3 KO mice fed *ad libitum* a chow diet are hypolipidemic (plasma triglycerides levels: 42,42±8,80 mg/dL in ANGPTL3 KO mice compared to 122,02±55,09 mg/dL in WT mice; plasma cholesterol levels: 44,00±9,11 mg/dL in ANGPTL3 KO mice compared to 76,51±15,87 mg/dL in WT mice).
After 16h fasting, ANGPTL3 KO mice on a chow diet are hypolipidemic and display small lipoproteins less rich in cholesterol and triglycerides, as established in humans, and the same holds true for mice fed a HFD diet.
On HFD, ANGPTL3 KO mice gain less body weight, suggesting an improved metabolic profile compared to WT animals.
The hypolipidemia is conserved during all the timepoints of OLTT, both in mice on chow or HFD, suggesting a different lipid management; in spite, no significant differences in the circulating glycaemia has been proved with a GTT after 16h of fasting; likewise, a similar sensitivity to insulin has been outlined with an ITT after 4h of fasting.
**Conclusions:** This metabolic profiling of ANGPTL3 KO mice on chow diet or HFD highlights that these mice are hypolipidemic and may have beneficial metabolic features compared to controls.

Abstract n SP7_10 - Presenting author**: Silvia Roda**

## Impact of mitochondrial dynamism on lipoprotein metabolism in metabolic syndrome

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**Aim**: Hepatocyte metabolism is highly dynamic and deeply affected by mitochondrial plasticity. Mitochondria are therefore crucial for energy production and the synthesis of hormones, sterols, lipid and bile acids. They are in a dynamic state between fused and fixed, affecting both outer and inner membranes. OPA1 represents a key protein involved in the inner membrane fusion, impacting mitochondrial function and cellular lipid metabolism. We aim to investigate how hepatic overexpression of OPA1 can affect morphology and lipid handling in a diet-induced liver steatosis.
**Methods**: OPA-1 overexpressing mouse (Opa1Tg) and WT (controls) mice were fed a high fat diet (HFD) 45% Kcal from lipids for 20 weeks and then in vivo metabolic responses, and liver characteristics were profiled.
**Results**: Opa1Tg mice fed with HFD show weight gain compared to controls animals, and despite this, it seems to be independent from hepatic lipid accumulation, as they do not present both micro and macro steatosis. Thus, Opa1Tg mice seem protected against steatosis progression. Histological analysis shows a reduction in fibrosis in Opa1Tg mice liver compared to controls. In accordance with the visible absence of lipid droplet accumulation, liver quantification show a significant reduction of both cholesterol and triglycerides levels Furthermore, plasma cholesterol levels were also reduced in Opa1Tg mice compared to control despite a significant increase in lipoprotein production. Preliminary observation on other active metabolic tissue as the heart shows that Opa1 overexpression promote lipid utilization increasing mitochondrial complexes and oxidative phosphorylation.
**Conclusions**: Results suggest that OPA1 overexpression can influence cellular metabolism, especially lipids handling and usage in the liver. This could be a consequence of more complex interactions and molecular mechanism between mitochondria and cellular lipid metabolism.

Abstract n SP8_01 - Presenting author**: Maria Laura Furnari**

## Management of a patient with heterozygous familial hypercholesterolemia (HeFH) and cancer: case report and challenge in lipid-lowering treatment in real life

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**Background:** FH is an inherited disorder of lipid metabolism characterized by elevated plasma levels of LDL-C and early atherosclerotic cardiovascular disease.
We describe the clinical and molecular characterization of a subject with severe hypercholesterolemia and the therapeutic approach to reach the LDL-C goal suggested by the most recent international guidelines.
**Methods:** The proband is a 55-year-old woman who has been diagnosed with FH 33 years ago. Treatment with high efficacy statin at the maximum tolerated dose (atorvastatin 40 mg/dl) in association to ezetimibe did not allow to reach the suggested LDL-C goal (LDL-C < 70 mg/dl).
**Results:** The patient was found to be a heterozygous carrier of a pathogenic mutation c.1285G/A V408M (V429M) exon 9, known as Afrikaner 2, affecting the LDLR gene and responsible of FH.
Beside a low fat diet and the standard lipid-lowering therapy (LLT), the patient did not reach the LDL-C goal. Therefore she added the treatment with PCSK9-i (Alirocumab 75 mg biweekly) and the goal was achieved.
In 2022, the patient was diagnosed with a metastatic synchronous endometrioid carcinoma of the ovary and endometrium. Hence, she underwent surgery and adjuvant maintenance chemotherapy with bevacizumab; PCSK9-i was temporarily suspended and inclisiran was started in association with background LLT.
**Discussion:** Although Alirocumab is a biological drug that does not interfere with other therapies and has no effect on cytochrome P450 enzymes, the patient decided to suspend the LLT with iPCSK9 until the end of the adjuvant chemotherapy with bevacizumab, opting for new therapeutic strategies.
**Conclusions:** This case describes the clinical management of a HeFH patient with neoplasia, underlining the efficacy, safety and tolerability of new therapeutic approaches in complex cases.

Abstract n SP8_02 - Presenting author**: Martina Ugolotti**

## PCSK9 inhibition as a potential pharmacological strategy to treat Alzheimer's disease: in vitro and in vivo studies

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**Aim:** The proprotein convertase subtilisin/kexin 9 (PCSK9), beyond regulating plasma cholesterol, is also expressed in the central nervous system (CNS), where a pathogenetic role in Alzheimer's Disease (AD) has been postulated. We previously demonstrated with *in vitro* studies that PCSK9 enhances the β-amyloid (Aβ)-induced neurotoxicity and neuroinflammation. This study aims to investigate the potential beneficial effects of its pharmacological inhibition using newly synthesised molecules through *in vitro* and *in vivo* studies.
**Methods:** Newly synthesised compounds (MR-3, MR-532, MR-533) with previously proven PCSK9 inhibitory activity were tested on human microglial cells (HMC3) to assess their potential protective effect on Aβ-induced neurotoxicity (MTT assay) and proinflammatory cytokines secretion (ELISA assay). The three molecules were also tested on wild-type mice (C57BL6/J) at a dose of 40 mg/Kg for 7 days to evaluate: their tolerability (body weight and locomotor monitoring), hepatic toxicity (histopathological observation of liver sections and ALT plasma detection) and biodistribution (LC-MS/MS).
**Results:** Microglial viability, significantly reduced after incubation with Aβ-fibrils (-28%; $p<0.0001$), was rescued by the compounds in a dose-dependent manner, with the most evident effect for MR-533 at 10μM ($p>0.05$ vs basal condition). Furthermore, under basal conditions, MR-533 at 10μM significantly reduced IL-6 release in HMC3 (-46%; $p<0.05$). All three molecules showed good *in vivo* tolerability and absence of hepatic toxicity as indicated by a significant reduction of ALT plasma levels; MR-3 and MR-532 were also detected in plasma and brain tissue.
**Conclusions:** Our data suggest that PCSK9 inhibition plays a protective role on Aβ-induced neurotoxicity and neuroinflammation in cerebral cell models; moreover, the three tested anti-PCSK9 molecules are well tolerated *in vivo*. All together these data lay the basis for a promising approach to treat AD, although further studies will be necessary to validate this novel pharmacological strategy.

Abstract n SP8_03 - Presenting author**: Marta Turri**

## Cholesterol esterification is hampered in alzheimer's disease and cholesteryl esters composition is consequently altered

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**Introduction and Aim:** Several epidemiological studies indicate a strong inverse association between the risk of developing Alzheimer's disease (AD) and plasma HDL-C levels. The mechanism by which plasma HDL influence the pathogenesis and progression of AD is still unsolved and since cholesterol esterification is a crucial step in HDL metabolism it could be involved. The purpose of this study was to evaluate cholesterol esterification and HDL subclasses in plasma and cerebrospinal fluid (CSF) of Alzheimer's Disease (AD) patients.
**Methods**: The study enrolled 70 AD patients and 74 cognitively-normal controls comparable for age and sex. Lipids and lipoprotein profile, cholesterol esterification, and cholesterol efflux capacity (CEC) were evaluated in plasma and CSF using assays set for measurement in plasma, which were appropriately modified for CSF.
**Results**: AD patients have normal plasma lipids, but significantly reduced unesterified cholesterol and unesterified/total cholesterol ratio. Lecithin:cholesterol acyltransferase (LCAT) activity and cholesterol esterification rate (CER), two measures of the efficiency of the esterification process, were reduced by 29% and 16%, respectively, in plasma of AD patients. Plasma HDL subclass distribution in AD patients was comparable to that of controls, but the content of small discoidal preβ-HDL particles was significantly reduced. In agreement with the reduced preβ-HDL particles, cholesterol efflux capacity mediated by the transporters ABCA1 and ABCG1 was reduced in AD patients' plasma. The CSF unesterified to total cholesterol ratio was increased in AD patients, and CSF CER and CEC from astrocytes were significantly reduced in AD patients. In the AD group, a significant positive correlation was observed between plasma unesterified cholesterol and unesterified/total cholesterol ratio with Aβ1-42 CSF content.
**Conclusions**: Taken together data indicate that cholesterol esterification is hampered in plasma and CSF of AD patients, and that plasma cholesterol esterification biomarkers (unesterified cholesterol and unesterified/total cholesterol ratio) are significantly associated to disease biomarkers (i.e., CSF Aβ1-42).

Abstract n SP8_04 - Presenting author**: Miriam Frosina**

## Impact of APOE genotype on body composition in elderly adults: an observational study

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**Aim:** Aging induces alterations in body composition, characterized by diminished muscle and bone mass and augmented fat mass, fostering conditions like sarcopenia and osteoporosis, linked to heightened fracture susceptibility, disability, and mortality risks. Apolipoprotein E (ApoE), a pivotal player in lipid metabolism, exhibits three common alleles (E2, E3, E4) featuring amino acid substitutions. Despite the critical role of ApoE, few and conflicting research have evaluated the influence of ApoE genotype and polymorphisms on body composition, especially in elderly Caucasians. Then, our study was to evaluate whether the ApoE genotype and its polymorphisms are related to osteoporosis and sarcopenia.
**Methods:** APOE rs7412 and rs429358 variants were genotyped in a cohort of 86 elderly individuals aged ≥ 65 years, of both gender. A dual X-ray absorptiometry scan was performed to assessed body composition. Sarcopenia was defined according to the EWGSOP criteria.
**Results:** Individuals with APOE4 genotype exhibited higher total bone mineral density compared to APO ε2 and APO ε3 genotypes (APOE4: 0.972 ± 0.1 g/cm2 vs APOE3: 1.050 ± 0.1 g/cm2 vs APOE2: 1.102 ± 0.1 g/cm2, p=0.04), as well as a lower prevalence of osteoporosis compared to the other genotypes (APO ε4: 0% vs APO ε3: 17% vs APO ε2: 30%, p=0.05). Moreover the effects of rs429358 and rs7412 polymorphisms were analyzed. Carriers of the ApoE rs429358 T/T variant, although it had no effect on BMI, showed higher total body fat mass compared to T/C carriers (27.4 ± 6 kg vs 23.5 ± 9 kg, p=0.04), along with a higher prevalence of dyslipidemia (47% vs 9%, p=0.02). On the other hand, carriers of ApoE rs7412 C/C exhibited higher bone mineral density compared to C/T carriers (1.058 ± 0.1 g/cm2 vs 0.971 ± 0.1 g/cm2, p=0.03). Both in the APOE genotype and in polymorphisms, no significant differences were found in the prevalence of fracture, and sarcopenia.
**Conclusions:** Our findings suggest that the APOE genotype is involved in the susceptibility of obesity and osteoporosis.

Abstract n SP8_05 - Presenting author**: Carola Garavaglia**

## Antiproliferative effects of HDL on prostate cancer cell lines: role of oxysterols

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**Aim:** Beyond their atheroprotective role, high density lipoproteins (HDL) were shown to reduce prostate cancer (PCa) cell content of cholesterol, thus inhibiting cell proliferation. Nevertheless, little is known about the overall effect on cholesterol homeostasis. Oxysterols are cholesterol metabolites with antiproliferative effects. However, tumor cells have an aberrant production of oxysterols, and some of them can contribute to tumor growth, as in breast cancer. Aim of the study was to assess the impact of oxysterols on PCa cell proliferation and to investigate whether HDL can affect their intracellular levels.
**Methods:** Experiments were performed in androgen-sensitive (LnCap) and androgen-independent (PC3) PCa cell lines, compared to non-tumor PNT2. HDL were isolated by ultracentrifugation from human plasma. Intracellular levels of oxysterols were assessed by LC/MS. Cell proliferation was evaluated by cell count and MTS assay on cells exposed to 27-hydroxycholesterol (27-HC) and/or HDL.
**Results:** PCa cell lines showed a different distribution of oxysterols compared to non-tumor PNT2. In particular, 27-HC levels were up to 5 times higher in PC3 cells than in PNT2. 27-HC significantly increased cell proliferation up to 30% in LnCap and to 15% in PC3. The exposure to HDL drastically reduced the content of all oxysterols, including 27-HC, in the three cell lines. Consequently, cell proliferation induced by 27-HC was completely prevented when cells were exposed to HDL.
**Conclusions:** Our results showed that 27-HC increased the proliferation of PCa cell lines, which is prevented by HDL. Therefore, the reduction of intracellular levels of oxysterols could contribute to the antiproliferative effects of HDL on tumor cells. Further studies are needed to deeply investigate the underlying mechanisms, which could be related to the activation of hormone receptors by 27-HC, as observed in breast cancer, and to the overexpression of the ABCG1 transporter in PCa cells.

Abstract n SP8_06 - Presenting author**: Arianna Moretti**

## Role of STEROL ELEMENT BINDING PROTEIN 1C (SREBP1c) in the metabolism and suppressive function of regulatory T cells

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**Aim:** Dysfunctional immunosuppressive Treg response supports inflammation in different pathological settings, including atherosclerosis. Several studies have demonstrated that Treg intracellular lipid metabolism is critical for their function. Therefore, the aim of this study is to investigate the role of Sterol Regulatory Element Binding Protein 1c, a key protein regulating intracellular fatty acid (FA) metabolism, in Tregs immunobiology.
**Methods:** T cells isolated from WT and SREBP-1c KO mice and in vitro induced Treg (iTreg) were analyzed through flow-cytometry, western blot and RT-qPCR. iTreg metabolism was studied using the Seahorse XF technology, which provides a real time measurement of mitochondrial respiration and glycolysis in living cells.
**Results:** The percentages of in vitro induced regulatory T cells (CD25high Foxp3+ T cells), analyzed by flow-cytometry, were reduced (-6,76%, p<0,0001) in KO cells compared to WT controls. The gene expression of hexokinase 2, known to be involved in the glycolysis pathways, was significantly increased (+74,76%, p<0,001) in KO Treg cells, while ACLY and FASN, which support fatty acid synthase, are reduced (-53,47%, p<0,001). At the same time, FoxP3 gene expression, which is the master regulator of Treg function, was reduced, in line with a reduce iTreg phenotype.
When cells were treated with C75 (FASN inhibitor), metabolism of WT iTregs switched to glycolysis. This was confirmed by Seahorse XF technology: glycolysis, defined as the ECAR rate, was significantly increased for KO iTreg cells compared to WT cells.
Moreover, p70S6K and S6 protein activation was observed in iTreg controls (not treated), as opposed to the treatment with 2DG (glycolysis inhibitor) which decreased the activation of the pathway, suggesting that 2DG can reverse the iTreg phenotype.
**Conclusions:** Our data have identified a key role of SREBP1c in the immune-metabolic response of Tregs. Therefore, modulating Treg metabolism might enhance their suppressive function, thus representing a new pharmacological tool in cardiovascular prevention.

Abstract n SP8_07 - Presenting author**: Sebastiano Cicco**

## Change of lipids in Granulomatosis with Polyangiitis (GPA) relates to glucocorticoids and hypertension

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**Introduction**: Granulomatosis with polyangiitis (GPA) is an ANCA-associated small-vessel vasculitis. Vessel wall inflammation induces multiple vascular damages leading to accelerated atherosclerosis. Metabolic profile and cardiovascular risk are marginally known in the GPA patients. Our purpose is to evaluate lipid profile and ASCVD-risk in GPA patients according to history of hypertension.
**Methods**: We selected 36 patients who received GPA diagnosis (T0) and evaluated them after 1 (T1) and 2 (T2) years follow-up. All patients were treated with high-dose glucocorticoid, one-year tapered, associated with immunosuppressants. Pathological history and a complete list of drugs at different time points were recorded.
**Results**: hypertensive patients exhibited a marked escalation in lipid levels when compared to normotensives. In particular, notable distinctions emerge between the two groups at both T1 and T2 concerning total cholesterol and LDL ($p<0.05$ each), despite comparable baseline values at T0. Then, while triglyceride levels start at similar values at T0, a substantial increase is observed at T1 in hypertensive patients. Conversely, at T2, normotensive individuals experience a significant rise in triglyceride levels, accompanied by a noteworthy reduction in hypertensive subjects. No difference there was in mortality.
**Conclusions**: The findings indicate that lipid profile alterations, likely influenced by glucocorticoid treatment, may not be directly linked to inflammation. Furthermore, there is a higher relation between hypertension and these alterations. Actual data doesn't reveal increased mortality in hypertensive GPA patients but further research is required to a specific pattern characterizing cardiovascular risk and progression in this context.

Abstract n SP8_08 - Presenting author**: Martina Ciarnelli**

## Mitochondrial modulation as a therapeutic strategy for attenuating microglia-driven inflammation in Alzheimer's Disease

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**Aim** We aimed to study the central role of microglia, brain-resident macrophage-like cells, in Alzheimer's disease (AD) pathogenesis, investigating the immunometabolic effects of toll-like receptor 4(TLR4)-mediated activation and studying translational applications in a murine model of AD.
**Methods** A human microglia cell line (HMC3) was activated by 24 hours LPS exposure and treated with dimethyl malonate (DMM), a succinate dehydrogenase (SDH) inhibitor with immunomodulatory properties. Mitochondrial respiration and glycolysis were quantified through oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), respectively, by using Seahorse XFe96 Extracellular Flux Analyzer (Agilent Technologies®). Furthermore, mitochondrial functions analysis, and RNA and protein isolation, were performed. In a second step, the effect of SDH inhibition was investigated *in vivo*, on primary microglia isolated from 6 and 18 months aged Non-Tg and 3xTg-AD mice intraperitoneally injected with DMM or PBS once a day for three days.
**Results** We demonstrated that LPS activated HMC3, showed a bioenergetic profile characterized by a remarkable increase of both glycolysis and mitochondrial respiration (MR), although the activity of respiratory chain (RC) complexes was mostly devoted to ROS production. Interestingly, the exposure to amyloid beta peptide (Aβ) activated HCM3 via TLR-4 and simulated LPS-induced metabolic effects. In a second step, inhibiting SDH with DMM, we modulated LPS-induced metabolic rewiring and mitochondrial biogenesis, and promoted an anti-inflammatory phenotype, via inhibition of hypoxia-inducible factor 1α (HIF-1α) recruitment. A hyper bioenergetic profile was also detected in microglia isolated from 3xTg-AD mice, and DMM *in vivo* administration revealed a potential strategy to control microglia metabolic reprogramming, dampening inflammation in the early stages of AD. Moreover, RNA-seq analysis from a public data repository supported our findings, by confirming a consistent up-regulation of mitochondrial pathways and genes encoding electron transport chain (ETC) subunits in microglia of 5xFAD mice.
**Conclusions** The TLR4-mediated activation in microglia stimulates metabolic alterations, triggering pro-inflammatory responses. Targeting SDH candidates as a potential and promising therapeutic strategy to prevent AD.

Abstract n SP8_09 - Presenting author**: Monica Pastorino**

## Chlorpyrifos exposure affects the regulation of the orexigenic neuropeptides Npy and AgRP both in *vivo* and in *vitro*

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**Background/Aim:** Obesity is a major health crisis affecting over a third of the global population. The hypothalamic nuclei are crucial in regulating appetite and energy homeostasis. Thus, dysregulation of these neuronal networks may lead to overnutrition and obesity. Recently, it was reported that Chlorpyrifos (CPF), a specific worldwide used pesticide, promotes the increase of body mass and adiposity and gets worse glucose tolerance and insulin sensitivity in obese mice. Whether CPF might also affect the regulation of hypothalamic pathways is not known yet. Here, I established the effect of CPF in the regulation of orexigenic neuropeptides, Npy and Agrp, both *in vitro* and *in vivo*.
**Methods:** Hypothalami from CD-1 mice chronically treated with CPF (10 mg/kg/day) from their conception to 6 months of age and from untreated mice have been used as experimental *in vivo* models. The hypothalamic mhypoE-N46 cells treated or not with CPF (1 pM) have been used as experimental *in vitro* models. The mRNA expression of genes encoding the orexigenic, *Npy* and *Agrp*, and anorexigenic, *Pomc* and *Cart**,*** neuropeptides, and the estrogen receptors, *ER-alpha* and *ER-beta*, has been assayed by qPCR. Secretion of Npy and Agrp has been evaluated by ELISA assay.
**Results**: *In vivo* data from mice treated with CPF revealed that the expression of both *Npy* and *AgRP* mRNA levels is increased by 2.0 ($p$<0.05) and 3.0-fold ($p$<0.05), respectively in the hypothalami of CPF-treated compared to untreated mice; while no differences were found among the two groups in the expression of both *Pomc* and *Cart* mRNA levels. Similarly, to what was observed *in vivo*, *in vitro* data from mhypoE-N46 cells acutely (4 h) exposed to CPF (1 pM) confirmed that the CPF caused in the treated cells an increase in the expression of both *Npy* (1.35-fold; $p$<0.01) and *AgRP* (1.31-fold; $p$<0.01) mRNA levels and was accompanied by a 2.2 ($p$<0.01) and 1.68-fold ($p$<0.001) increase in the basal secretion of both Npy and AgRP neuropeptides, respectively. Noteworthy, CPF (1 pM) caused a similar extent in the increase of the gene expression of both the orexigenic neuropeptides even upon a chronic treatment (6 days). Since it was reported that CPF may modulate estrogen receptor expression and activation, firstly both ER-alpha and ER-beta mRNA levels have been assayed both *in vivo* and *in vitro.* Noteworthy, mice treated with CPF and mhypoE-N46 cells exposed to both acute and chronic doses of CPF showed an increase of about 2.60- (p<0.05), 1.28- (p<0.001), and 1.60-fold (p<0.01), respectively, in the expression of the ER-beta mRNA levels compared to their respective controls; while no differences were found among the groups both *in vivo* and *in vitro* in the expression of *ER-alpha* mRNA levels. Finally**,** computational analyses of the *Npy* and *AgRP* gene promoters also predicted two estrogen-responsive elements for ER-beta binding to these regions.
**Conclusions**: Here I found through *in vivo* and *in vitro* approaches that the pesticide CPF may affect the regulation of hypothalamic pathways by dysregulating both the expression and secretion of the orexigenic neuropeptides Npy and Agrp. Additional experiments will be required to better clarify the involvement of ER-beta in these dysfunctional processes.

Abstract n SP8_10 - Presenting author**: Carmelo Pujia**

## Effect of Citrus Bergamia and Cynara Cardunculus supplementation on body composition in overweight and obese adult: A clinical trial

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**Aim:** Obesity is a major risk factor for cardiovascular diseases, diabetes, and cancer. A weight loss ≥ 5% is enough to induce clinically relevant improvements in health risk factors. To achieve successful maintenance of weight loss over time, changes in lifestyle including diet and physical exercise were recommend. However, 80% of obese people do not achieve long-term weight loss with diet and exercise alone. Nutraceuticals have been proposed as potential strategies for managing obesity. Some preclinical and clinical studies suggest that *Citrus bergamia* and *Cynara Cardunculus* is capable of promoting weight loss. Therefore, in a clinical trial, we examined the effects of this nutraceutical on body composition in overweight and obese adults.
**Methods:** The study included 131 overweight/obese individuals. For 12 weeks, the intervention group was given a nutraceutical (300 mg/day) containing a Bergamot polyphenol fraction and *Cynara Cardunculus* extract. The control group received a daily dose of placebo. All subjects received a calorie restriction of 400–500 calorie from their baseline energy intake. Body weight and other anthropometric parameters were assessed at baseline and after 12 weeks.
**Results:** We found a greater weight loss in the overweight/obese participants taking the nutraceutical rather than placebo (-4.1±0.4 kg vs. -1.7±0.2 kg, adjusted $p<0.001$), as well as of BMI, waist circumference, and fat mass. Furthermore, the percentage of individuals who achieved a 5% or greater weight loss after 12 weeks of treatment was greater in the intervention group compared to the placebo group (60% vs 20%, adjusted $p<0.001$; respectively).The stepwise multivariable analysis confirmed the association between the weight loss and nutraceutical treatment ($B = -2.35$; $p<0.001$).
**Conclusions:** This analysis demonstrated that a nutraceutical with bergamot and wild cardoon appears to have an anti-obesity effect. Future investigations are needed to evaluate the efficacy of this nutraceutical in the treatment of obesity.

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