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P1 Influence of combined therapy on inflammatory state and pro-inflammatory cytokines in patients with coronary artery disease and metabolic syndrome

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Background and Aims:
Aim of the study was to investigate the influence of combined lipid lowering therapy with rosuvastatin and ezetimibe on lipid profile, inflammatory state and pro-inflammatory cytokines in dyslipidemic patients with coronary heart disease (CHD) and metabolic syndrome (MS).

Material and Methods:
128 patients with CHD and MS were randomly divided into two groups per 64. First group was provided rosuvastatin (10 mg) + ezetimibe (10 mg) and the second group (control) was provided only rosuvastatin (10 mg). Plasma lipids, inflammatory state (hs-CRP), and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) were measured at baseline and in 12 weeks.

Results
The level of TC, LDL-C was decreased significantly in combination group than controls (P<0.05), however there was not significant difference between 2 groups on HDL-C (P>0.05). Hs-CRP was decreased by 38% in the first group (P=0.003) vs. 31% in control group (P=0.005) from baseline, however there was no obvious changes between 2 groups. Even though, pro-inflammatory cytokines: TNF-α (from 1.42±0.98 to 0.87±0.18 in 12 weeks, P=0.018), IL-6 (from 7.8 pg/mL to 4.1 pg/mL, P=0.012), IL-1β (from 28.4±19.5 pg/ml to 17.5±15.8 pg/ml, P=0.010) in the combination group vs. TNF-α (from 1.48±1.12 to 1.12±0.25, P=0.047), IL-6 (from 8.0 pg/mL to 5.9 pg/mL, P=0.037), IL-1β (from 29.6±20.6 pg/ml to 20.6±17.4 pg/ml, P=0.040) significantly decreased in both groups from baseline however, there were statistically significant changes observed only in the first group (P<0.05) when compared two groups.

Conclusions:
Therapy with rosuvastatin and ezetimibe is superior than rosuvastatin alone to improve TC, LDL-C and pro-inflammatory cytokines in patients with CHD and MS.

P2 Association of Hyperhomocysteinemia with Acute Myocardial Infarction in Iraqi Patients

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Background: Coronary Artery Disease (CAD), and its major manifestation, Acute Myocardial Infarction (AMI) are the most common causes of death worldwide. Hyperhomocysteinemia (HHcy) has been recently recognised as a new emerging cardiovascular risk factor mediating in development of CAD risk. HHcy causes endothelial dysfunction, resulting in local thrombosis and subsequent ischemia. However, the role of HHcy in increasing risk of CAD still remains controversial and elusive.

Aim: The major aim of this study is to determine the association between HHcy with increased risk of CAD in patients with AMI in Kurdish population. Its role in development of CAD could be pivotal.

Design and method: In this case-control study, a total of 74 patients with AMI and 74 age and gender-matched individuals as control group were enrolled. The serum Hcy level was measured by enzymatic immunoassay. HHcy was defined as Hcy>15µmol/l.
Results: The prevalence of HHcy was significantly higher in AMI patients (68.9%) than in control group (29.7%) (P<0.0001). The mean serum tHcy level was higher in AMI patients than that in control group (22.8µmol/l and 15.1µmol/l, respectively, P<0.0001). Moreover, the mean tHcy level for the male patients were about 7 μmol/L greater than those for the female patients.

Conclusion: HHcy is strongly associated with increased risk of CAD independent of conventional risk factors such as hyperlipidemia, Diabetes, hypertension, smoking and family history of premature CAD factors. This study concludes that HHcy is a new independent cardiovascular risk factor of CAD and AMI.

P3 Association of Vitamin D Deficiency with Acute Myocardial Infarction in Iraqi Patients

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Background: Globally, Coronary Artery Disease (CAD), and its complications such as Acute Myocardial Infarction are the leading cause of morbidity and mortality. Vitamin D deficiency is a prevalent condition and it is emerging as a new risk factor for coronary artery disease. However, the correlation between Vitamin Deficiency and increasing risk of CVD development remains elusive.

To determine the association between vitamin D deficiency with acute myocardial infarction among Kurdish population in relation to age, gender. Vitamin D deficiency was defined as a serum 25-hydroxyvitamin D concentrations ≤20 ng/mL. The role Vitamin D in development of acute MI could be pivotal.

In a case-control study, a total of 222 patients (153 male; 69 female; aged 22-80 years) with AMI and 225 gender and age-matched non-CAD individuals as the control group were enrolled. The serum vitamin D concentrations was measured by enzymatic immunoassay.

High significant level of Vitamin D deficiency was observed in AMI patients (95.9%), compared to that in control group (78.4%). It was observed that 67.6% were severely vitamin D deficient (0 to<10 ng/ml) and 4.1% were insufficient. Furthermore, the prevalence of Vitamin D deficiency was greater in male MI patients than female.

Findings of this study show that Vitamin D deficiency is strongly associated with development of acute myocardial infarction. This concludes that Vitamin D deficiency is an important new emerging risk factor for CAD. This implies that supplementation of Vitamin D may be important in maintaining cardiovascular health.

P4 Adherence to Statin therapy drives survival of patients with symptomatic peripheral artery disease

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Background: Statins reduce cardiovascular morbidity and mortality, but adherence is suboptimal. We hypothesized that adherence to statins determines survival in patients with peripheral artery disease (PAD).

Methods and Results: Single center observational study with 691 symptomatic PAD patients admitted to a tertiary university center between 2010 and 2017. Mortality was evaluated over a mean follow-up of 50±26 months. Statin adherence and LDL-C target attainment was related to total mortality.

Initially, 73% of the patients were on statins with an increase in statin use to 81% (p<0.0001) at follow-up: Statin dosage, normalized to simvastatin 40 mg, increased from 50 to 58 mg/day (p<0.0001), paralleled by mean decrease of LDL-C from 97 to 82 mg/dL (p<0.0001). Proportion of patients on a high intensity statin treatment increased over time from 38 to 62% (p<0.0001).
Patients never receiving statins had a higher mortality rate (34%) as compared to patients being on statins (20%) or having newly received a statin (15%; \( p < 0.01 \)). Moreover, patients on intensified statin medication had the lowest mortality (10%), whereas patients who terminated statin medication or reduced the statin dosage had a higher mortality rate (33% and 43%, respectively; \( p < 0.05 \)).

**Conclusion:** Statin treatment, particularly high-intensity therapy, reduces mortality in symptomatic PAD. Patients benefit even from **de novo** statin therapy, whereas dose reduction or statin discontinuation have deleterious effects. A strategy of intensive and sustained statin therapy is worthwhile.

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**P5 Prescription of sacubitril/valsartan in patients with heart failure and reduced ejection fraction attending to an outpatient heart failure clinic**

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Aims: To assess the clinical and neurohormonal characteristics of patients eligible to sacubitril/valsartan (SV) attending to our heart failure outpatient clinic and describe variables related to SV prescription in real life heart failure patients.

**Design & methods:** We collected data from 119 consecutive patients attending to our heart failure outpatient clinic between May 2018 and November 2018.

**Results:** At baseline, mean age was 64±10 years and 75.5% were men. Mean LVEF was 28±6%. 42% ischemic etiology. 83 patients (70%) NYHA class II. Median NT-proBNP was 1288 pg/ml (IQR 377-3967), mean glomerular filtration rate (GFR) 67.0±22.8 mL/min and potassium 4.5±0.4 mEq/L. 85% of patients were treated with ACE inhibitors or angiotensin receptor blockers. 96% received \( \beta \)-blockers and 86% mineralocorticoid receptor antagonists. Of this 119
eligible patients, 64 (53.8%) were treated with SV. Achieving >50% of β-blocker target dose, TFG ≥ 60 mL/min and systolic blood pressure (SBP) ≥110 mmHg were significantly associated with the prescription of SV. In a multivariate analysis adjusted for age and β-blockers dose, a higher SBP (OR 1.26 95%CI 1.16-2.01) and GFR (OR 1.02 95%CI 1.01-1.14) were independently associated with the prescription of SV.

Conclusions: The rate of prescription of SV in our cohort is relatively higher than in other real life registries. Low SBP and TFG suggest a subgroup of patients with higher risk of adverse events, requiring an optimization of concomitant treatment, mainly diuretics and vasodilators, leading to higher rate of SV prescription.

P6 Tolerability profile and discontinuation causes of sacubitril/valsartan treatment in “real-life” patients with heart failure and reduced ejection fraction


Aims: To describe the clinical characteristics, safety and tolerability profile, and discontinuation causes of sacubitril/valsartan (S/V) treatment in patients attending to an outpatient heart failure clinic.

Design & methods: We collected data from 119 consecutive patients between May and November 2018. Variables were collected baseline and post-S/V titration period.

Results: 64 patients (53.8%) were treated with S/V. At baseline, mean age was 63±10 years, 76.6% men. Mean LVEF 28±6%. 39% ischemic etiology. 67% NYHA II. Median NT-proBNP 1176pg/ml (IQR 364-3945). Mean glomerular filtration rate (GFR) 71,7±20,6mL/min and potassium 4,4±0,4mEq/L. 84% of patients were treated with ACE inhibitors or ARBs, 95% beta-blockers and 86% mineralocorticoid receptor antagonists. Median titration time was 6,5 weeks (IQR 3-13,2). Target dose was achieved in 23 patients (40%). 24 (37,5%) needed dose reduction and 10 (15.6%) discontinued therapy. Causes for therapy discontinuation were hypotension defined as SBP <90 mmHg (<n=4, 6,2%), Potassium >5,5meq/L (n=2, 3,1%) and diarrhea (n=1, 1,6%). Patients who presented at least one adverse event were older, with lower SBP and GFR (all p<0.05). In a multivariate analysis a lower SBP (OR 0,94 95%CI 0.90-0.99) was the only variable independently associated with adverse events.

Conclusions: In our cohort, S/V has an acceptable tolerability profile. The proportion of patients who achieved target dose was lower than the reported in clinical trials, despite a longer titration time. Hypotension represents the main cause of reduction or discontinuation of S/V.

P7 Mechanisms of cardiotoxicity associated with tyrosine kinase inhibitors in H9c2 cells and mice

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Purpose: Tyrosine kinases inhibitors (TKI) are known to induce cardiac toxicity in patients, which may be caused by mitochondrial damage. The aim of the current study was to improve our knowledge about the role of mitochondria in cardiac toxicity of TKIs, in particular concerning oxidative stress and cell death.

Design & methods: We exposed cardiac H9c2 cells for 24h with imatinib, sorafenib or sunitinib. In addition, we treated mice with sunitinib (7.5 mg/kg/day) for two weeks.

Results: In H9c2 cells exposed for 24 h, all TKIs investigated showed a higher cytotoxicity profile in the presence of galactose (favoring mitochondrial metabolism) compared to glucose (favoring glycolysis). The TKIs dissipated the mitochondrial membrane potential and reduced activities of mitochondrial enzyme complexes of the electron transport chain (ETC). In addition, the TKIs increased superoxide accumulation and decreased the cellular GSH pool, inducing
apoptosis. Electron microscopy showed swollen mitochondria with loss of cristae. In mice, treatment with sunitinib for two weeks increased plasma troponin I and creatine kinase MB, indicating cardiomyocyte damage. The activity of enzyme complexes of the ETC was decreased and the mitochondrial content of reactive oxygen species (ROS) was increased. Cleavage of caspase 3 was increased in hearts of sunitinib-treated mice, suggesting cardiomyocyte apoptosis.

Conclusions: Mitochondrial ROS accumulation appears to be an important mechanism of cardiotoxicity associated with sunitinib and other cardiotoxic TKIs, leading to the activation of apoptosis.

Figure 1

Membrane toxicity and intracellular ATP content in H9c2 cells exposed for 24 h with different TKIs
Effects of tyrosine kinases inhibitors on mitochondrial enzyme complexes of the electron transport chain and on redox status in H9c2 cells exposed for 24 h

Mitochondrial morphology and mtDNA content of H9c2 cells exposed with different TKIs for 24 h

P8 Direct oral anticoagulants concentration testing in clinical practice for high-risk patients with atrial fibrillation

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The aim of this study was to analyze the necessary of coagulation tests for AF patients with high cardiovascular risk in clinical practice.

Design and methods. Quantitative, analytic, cross-sectional clinical study, during the period from April 2018 to February 2019, was performed at Pauls Stradins Clinical University Hospital, Cardiology Centre of Latvia. There were collected data about patients with non-valvular AFib under anticoagulative therapy ≥3 months, defined as a high-risk group by CHA2DS2-VASc score – from score 2. Concentration was measured using anti-Xa assay un direct thrombin inhibitors’ assay. Data were analyzed using SPSS.

Results. There were collected data about 7 patients of whom 85.7% (n=6) were male; the mean age was 66.3 (SD±5.77) years. The mean CHA2DS2-VASc score was 2.86 (SD±1.57). The most common comorbidities were arterial hypertension and coronary artery disease (42.86%; 3), stroke (42.86%; 3) and diabetes mellitus (28.57%; 2). 71.43% used rivaroxaban. Increased risk of possible drug-drug interactions most frequently was with statins (71.43%; 5), proton pump inhibitors and anti-inflammatory drugs (42.86%; 3). 2/3 of patients were taking ≥1 drug with potential pharmacokinetics interactions increasing the risk of bleeding. The average Cmax drug concentration in blood was lower than expected, reaching 216.28 ng/ml and decreasing about 67.17% within 24 hours.

Conclusion. Rivaroxaban measurements varied from 27 to 407 ng/ml (median value 143.64 ng/ml) within 24 hours. Three patients had higher-than-expected rivaroxaban levels.

P9 Role of PGC-1α associated mitochondrial biogenesis in statin-induced myotoxicity

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Aim: Statins are well tolerated but can be associated with mitochondrial dysfunction in skeletal muscles. Statins impair mitochondrial proliferation by decreasing PGC-1α expression in human and rat skeletal muscle, suggesting a role of PGC-1α in statin-induced myotoxicity. This study aimed to investigate these effects in differentially expressed PGC-1α mouse models.

Methods: We used three mouse models: mice with muscle PGC-1α knockout (MKO), mice overexpressing PGC-1α (MCK), and wild-type (WT) mice. Mice were treated for 3 weeks with water or simvastatin (5 mg/kg/d) by oral gavage and we determined exercise capacity, muscle function and the function of muscle mitochondria from glycolytic gastrocnemius and soleus oxidative muscles.

Results: Simvastatin showed muscular impairments in WT mice, manifested by decreased exercise capacity, grip strength and mitochondrial respiration in the glycolytic muscle coupled with increased H2O2 production. Moreover, MKO mice treated with simvastatin exacerbated these muscular dysfunctions and showed impaired mitochondrial respiration in oxidative and glycolytic muscle types. However, MCK mice showed no impairments of exercise capacity and muscle function.

Conclusion: Increased muscle PGC-1α expression ameliorated statin-induced muscular dysfunctions, while decreased muscle PGC-1α expression further exacerbated the toxicity. Therefore, PGC-1α seems to be a susceptibility factor and has an important role in mitigating simvastatin induced myotoxicity.

P10 Blood Lead Level and Hypertension Risk in the United States National Health Nutrition and Examination Survey (NHANES) 1999-2016

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Aim: Hypertension is a known manifestation of lead toxicity. However, whether low level exposure is related to hypertension is uncertain.

Methods: NHANES participants aged >20 years with blood pressure and lead measurements were included in this analysis. If not already diagnosed, a mean blood pressure ≥130/80 mmHg was regarded as hypertension. R statistics version 3.5.1 with package ‘survey’ and sample weight adjustment were used.

Results: 39477 participants (20803 of whom had stage 1 or 2 hypertension) were included in this analysis. Each doubling in blood lead level increased the odds of hypertension (OR [95%CI]: 1.45 [1.40-1.50]). The association remained significant after adjusting for age, gender, ethnicity, waist circumference and smoking. Using quartile 1, blood lead level <0.89 µg/dL, as reference, quartiles 2, 3 and 4 (0.89-1.29; 1.30-2.09; ≥2.10 µg/dL) were associated with increased adjusted odds of hypertension (1.14 [1.05-1.25]; 1.15 [1.04-1.28]; 1.22 [1.09-1.36]) respectively.

Conclusion: Blood lead level is associated with hypertension in the US general population, most of whom do have elevated blood lead level. Our findings suggest that reducing present levels of environmental lead exposure may potentially reduce blood pressure and the consequent cardiovascular risk in adults.

P11 Evaluation of the effect of HFRT on the anthropometric obesity parameters in Patients of Chronic Heart Failure – A retrospective analysis

R. Sane (Mumbai IN)

Aim: Chronic heart failure (CHF) is a common cause of mortality and morbidity. Obesity influences the CHF development and prognosis. This study was conducted to assess effect of Heart failure reversal therapy (HFRT), a combination of panchakarma and allied therapies, on anthropometric parameters in CHF patients.

Methods: This retrospective study was conducted on data of patients who visited Madhavbaug clinics in Maharashtra, India between July-December 2018. Selection was based upon the availability of complete baseline (day 1 of HFRT) and follow-up data (day 30 of HFRT) of CHF patients who were admitted for minimum 5 days for HFRT.

Results: Out of 147 patients, 74.15% were males with mean age 59.15±10.28 years. There was statistically significant decrease (p<0.05) in both mean BMI and abdominal girth at day 30 of HFRT. 42 of 147 patients (28.57%) had hypertension (HTN) with CHF, 22 patients (14.97%) had diabetes mellitus (DM) and 61 patients (41.49%) had both HTN and DM. In all these sub-groups, mean BMI and abdominal girth was significantly decreased (p<0.05) at day 30. Strong positive correlation was found between BMI and abdominal girth on day 1 (R=0.9, P<0.05) and day 30 (R=0.83, P<0.05) by Pearson’s correlation. Similar correlation was found between the two parameters in subsets of CHF patients having HTN or DM or both DM and HTN (p<0.05).

Conclusion: HFRT decreased BMI and abdominal circumference significantly in CHF patients, irrespective of the presence of HTN or DM. Both the anthropometric parameters correlated strongly in all co-morbidity subsets of CHF patients.

P12 The Role of the Central Autonomic Nervous System and Psychosocial Factors in Microvascular Angina and Tako-Tsubo Syndrome
Purpose. We hypothesized that Tako-Tsubo syndrome (TTS) and primary microvascular angina (MVA) may exhibit peculiar functional organization of the central autonomic nervous system network (CAN) at rest, as well as specific psychological patterns as compared to patients with acute myocardial infarction (AMI).

Design & methods. We prospectively enrolled patients in 3 groups: MVA, after TTS or AMI. Subjects underwent a clinical-diagnostic interview, Millon Clinical Multiaxial Inventory III, State-Trait Anxiety Inventory form Y, short form (SF-36) Health Survey related to quality of life questionnaire. Patients underwent a blinded resting state functional MRI (RS-fMRI), to compare the intrinsic connectivity strength among the CAN nodes.

Results. We evaluated 50 (46 women) matched patients (16 MVA, 17 TTS, 17 AMI). There was a high prevalence of obsessive-compulsive personality disorder. MVA showed a significantly lower SF-36 Body-Pain score than AMI (p 0.046) and a significantly higher SF-36 Mental-Health score than AMI (p 0.039). RS-fMRI in TTS showed stronger connectivity between two nodes of the sympathetic (midcingulate cortex) and parasympathetic (sub-central motor area) CAN (F 6.25, p 0.005).

Conclusions. The peculiar self-reported body pain and mental health in MVA as well as the increased level of functional integration between areas of the CAN subdivisions in TTS may link psychosocial distress with clinical manifestations. This data are hypothesis-generating for future potential endorsement of psychotherapy and stress-reducing techniques as therapeutic strategies.

P13 Evaluation of the effect of Heart Failure Reversal Therapy (HFRT) on the Exercise Capacity in patients with Chronic Heart Failure and their association with co-morbidities

R. Sane (Mumbai IN)

Aims: New treatment modalities are needed to improve the aerobic capacity of patients with chronic heart failure(CHF)considering the increasing disease prevalence. This study was done to evaluate the effect of Heart Failure Reversal Therapy(HFRT)on exercise indices viz VO2max and metabolic equivalents(METs).Methodology: This retrospective study screened data of 147 patients who had visited Madhavbaug Clinics between July 2018 to December 2018. The mean VO2max and METs on day 30 of HFRT initiation was compared with that at baseline. Regression analysis was used to calculate the odds for increase in VO2max and METs by HFRT in specific co-morbidity. Results: Of the 64 patients who fit the study criteria, majority were males (n=51) with mean age of 57.89 ± 8.14 years. Most common co-morbidity was hypertension(HTN)(n=45)followed by diabetes mellitus(DM)(n=36) and coronary artery disease(CAD)(n=27). Mean VO2max and METs increased significantly at day 30 of HFRT initiation compared to the mean values on day 1(p<0.05). Odds for elevation in VO2max and METs were maximum in patients with myocardial infarction(VO2max: OR=4.95; CI=0.26-91.5. METs: OR=3.46; CI=0.18-65.54), ischemic heart disease (VO2max: OR=2.85; CI=0.32-24.7. METs: OR=1.67; CI=0.18-15.29) or obesity (VO2max: OR=2.57; CI=0.29-22.4. METs: OR=1.5; CI=0.16-13.78). All odds were statistically insignificant (p>0.05). Conclusion: HFRT leads to significant increase in the VO2max and METs in CHF patients, indicating improved aerobic capacity.

P14 Network Meta-analysis to Determine the Optimal Level of Systolic Blood Pressure for Hypertensive Patients

B. M. Y. Cheung, Y. Fei, M. F. Tsoi (‘Hong Kong HK)

Aim: Lowering systolic blood pressure (SBP) to <120 mmHg has been shown to reduce cardiovascular events and mortality. Whether this should be the target is controversial. We therefore studied the relationship between SBP attained and outcome using network meta-analysis.
Methods: We searched for randomised trials comparing different SBP targets. The mean SBP attained was classified into five groups (110-119, 120-129, 130-139, 140-149 and 150-159 mmHg). The outcome variables analysed using R were major adverse cardiovascular events (MACE), cardiovascular mortality, stroke and myocardial infarction.

Results: 14 trials with altogether 44015 patients were included (fig. 1). Lowering SBP to 120-129 mmHg significantly reduced stroke and MACE when compared to 130-139 mmHg (OR 0.83, 95% CI 0.69-0.99 and 0.84, 0.73-0.96), 140-149 mmHg (0.73, 0.55-0.97 and 0.74, 0.60-0.90), and 150-159 mmHg (0.43, 0.26-0.71 and 0.41, 0.30-0.57), respectively. The risk of stroke was further lowered with more intensive control to <120 mmHg (0.58, 0.38-0.87, 0.51, 0.32-0.81, and 0.30, 0.16-0.56, respectively). In contrast, the risk of cardiovascular mortality and myocardial infarction was significantly higher with SBP ≥150 mmHg when compared to 120-129 mmHg (2.18, 1.32-3.59 and 1.73, 1.06-2.82) and 130-139 mmHg (1.71, 1.11-2.61 and 1.53, 1.01-2.32).

Conclusions: Lowering SBP to <130 mmHg reduces MACE and stroke. Further lowering to <120 mmHg can reduce stroke if the treatment is tolerated. Long-term SBP should not exceed 150 mmHg because of the increased risk of cardiovascular events and deaths.

P15 Cardiovascular benefits of new antidiabetic drug classes: a network meta-analysis

B. M. Y. Cheung, Y. Fei, M. F. Tsoi (Hong Kong HK)

Aim: New antidiabetic drugs are required to be evaluated in cardiovascular outcome trials (CVOTs). Few of these are direct comparisons between new drugs, so we performed a network meta-analysis to compare the new drug classes in terms of cardiovascular outcomes.
**Method:** We searched for CVOTs involving glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose co-transporter 2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes using major adverse cardiovascular events (MACE) and mortality as endpoints. Network meta-analysis was performed using random-effects model in R.

**Results:** 13 CVOTs with altogether 116746 patients were included (fig. 1). GLP-1 RAs and SGLT-2 inhibitors significantly lowered the risk of MACE (OR 0.87, 95% CI 0.82-0.94 and 0.89, 0.82-0.97), all-cause mortality (0.90, 0.82-0.99 and 0.84, 0.76-0.93), heart failure (0.87, 0.82-0.93 and 0.70, 0.62-0.80), and renal composite outcome (0.85, 0.75-0.97 and 0.63, 0.55-0.72) when compared to placebo (fig. 2). GLP-1 RAs reduced nonfatal stroke (0.88, 0.77-0.99) while SGLT-2 inhibitors reduced cardiovascular mortality (0.83, 0.72-0.96). In contrast, DPP-4 inhibitors did not significantly alter the risk of these outcomes.

**Conclusion:** GLP-1 RAs and SGLT-2 inhibitors both reduce MACE, heart failure, renal composite outcome, and all-cause mortality when compared to placebo. DPP-4 inhibitors did not show any cardiovascular benefits. Our findings support using SGLT-2 inhibitors and GLP-1 RAs for diabetic patients with high cardiovascular risk.
Fig. 2

P16 The perilousness of antidepressant drugs in a real-world cohort of patients with acute coronary syndrome.


**Background:** Although antidepressant therapy has been related to increased cardiovascular risk, depression and its adverse effects on prognosis is a well-recognized entity among acute coronary syndrome (ACS) patients. The aim of the study was to evaluate prevalence and outcome of antidepressant treatment in a real-world cohort of ACS patients.
Methods: We sought to assess the prevalence of established antidepressant therapy (ADT) and its impact among 2,168 all-comers patients admitted to four Swiss University Hospital for acute coronary syndrome (ACS) and enrolled in the prospective multicenter SPUM registry (NCT 01000701). The primary endpoint was all-cause mortality. The association between ADT and mortality was tested by adjusted multivariable conditional logistic regression.

Results: Out of 2,168 ACS patients, 141 patients (6.5%) had ADT. Compared with the general ACS population, ADT patients were more likely to be unemployed (p=0.001) male (p=0.002), diabetic (p=0.010) already treated with cardiovascular preventive therapy with statins or beta-blockers (p<0.001). Patients with ADT presented a 2-fold risk of all-cause mortality (OR 2.2, 95%CI 1.20-4.00, p=0.009) with a 3-fold risk of non-cardiovascular (CV) death (OR 3.24, 95%CI 1.10-9.70, p=0.026) and a 77% not significant higher risk of CV death (OR 1.77, 95%CI 0.83-3.80, p=0.130). This enhanced risk persisted after adjustment for confounding significant baseline characteristics, with a 47% (Adjusted HR 1.47, 95%CI 1.05-1.70, p=0.032, Figure 1).

Conclusions: Among a real-world cohort of ACS-patients, ADT is associated with a significant increased rate of all-cause mortality and non-CV death. These observations should lead clinicians to furtherly individualize ADT, employing newer and safer ADT, generally associated with a lower CV risk.

**P17 Protocol of A Randomized, Single blind, placebo -controlled RESCAP, intervention study to determine the safety of RESCAP in Diabetes: RAPID protocol-Rational and design.**

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Type 2 diabetes (T2DM) affects 5.3% of world population with huge impact on healthcare cost, morbidity and mortality. Low grade chronic systemic inflammation results in complications like retinopathy, ESRD, diabetic wounds and adverse pregnancy conditions. Alkaline Phosphatase (AP) supplementation restores diabetes insulin and blood-lipid chemistry in preclinical models. A human field study in T2DM patients reports that AP in feces is reduced 50%.

We propose oral AP supplementation in T2DM patients. AMRIF, leveraging on the RESCAP® platform, develops therapies for TDM and other chronic inflammatory diseases. The RESCAP in Diabetes (RAPID) study is an exploratory interventional, multicenter, blinded, randomized controlled trial that is designed to determine safety of RESCAP in T2DM patients with high HbA1C, partially responsive to standard care treatment on metformin. The safety of bRESCAP has been extensively investigated. bRESCAP safety and efficacy is established in a variety of preclinical disease models and in a clinical trials, either i.v. or s.c. formulations. To date, APPIREDD-III study with RESCAP is in phase 3 of development in cardiothoracic surgery patients. In topical/oral settings, safety & efficacy was established in patients with IBD. RAPID may yield long term safety data (primary outcome) and health benefits in T2DM. Secondary outcome parameter changes: e.g. HbA1C, blood-lipid chemistry, low-grade systemic inflammation, adverse events, general well-being.

Duration: 9 months (the Clinical phase). Upon ethical approval, RAPID is conducted under ICH GCP.

P18 Evaluating the potential effect of L-Carnitine on the prevention of atrial fibrillation following coronary artery bypass graft surgery: a Randomized Clinical Trial

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Aim: Atrial Fibrillation [AF] is one of the most common complications in patients who undergo coronary artery bypass graft surgery [CABG]. The aim of this study was to evaluate the effect of L-carnitine administration on postoperative AF and acute kidney injury following CABG.

Design & methods: One hundred and thirty four patients undergoing elective CABG, without history of AF or previous L-carnitine treatment, were randomly assigned to an L-carnitine group (3000 mg/day L-carnitine) or a control group. CRP levels, as a biomarker of inflammation, were assessed in all the patients before surgery as baseline levels and 48 hours postoperatively. Neutrophil gelatinase-associated lipocalin (NGAL), as a kidney biomarker, was also measured in the patients before surgery and 2 hours thereafter.

Results: The incidence of AF was 13.4% in our population. L-carnitine significantly reduced the incidence of postoperative AF (7.5% in the L-carnitine group vs. 19.4% in the control group; p value=0.043) and postoperative CRP level (8.79±6.9 in the L-carnitine group vs. 10.83±5.7 in the control group; p value=0.021). Postoperative NGAL concentration demonstrated no significant rise after surgery compared with the preoperative concentration (72.54±20.30 in the L-carnitine group vs. 67.68±22.71 in the placebo group; p value=0.19).

Conclusions: Our study showed that L-carnitine administration before CABG may inhibit and reduce the incidence of post-CABG AF. It seems that a rise in the CRP level, as an inflammation marker, may be associated with the incidence of AF.

P19 HYPOTENSIVE ACTION OF MELATONIN IN PATIENTS WITH ARTERIAL HYPERTENSION

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Objective: to evaluate efficacy and safety of melatonin therapy in hypertensive patients based on the assessment of daily blood pressure monitoring.

Materials and Methods: 30 male patients with arterial hypertension aged from 27 to 58 yrs, mean age 45.5 ± 9.2 yrs, were included in the study. Daily ambulatory blood pressure monitoring (ABPM) with a portable BR-102 Plus blood
pressure registrar (Schiller, Switzerland) was conducted on the first day of the study and on the next day after receiving a therapeutic dose of melatonin. Melatonin (Melaxen, Unipharm, Inc. (USA) was administered on the second day of the study, 3 mg once daily, 9:00-10:00 a.m. Average value of 24-hour, day-and night-time brachial systolic (SBP) and diastolic blood pressure (DBP) were assessed.

Results. Average 24-hour SBP and DBP values decreased after melatonin intake – from 124.6 ± 12.1 to 121.0 ± 10.2 mm Hg. (p <0.03), and 79.7 ± 8.8 to 77.3 ± 6.5 mm Hg. (p <0.03), respectively, as well as average day-time SBP and DBP values - from 128.2 ± 13.2 to 122.5 ± 9.9 mm Hg. (p <0.003) and 82.3 ± 9.7 to 78.5 ± 7.2 mm Hg. (p <0.006). Average night-time DBP and SBP values did not change (p> 0.05). There were no side effects observed after melatonin treatment.

Conclusions. A single administration of melatonin in a therapeutic dose causes a short-term reduction in blood pressure, predominantly due to the reduction of 24-hour and day-time systolic and diastolic blood pressure. Further studies are needed to prove the efficacy of melatonin in arterial hypertension treatment.

P20 Statins and insulin resistance

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Statins are lipid-lowering drugs that are beneficial for the cardiovascular system. However, they are associated with skeletal muscle disorders and recently with insulin resistance and new-onset diabetes. To date, mechanisms underlying statin-induced insulin resistance are not fully elucidated. Goals of the study were to characterize effects of simvastatin on glucose metabolism and processes leading to the induced insulin resistance in skeletal muscle cells and mice.

C2C12 skeletal myotubes were treated with simvastatin (10 µM) and/or insulin for 24 hours. Insulin receptor activation, GLUT4 translocation and glucose uptake were investigated. Male C57BL/6J were treated with water or 5 mg/kg/day simvastatin for 21 days. Basal glucose and insulin were measured in fasted mice. ip glucose tolerance test (IGTT) and glucose uptake were performed and insulin concentrations were measured.

Simvastatin reduced activation of the insulin receptor in C2C12 and significantly decreased translocation of GLUT4 to the cell surface. Glucose uptake was reduced by half in simvastatin-treated myotubes and the absorption rate was restored with insulin. Simvastatin-treated mice had higher glucose plasma concentrations during the IGTT, higher insulin levels and higher HOMA-IR. Glucose uptake in their gastrocnemius was decreased.

Simvastatin induced insulin resistance in mice and impaired insulin signalling in C2C12 myotubes. In co-treatment, insulin prevented these adverse events. Future studies are needed to show if the identified processes contribute to diabetes in patients treated with statins.

P21 Bile Acids as Novel Vascular Signalling Molecules and Therapeutic Target

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Background: Bariatric surgery (RYGB) reduces cardiovascular mortality and improves HDL mediated vasoprotection. Bile acids (BA) are emerging as signaling molecules controlling cardio-metabolic health. Plasmatic BA circulate partly bound to HDL. Purpose: we tested whether and how changes in composition of BA bound to HDL (HDL-BA) after RYGB contribute to HDL-mediated endothelial protection. Methods: HDL isolated from 47 obese patients before and 1 year after RYGB were tested for their protective properties using human endothelial cell in vitro. HDL BA and lipid composition was quantified by liquid chromatography-mass spectrometry (LC/MS). Results: 1 year after RYGB, higher concentrations (up to 25%) of BA were bound to HDL with an increase on HDL of BA agonists for nuclear FXR,
e.g. cholic acid (CA) and chenodeoxy-CA (CDCA), or for membrane receptor TGR5, e.g. taurolitho-CA (TLCA). After RYGB, HDL levels were increased and HDL-mediated endothelial NO production, anti-apoptotic and cholesterol efflux capacity were restored. The composition-function analysis showed that higher HDL-CA correlated with improved anti-apoptotic capacity. Further, RYGB improves the lipidomic profile of HDL with reduced cholesteryl esters and toxic ceramides, and increased anti-oxidant plasmalogens.

Conclusions: RYGB increases the concentration and improves the function and the molecular lipid composition of HDL. Interestingly, higher concentrations of BA bound to HDL after RYGB may mediate HDL’s improved endothelial-protective effects via enhanced endothelial activation of FXR and TGR5.

P22 Impacts of Adipocytokines and Obesity-associated Inflammatory Markers on Apolipoprotein A-1 and B in Patients on Statin Therapy

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Background and Aims: Obesity-induced chronic low-grade inflammation is causally associated with insulin resistance leading to dyslipidemia, which is residual risks for coronary artery diseases (CAD) in patients on statin therapy. The aim of this study is to clarify the impacts of adipocytokines and obesity-associated inflammatory markers on apolipoprotein (apo) A1 and B in patients on statin therapy.

Methods: In 156 patients on statin therapy (age, 70±10 years; male, 73%; low-density lipoprotein cholesterol, 93±22 mg/dL), serum levels of apoA1 and apoB, high-sensitive C-reactive protein (hs-CRP), interleukin 6 (IL-6) and adipocytokines including adiponectin, leptin and resistin were measured using respective ELISAs.

Results: Serum apoA1 levels were significantly correlated with serum adiponectin (p<0.0001) and resistin (p<0.001), but not with leptin. Inflammatory markers such as hs-CRP (p=0.003) and IL-6 (p<0.0001) showed strong impacts on apoA1 levels. In multivariate logistic analysis, IL-6 (p=0.004) and adiponectin (p=0.02) were significant determinants for apoA1 levels. On the other hand, serum apoB levels were significantly associated with serum leptin (p<0.001), but not with other adipocytokines or inflammatory markers.

Conclusions: IL-6 and adiponectin are strong determinants for apoA1 level, and leptin is an important factor for apoB level in patients on statin therapy.

P23 Comorbidity differentiation and risk stratification in the elderly patient with polypharmacy: a prospective primary care registry on oral anticoagulation therapy

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Objectives Although polypharmacy is an accepted proxy for multi-morbidity, there has been limited attention for risk stratification among polypharmacy patients, especially in the elderly. We used the number of drug classes prescribed to determine the extent of co-morbidity and the risk of adverse outcome.

Methods Prospective study among elderly patients (≥75 years) with polypharmacy (≥5 drugs) using a vitamin K antagonist (VKA) for atrial fibrillation. The reference group used VKA and cardiovascular drugs only, the other groups used 1, 2 or ≥3 additional drug classes (defined by the Anatomical Therapeutic Chemical (ATC) classification system).

Measurements Charlson Comorbidity Index and cumulative comorbidity count; 3-year clinical follow-up.
Results Median age and CHA2DS2-VASc score (n=1430) were 81 years (IQR 78 to 85) and 5 (IQR 4 to 6). Across groups, there was a significant increase in hierarchical and cumulative comorbidity counts. Patients with ≥3 additional drug classes had a higher risk of major bleeding (aHR 3.17, 95% CI 1.24 to 8.05) than the reference group. The aHRs of all-cause mortality for the groups with one, two or ≥3 additional drug classes were 2.25 (95% CI 1.27 to 3.96); 3.04 (95% CI 1.75 to 5.29) and 3.88 (95% CI 2.23 to 6.76), respectively.

Conclusions In this AF cohort of elderly patients with polypharmacy, ATC drug class counts are associated with comorbidity burden and adverse outcome. These findings support the concept of risk stratification among the heterogeneous group of patients.

P24 A multicenter, open-label, randomized controlled clinical trial to assess the efficacy and safety of appropriate target values for lipid management in patients who have mild to moderate stenotic lesions with high-risk plaques in coronary arteries: Study protocol

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Aims

To investigate the efficacy of strict lipid management by secondary prevention high-risk criteria in preventing major cardiovascular events and progression of coronary artery stenosis in study subjects without proven history of coronary artery diseases (CAD) who have non-occlusive lesions with unstable plaques or severe calcification detected by coronary artery computed tomography (CACT), in comparison with standard lipid management as per the primary prevention criteria.

Design & Methods

This is a multicenter, open-label, randomized controlled parallel-group clinical study. Patients with mild-to-moderate stenotic lesions with positive remodeling or severe calcification, but without any history of CAD, will be randomly allocated to group A (reduce LDL-C to < 120~160 mg/dL according to the primary prevention criteria based on the Japanese Guideline for Prevention of Atherosclerotic Cardiovascular Diseases) and group B (reduce LDL-C to < 70 mg/dL according to the secondary prevention criteria at a high risk based on the Guideline). They will be strictly managed to achieve the LDL-C targets. We will follow-up and evaluate the composite endpoints consisting of major cardiovascular events (death from coronary artery disease, nonfatal myocardial infarction, operation for coronary revascularization, and stroke) and stenosis progression or new stenosis development for 3 years.

Conclusions

Our study will contribute to the development of a better preventive therapy for patients who have non-occlusive lesions with unstable plaques or severe calcification detected on CACT.