BAND 28

Diabetes Metabolism and the Heart

Diabetes, Stoffwechsel und Herz

CVOT Summit 2019

FINAL PROGRAMME AND ABSTRACTS

Munich, Germany, 24–25 October 2019

6 European CME credits (EACCME)

KIRCHHEIM

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Highlights of the CVOT Summit 2019 will be online soon after the meeting.

Please visit www.cvot.org and www.diabetes-symposium.org.

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KIRCHHEIM

Oliver Schnell
(Munich, Germany)

Welcome

Dear Colleagues,

*On behalf of the local organizing committee, we are delighted to welcome you to the 5th **Cardiovascular Outcome Trial (CVOT) Summit** in Munich, Germany. It is an honour to host and organize the meeting on 24th–25th October 2019.*

We invite you to be a part of the CVOT Summit, bringing together general practitioners, diabetologists, cardiologists and nephrologists. Over the past decade, CVOTs have tremendously impacted knowledge on diabetes mellitus and its cardiovascular and renal comorbidities, reflected in new treatment options and guidelines. The CVOT Summit has become a well-established platform to discuss developments and opinions linked to CVOTs and aims at building a high-level framework for future scientific exchange.

Presentations and discussions will be given by distinguished professionals in the field and will include topics such as new CVOT outcomes, their impact on diabetes care, new treatment options and many more.

The 5th CVOT Summit promises to be an outstanding event. With your participation, interest, and support you will highly contribute to the success of the meeting.

We look forward to seeing you at the 5th CVOT Summit in Munich.

Oliver Schnell
President, Local Organizing Committee

Local organizing committee

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DDG Deutsche Diabetes Gesellschaft

General information

Meeting venue
Infinity Hotel & Conference Resort Munich
Andreas-Danzer-Weg 1
85716 Unterschleissheim, Germany
Tel.: +49 (0)89 3 70 53 00
www.infinity-munich.de

Registration
The registration desk is located in the foyer of the convention venue.

Opening hours:
Thursday, 24 October: 16:00 – 20:00 h
Friday, 25 October: 07:45 – 19:00 h

Food & Beverages
Dinner will be served in the room "Alpsee" at 19:30 h on Thursday.
Lunch will be served in the restaurant "Viktualien" from 12:40 – 13:40 h on Friday.
Refreshment buffet will be served at the coffee area.

CME accreditation
The meeting was granted 6 European CME credits by the European Accreditation Council for Continuing Medical Education (EACCME). CME certifications of attendance will be provided on Friday afternoon at the registration.

THURSDAY, 24 OCTOBER 2019

Room Alpsee

18:00–18:30 **Welcome and introduction to the CVOT Summit 2019**
Schnell O (Munich, Germany), Ceriello A (Milan, Italy)

18:30–19:20 **Hellmut Mehnert Award 2019**
Chair: Holman R (Oxford, UK)

18:30–18:40 **Award ceremony**

18:40–19:00 **Award lecture: Protection from cardiovascular events due to dysglycaemia – from a glucocentric to a holistic view on patient management**
Rydén L (Stockholm, Sweden)

19:00–19:20 **Award lecture: The role of postprandial blood glucose in diabetes & CVD**
Hanefeld M (Dresden, Germany)

19:30 **Welcome reception**

FRIDAY, 25 OCTOBER 2019

Room Ammersee I & II

08:30–09:30 **Cardiological and nephrological perspectives in diabetes**
Chair: Cosentino F (Stockholm, Sweden)

08:30–09:00 **It's a matter of the heart: the future of SGLT-2 inhibition and DDP-4 inhibition in cardiology**
Marx N (Aachen, Germany)

09:00–09:30 **CREDENCE: renal outcomes with canagliflozin**
Wanner C (Wuerzburg, Germany)

09:30–10:15 **The SGLT-2 inhibitors … today and tomorrow**
(Supported by AstraZeneca)
Chair: Cos X (Barcelona, Spain)

09:30–09:45 **Cardiovascular protection with SGLT-2 inhibitors**
Rosano G (London, UK)

09:45–10:00 **Impact of SGLT-2 inhibitors on the kidney**
Groop PH (Helsinki, Finland)

10:00–10:15 Discussion

10:15–10:45 **Approaching the burden of heart failure**
Chair: Standl E (Munich, Germany)

10:15–10:45 **Heart failure in diabetes: treatment strategies with sacubitril/valsartan**
(Supported by Novartis)
Cosentino F (Stockholm, Sweden)

10:45–11:15 **Coffee break**

11:15–12:00 **Can we improve secondary cardiovascular prevention in our diabetic patients? Results of the PADDIA/CADDIA survey**
(Supported by Bayer)
Chair: Ceriello A (Milan, Italy)

11:15–11:30 **Management of PAD**
Brodmann M (Graz, Austria)

11:30–11:45 **Management of CAD**
Valensi P (Paris, France)

11:45–11:55 **Upcoming therapy of chronic kidney disease in patients with type 2 diabetes**
Ceriello A (Milan, Italy)

11:55–12:00 Discussion

12:00–12:40 **GLP1 RAs: a focus on the heart and the kidney (1)**
Chair: Rodbard H (Rockville, USA)

12:00–12:20 **Liraglutide and its cardiovascular and renal effects**
(Supported by Novo Nordisk)
Bain S (Swansea, UK)

12:20–12:40 **Cardiovascular benefits of GLP1 RAs: shedding light on the mechanisms**
Nauck M (Bochum, Germany)

12:40–13:40 **Lunch break**

13:40–14:00 **GLP1 RAs: a focus on the heart and the kidney (2)**
Chair: Rodbard H (Rockville, USA)

13:40–14:00 **Looking beyond secondary prevention – once-weekly dulaglutide and cardiovascular outcomes: REWIND**
Colhoun H (Edinburgh, UK)

14:00–14:40 **Practical considerations of diabetes management**
Chair: Itzhak B (Haifa, Israel)

14:00–14:20 **Primary versus secondary cardiorenal prevention in type 2 diabetes: Which newer antihyperglycaemic drug matters?**
Giugliano D (Naples, Italy)

14:20–14:40 **The important role of primary care in type 2 diabetes with cardiovascular disease – translating latest guidelines into practice**
Cos X (Barcelona, Spain)

14:40–15:20 **Discussion round with experts: Cardio-renal management of diabetes**
Chair: Rydén L (Stockholm, Sweden)

Groop PH (Helsinki, Finland)
Rydén L (Stockholm, Sweden)
Cos X (Barcelona, Spain)
Rodbard H (Rockville, USA)

15:20–15:45 **Coffee break**

15:45–16:45 Industry's perspective – panel discussion

Chair: Schnell O (Munich, Germany)

16:45–17:35 Oral presentations

Chair: Standl E (Munich, Germany)
Valensi P (Paris, France)

16:45–16:55 **Cardiovascular dysfunction in type 1 diabetes: the key functional proteins of the heart as targets for combined treatment with GABA and NAm**
Kuchmerovska T (Kyiv, Ukraine)

16:55–17:05 **Metformin suppresses the senescence-associated secretory phenotype and eIF4e phosphorylation in senescent endothelial cells**
Prattichizzo F (Segrate, Italy)

17:05–17:15 **Empagliflozin leads to a rapid and sustained improvement of diastolic function in patients with type 2 diabetes**
Thiele K (Aachen, Germany)

17:15–17:25 **Predicting the onset of chronic kidney disease in patients with diabetes by electronic health records**
Ringemann C (Mannheim, Germany)

17:25–17:35 **Managing coronary patients with dysglycaemia – a persistent challenge. A report from EUROASPIRE V**
Ferrannini G (Turin, Italy)

17:35–18:15 Poster presentations

Poster session 1:
Clinical studies, epidemiology
Chair: Rodbard H (Rockville, USA)

Poster session 2:
Micro- and macrovascular comorbidities
Chair: Itzhak B (Haifa, Israel)

Poster session 3:
Experimental cardiovascular, renal and metabolic research
Chair: Rydén L (Stockholm, Sweden)

Poster session 4:
Diagnostic approaches, technologies
Chair: Colhoun H (Edinburgh, UK)

Poster session 5:
Treatment approaches
Chair: Standl E (Munich, Germany)

Poster session 6:
Glycaemic variability, clinical aspects
Chair: Valensi P (Paris, France)

18:15–18:30 Abstract award ceremony

OP 1

Cardiovascular dysfunction in type 1 diabetes: the key functional proteins of the heart as targets for combined treatment with GABA and NAm

Kuchmerovska T, Guzyk M, Tykhonenko T, Yanitska L; Kiev, Ukraine

Rationale and objective: Earlier we established that nicotinoyl-GABA can prevent heart dysfunction induced by diabetes (D). It is likely that vascular impairments and key protein dysfunctions may lead to deleterious effects on heart dysfunction. The purpose of the study was to elucidate whether combined treatment with γ-aminobutyric acid (GABA) and nicotinamide (NAm) can affect key functional protein targets on a molecular level in the heart, aiding against diabetes-induced cardiovascular dysfunction.
Methods: Diabetes was evoked by streptozotocin (60 mg/kg) in male Wistar rats. All studies were carried out after 5 months of diabetes induction. GABA (250 µg/kg, b.w., i.p., three times per week) and NAm (100 mg/kg, daily) treatment was started in 2.5 months of D for 5 weeks and in 2 months for 2 weeks, respectively. The levels of investigated proteins in heart tissues were evaluated by Western blot.
Results: In 5 months diabetic animals 24.4 % lost weight, while the blood glucose level was increased by 4.6 compared to control rats (C). Combined (GABA, then NAm) treatment partly alleviated weight loss and lowered blood glucose level by 1.8-fold, $p < 0.05$. Despite, the weight of the heart was decreased by 12.5 % and the ratio of heart to body weight was increased 1.21-fold in diabetic rats, which can be a result of cardiac hypertrophy, $p < 0.05$. Combined treatment normalised this ratio. It was shown that expression of NF-κB was increased 1.7-fold in the heart of diabetic rats as result of this factor activation. Combined treatment of diabetic rats slightly decreased its expression. In spite of vascular endothelial growth factor (VEGF) expression in the heart of diabetic rats being practically similar to that in control rats, the combined treatment of diabetic animals with GABA and NAm led to a decrease of VEGF expression by 80 %, as compared to diabetic animals $p < 0.05$. Total PARP-1 expression levels in the heart of diabetic rats were increased 1.3-fold as compared to C and co-treatment also slightly elevated PARP-1 expression. iNOS expression levels in the heart of diabetic rats were 1.4-fold higher as compared to control rats, and co-treatment did not influence iNOS expression, $p < 0.05$. In heart tissues of diabetic rats the ratio of phosphorylated p38 to total p38 was increased 3.9-fold against control as result of MAPK p38 activation, whereas inhibition was observed at co-treatments by 41.7 % as compared to diabetes, $p < 0.05$. Moreover, these alterations were accompanied by 2-fold elevation of SIRT 2 expression in heart tissues of diabetic rats, however co-treatment did not influence SIRT 2 expression.
Conclusion: These findings suggest that combined (GABA and NAm) treatment can protect heart function through improving key functional protein expression in injured cardiac cells by diabetes.

OP 2

Metformin suppresses the senescence-associated secretory phenotype and eIF4e phosphorylation in senescent endothelial cells

Prattichizzo F, Giuliani A, Mensà E, Matacchione G, De Nigris V, La Sala L, Ceriello A; Milano, Italy

Rationale and objective: Epidemiological and experimental evidence indicates that metformin, the most used antidiabetic drug, affects the aging process at organism level and possibly the senescence process at cellular level. Metformin has a number of demonstrated targets, but its mechanism of action is still debated.
Methods: We explored the effect of metformin treatment in senescent endothelial cells (ECs), focusing on the senescence-associated secretory phenotype (SASP) and the mTOR pathway, two candidate targets of metformin action and master modulators of the aging process.
Results: At pharmacologically pertinent doses (20 µM), one-week treatment with metformin suppresses the SASP and modulates the phosphorylation of the translation factor eIF4e in senescent ECs, without affecting the other arm of the mTOR pathway.
Conclusion: These preliminary findings indicate that metformin suppresses the SASP in senescent ECs in vitro and that this modulation is associated with a decreased phosphorylation of eIF4e.

OP 3

Empagliflozin leads to a rapid and sustained improvement of diastolic function in patients with type 2 diabetes

Thiele K, Rau M, Hartman NUK, Schuh A, Altiok E, Keszei AP, Böhm M, Marx N, Lehrke M; Aachen, Germany

Rationale and objective: In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial) treatment with the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin significantly reduced heart failure hospitalisation (HHF) in patients with type 2 diabetes mellitus (T2D) and established cardiovascular disease. The early separation of the HHF event curves within the first 3 months of the trial suggests that immediate effects of cardiac function may play a role, but to date this has not been firmly investigated. Thus, this study examined early and delayed effects of empagliflozin treatment on echocardiographic measures of cardiac function, including left ventricular systolic and diastolic function.
Methods: In this placebo-controlled, randomised, double blind, exploratory study patients with T2D were randomised to empagliflozin 10 mg/d or placebo for a period of 12 weeks in addition to their concomitant medication. We assessed echocardiographic parameters after 1 day, 3 days and 12 weeks of treatment. Left ventricular systolic function (LV-EF) was measured by Simpson's biplane method. Additionally we performed myocardial deformation analysis of the left ventricle to assess peak global longitudinal strain (GLS) of the endocardial layer. For diastolic function we determined early (E) and late (A) diastolic

mitral inflow velocities, deceleration time (DT), septal early diastolic mitral annular tissue velocity (septal e') and lateral early diastolic mitral annular tissue velocity (lateral e') as well as we calculated E/e' ratio and E/A ratio.
Results: Baseline characteristics were comparable in the empagliflozin (n = 20) and placebo (n = 22) group. Empagliflozin led to a significant increase in urinary glucose excretion (baseline: 7.3 ± 22.7 g/24 h; day 1: 48.4 ± 34.7 g/24 h; p < 0.001) as well as urinary volume (1 740 ± 601 ml/24 h to 2 112 ± 837 ml/24 h; p = 0.011) already after one day compared to placebo. Echocardiography showed no difference in left ventricular systolic function as assessed by left ventricular ejection fraction and strain analysis. However, empagliflozin significantly improved left ventricular diastolic function as assessed by a reduction of early mitral inflow velocity relative to early diastolic left ventricular relaxation (E/e') which became already significant at day 1 of treatment (baseline: 9.2 ± 2.6; day 1: 8.5 ± 2.2; p = 0.005) and remained apparent throughout the study. This was primarily attributable to reduced early mitral inflow velocity E (baseline: 0.8 ± 0.2 m/s; day 1: 0.73 ± 0.2 m/s; p = 0.003).
Conclusion: Empagliflozin treatment of patients with T2D leads to a rapid and sustained significant improvement of diastolic function.

OP 4

Predicting the onset of chronic kidney disease in patients with diabetes by electronic health records

Ringemann C, Ravizza S, Huschto T, Adamov A, Böhm L, Büsser A, Flöther FF, Hinzmann R, König H, McAhren SM, Robertson DH, Schleyer T, Schneidinger B, Petrich W; Mannheim, Germany

Rationale and objective: Traditionally, clinical trials serve as the gold standard to establish medical evidence and guide medical decision making. Nevertheless, it is well known that there is a substantial "efficacy effectiveness gap" between what is seen in clinical trials and what can be observed in routine care. The ever growing amount of medical data from electronic health records (EHRs), as well as the improvements in data analytics offer an opportunity to substantially reduce this gap. To substantiate this claim, we have carried out a comparison between prediction algorithms derived from clinical trial data and from real world data (RWD). Our goal was to build an algorithm that is able to predict the risk of an individual patient to develop chronic kidney disease (CKD) within three years after the initial diabetes diagnosis. CKD was chosen as an example due to its immense medical and economical importance for the healthcare system.
Methods: We extracted longitudinal medical records of 522 416 and 82 912 people with diabetes from the IBM Explorys database and the Indiana Network for Patient Care database (INPC). Diabetes (type 2 and 1) and chronic kidney disease were defined by the appropriate ICD codes contained in the EHRs of individual patients, whereby the date of the first occurrence is marked as the respective disease starting point. The final dataset contained about 300 independent medical features. The Explorys data was randomly split into a teaching set (417 912 people) and a validation set (104 504 people). The patients from the INPC data were used for independent validation. We built a logistic regression model with forward selection for feature reduction.
Results: Using seven prioritised features our algorithm achieves a mean area under the curve (AUC) of 0.794 (0.790–0.797], if applied to both the IBM Explorys database validation set (AUC = 0.761) and to the INPC dataset (AUC = 0.831). There were only minor differences in the prediction performance between patients with type 1 and type 2 diabetes and no discernible gender bias. Including more features into the model yielded only minor improvements in the model performance (e.g. AUC = 0.796 for 12 features). A comparison with algorithms from major clinical trials (ONTARGET, ORIGIN, RENAAL and ADVANCE), while built on a similar subset of features, showed superiority of our algorithm even if applied to only a subcohort of patients mimicking the original cohort of the clinical trial (e.g. AUC = 0.780 [0.767–0.793] vs. AUC = 0.730 [0.715–0.743] for Keane et al.
Conclusion: Based on the comparison with literature algorithm, we conclude that in this particular case algorithms based on real world data achieve a superior performance in predicting the risk of diabetes patients to develop CKD. We speculate that the diverse nature of RWD is the main driver of this difference, but caution that further investigations are necessary before such a statement should be generalised.

OP 5

Managing coronary patients with dysglycaemia – a persistent challenge. A report from EUROASPIRE V

Ferrannini G, de Bacquer D, de Backer G, Kotseva K, Mellbin L, Wood D, Rydén L, on behalf of the EUROSPIRE Investigators; Stockholm, Sweden

Rationale and objective: Dysglycaemia, defined as impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM), is common in patients with coronary artery disease (CAD) and associated with poor prognosis. Data from scientific literature show that this enhanced risk can be reduced if the dysglycaemic state is detected and patients receive multifactorial risk management. Nonetheless, dysglycaemia remains unrecognised in approximately two thirds of coronary patients. To improve cardiovascular prevention, the European Society of Cardiology (ESC) engages in implementation of guidelines and educational programs for patients with dysglycaemia. The aim of the EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) cross-sectional surveys is to describe the European prevention picture in the cardiovascular field by comparing diagnostic and therapeutic strategies to the standards of care established by the guidelines.
Methods: The EUROASPIRE V included 8 261 CAD patients from 27 countries, aged 18–80 years. If the glycaemic state was unknown patients had an oral glucose tolerance test (OGTT)

and HbA_{1c}. Patients were divided in 3 groups: previously known diabetes, newly detected dysglycaemia (including T2DM and IGT) and no dysglycaemia. Cardiovascular risk factors including blood pressure, lipid profile and glucose perturbations were described in the 3 groups. Lifestyle and level of care of patients with known T2DM were investigated, including smoking, physical activity, educational programs and pharmacological treatment.

Results: A total of 2452 (29.7%) patients had known T2DM. Compared to the other 2 groups, they were older, heavier, more sedentary, and with higher proportion of persistent smoking. OGTT was performed in 4440 patients: 45.6% were normoglycaemic and 41.1% dysglycaemic. 30% of patients with newly diagnosed T2DM and 70% of those with newly diagnosed IGT would not have been detected without the OGTT. In all 3 groups, blood pressure and LDL-cholesterol were above the recommended targets. Regarding patients with previously known diabetes, 31% had been advised to attend a diabetes clinic and only 24% attended. 16% were smokers, 88% obese or overweight and 49% sedentary. HbA_{1c} was above the recommended target of 53 mmol/mol (7.0%) in 55%. 92% were prescribed ASA, 83% beta blockers, 81% RAAS blockers and 84% statins; all 4 cardioprotective drugs were prescribed in 58%. The use of novel glucose-lowering agents was small.

Conclusion: Screening for dysglycaemia is poorly practiced in CAD patients despite clear guideline recommendations. The achievement of guideline recommended life-style and pharmacological management is unacceptably scarce considering their higher cardiovascular risk. There is an obvious need for improvement with regards to both screening and management, in the expectation of a reduced risk of further cardiovascular events, complications of diabetes and a longer life expectancy.

Grant: The EUROASPIRE V was carried out under the auspices of the European Society of Cardiology, EURObservational Research Programme. The survey was supported by research grants to the European Society of Cardiology from Amgen, Eli Lilly, Sanofi (Gold Sponsors), Pfizer (Silver Sponsor), and Ferrer and Novo Nordisk (Bronze Sponsors). The sponsors of the EUROASPIRE surveys had no role in the design, data collection, data analysis, data interpretation, decision to publish, or writing the manuscript.

PS 1: Clinical studies, epidemiology

P 01

Renal function and cognition in patients with type 2 diabetes mellitus at elevated cardiovascular risk: the CARMELINA® and CAROLINA® cognition substudies

Verhagen C, Janssen J, Minderhoud CA, van den Berg E, Wanner C, Passera A, Schnaidt SY, Johansen OE, Biessels GJ; Utrecht, Netherlands

Rationale and objective: Type 2 diabetes (T2D) is associated with impaired renal as well as cognitive functioning. Both of these diabetic complications may be due to microvascular changes and might even be interrelated. We assessed the relationship between renal function and cognitive performance in a population of T2D patients at elevated cardiovascular risk.
Methods: The cognitive substudies were integral parts of CARMELINA® (NCT01897532) that studied patients with advanced T2D and cardio-renal complications, and CAROLINA® (NCT01243424) that studied patients with relatively early T2D with risk factors for, or established, cardiovascular disease. Both assessed the effect of linagliptin versus comparators on accelerated cognitive decline. In the current research, baseline estimated glomerular filtration rate (eGFR) was related, in a post hoc analysis, to cognitive performance at baseline, assessed by Mini-Mental State Exam (MMSE), and a composite of the Trail Making Test (TMT) and Verbal Fluency Test (VFT), reflecting attention and executive functioning (A&E score).
Results: The cognition substudy of CARMELINA included 2 694 participants (mean ± SD: age: 68.1 ± 8.7 years, T2D duration: 15.5 ± 9.6 years) with impaired renal function (eGFR: 49.5 ± 22.1 ml/min/1.73 m^2) and CAROLINA 4 529 participants (age: 75.8 ± 19.2 years, T2D duration: 7.8 ± 6.2 years). Participants in CAROLINA had better preserved renal function (eGFR: 75.8 ± 19.2 ml/min/1.73 m^2) than those in CARMELINA. In CARMELINA, linear regression analyses revealed that eGFR was related to baseline A&E score (b = 0.03 per 10 points, 95 % CI 0.02 – 0.04, p < 0.0001). Also a relationship between eGFR and baseline MMSE was found (b = 0.10 per 10 points, 95 % CI 0.05 – 0.16, p = 0.0002), but this attenuated after adjusting for demographic factors. In CAROLINA, positive associations at baseline were also found between eGFR and cognition (A&E: b = 0.02 per 10 points, 95 % CI 0.004 – 0.027, p = 0.010, MMSE: b = 0.06 per 10 points, 95 % CI 0.02 – 0.10, p = 0.005). All associations attenuated after adjusting for demographic factors.
Conclusion: The CARMELINA and CAROLINA cognition studies found that impaired renal functioning is associated with impaired cognition in T2D, and underscores that measures to preserve cognition should in particular be prioritised in this group.

P 02

The 2-hour glucose tolerance test (GTT) and its parameter change may show cardiovascular morbidity and mortality in 10 years in primary care

Peceliuniene J, Zukauskaite I, Kazlauskiene L, Norkus A, Butnoriene J; Vilnius, Lithuania

Rationale and objective: The 2-hour GTT is considered the most accurate and functional test for type 2 diabetes diagnosis for the majority of clinicians. The progressive relationship between glucose levels and cardiovascular risk extends below the diabetic threshold, but little is known about the change between the first and the second GTT parameter, and its relation to cardiovascular events and deaths. The aim of the study was to evaluate cardiovascular morbidity and mortality in relation to GTT results and its change in 10 years follow-up in primary care (PC).
Methods: The study analysed data from 1 082 PC patients – 551 men and 531 women. Mean age was 63.11 years (SD = 9.59). There was no difference in age between males and females (p > 0.05). Patients were subjected to a standard 2-hour GTT procedure with 75.0 grams of oral glucose. A glucose level below 6.1 mmol/l at fasting and 7.8 mmol/l in 2 hours were considered as normal. In addition, the difference between the second GTT hour result and fasting glucose result was calculated. Patients' cardiovascular events and/or deaths were assessed in 10 years follow-up. Chi square, ANOVA, Pearson correlation coefficient were used to analyse the results.
Results: Patients were divided into 3 groups based on their baseline GTT data – alive and without cardiovascular events (w/o CV) (N = 754), non-survivors, those who died before the end of the follow-up phase (NSv) (N = 228), and those who experienced cardiovascular events during the analysis' period and remained alive (CV) (N = 100). 72.8 % of w/o CV had normal GTT, as well as 74.1 % in the NSv group and 62.0 % of CV patients (p = 0.057). The mean fasting glucose scores for all GTT groups were within the norm, although differences between groups were found in 2 hours: baseline of GTT in w/o CV group – M = 5.57 mmol/l, in NSv group – M = 5.79 mmol/l and M = 5.67 mmol/l in CV group (p = 0.019), with the second hour result M = 6.32 mmol/l, M = 7.16 mmol/l and M = 6.52 mmol/l, respectively (p < 0.001). Moreover, comparing the change in GTT measurements between groups, a statistically significant difference was found: the mean change was M = 0.81 in w/o CV group, M = 0.94 in CV group and M = 1.37 in the NSv group, p = 0.002. While interpreting these results it should be taken into account that the age differences between groups were found: w/o CV patients were younger, M = 61.11 years, compared to CV group patients, M = 64.87 years, and NSv group, M = 68.32 years, p < 0.001. The estimated correlation coefficient showed that the older the age, the greater the variation in GTT measurements between first and second parameters (r = 0.213, p < 0.001).
Conclusion: The evaluation of change in GTT parameters' results, not only GTT norms, may help to explain cardiovascular morbidity and mortality in primary care in 10 years. Cardiovascular PC patients have 10 % less frequent the rate of normal glucose results, evaluated by GTT, but those with higher glucose

values' change between the first and the second GTT measurement are more likely to die.

P 03

Diabetes mellitus as a risk factor for multivessel atherosclerotic disease

Begic E, Dzubur A, Mekic M, Begic N, Dzubur A; Sarajevo, Bosnia and Herzegovina

Rationale and objective: The aim of this study is to determine the frequency and impact of diabetes mellitus (DM) in the occurrence of multivessel atherosclerotic disease in patients with changes in two or more vascular pools, and to compare them with patients with coronary disease.
Methods: Patients with documented atherosclerotic disease localised at the carotid, coronary and peripheral blood vessels were included in the study. The first group consisted of 40 patients with documented atherosclerotic changes in the coronary vascular pool (COR group).
The second group consisted of 40 patients with documented atherosclerotic changes in the carotid and iliac-femoral vascular pool (CAR-IF group). The third group consisted of 40 patients with documented atherosclerotic changes in the coronary and iliac-femoral vascular pool (COR-IF group). The fourth group consisted of 40 patients with documented atherosclerotic changes in the coronary, carotid and iliac-femoral vascular pool (COR-CAR-IF group). Inclusion criteria for the study were proven atherosclerotic disease of coronary vessels, proven atherosclerotic disease of iliac-femoral and carotid blood vessels.
Results: The largest percentage of respondents with diabetes mellitus was in the COR-CAR-IF group (77.5 %), and the difference between the prevalence of diabetics in this group and other groups was statistically significant ($p < 0.05$). In terms of gender, the largest proportion of male (76.1 %) and female (84.2 %) diabetic subjects belonged to the COR-CAR-IF group. There was a statistically significant difference in the prevalence of diabetics of both genders in the COR-CAR-IF group compared to the other groups ($p < 0.05$). The highest percentage of diabetics younger than 59 years (100 %) belonged to the COR group, with a statistically significant difference ($p < 0.05$). The highest percentage of diabetics over the age of 59 (93.5 %) was in the COR-CAR-IF group and a statistically significant difference was found in the prevalence of diabetics in this group compared to other groups of subjects ($p < 0.05$).
The analysis of correlation coefficients verified that the age of the subjects was not related to fasting blood glucose measured on the day of the examination for COR ($r = -0.12$, $p > 0.05$), CAR-IF ($r = 0.23$, $p > 0.05$), COR-IF ($r = 1.56$, $p > 0.05$) and COR-CAF-IF ($r = 3.4$, $p > 0.05$). DM was significantly more common in men in the COR, CAR-IF, and COR-IF groups. Subjects in the COR group were less likely to be over 59 years of age (OR 0.062; 95 % CI 0.018–0.22) and less likely to have DM (OR 0.076; 95 % CI 0.017–0.34) than subjects in the COR-IF group, CAR-IF and COR-CAR-IF groups.
Conclusion: Prevalence of atherosclerotic process is correlated with DM. With increasing age in diabetics, the prevalence of the atherosclerotic process increases. The occurrence of an atherosclerotic process in the coronary vascular pool is more common in younger patients, and then DM is the rarest.

P 04

A cross sectional study for risk factors and preventive measures among patients presenting to a cardiac centre

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Rationale and objective: Cardiovascular disease is highly prevalent and in spite of advances in treatment, the outcome still does not reflect these improvements in intervention. Prevention of risk factors has been more successful and with availability of educational material it is expected that patients will become more knowledgeable.
Methods: A cross sectional study among patients presenting to a cardiac center was conducted.
Results: 350 participants were included, both diabetic and non-DMs. 51 % were males with a mean age of 49 years. 30 % of both groups were hypertensive and 24 % were aware of being hyperlipidaemic. 40 % were overweight. Of these, 45 % had no previous education regarding diabetes mellitus, 34 % were unaware of the complications of diabetes. 56 % were not following a diet, 52 % not controlling diabetes to avoid its complications. 47 % of participants did not perform any physical activity. 41 % reported that physicians did not provide appropriate education, half of the sample believed that the media was not providing appropriate education.
Conclusion: There is a significant gap in the public's knowledge of diabetic risk factors, how to control them and possible lifestyle changes required. Information from physicians or the media is far below patient expectations. A combined effort that starts in schools and is continued by government authorities is needed to decrease cardiovascular burden.

P 05

Prevalence and risk factors of type 2 diabetes in a female population in Oujda, eastern Morocco: preliminary results

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Rationale and objective: Due to longer life expectancy and increased exposure to risk factors (tobacco, alcohol, sedentary lifestyle, precariousness), chronic non-communicable diseases (NCDs) are increasing worldwide and account for 75 % of years lived with disabilities and more than 59 % of deaths. The four main types of NCDs are cardiovascular diseases, cancers, chronic respiratory diseases and diabetes. All these serious pathologies require highly qualitative and multidisciplinary care. The objective of this research is to determine the prevalence and risk factors that predispose to diabetes mellitus in rural and urban areas of Oujda Angad prefecture in eastern Morocco.
Methods: This is a cross-sectional study conducted between March and August 2019 and which involved a sample of 290 patients, aged 18 and over, followed

at 14 health centers spread across the entire territory of the Oujda Angad prefecture. Cluster sampling was applied to select only 14 centers out of 35 health facilities. The data were collected using three questionnaires relating to three key areas: socio-economic and demographic, physical activity (IPAQ) and nutrition. The data were exploited and analysed on the spss25 software.

Results: The study population, 74 % of whom were from rural areas, was characterised by a high unemployment rate (79 % without a job), 44 % had more than five children and 71 % had only a RAMED medical coverage. The sex ratio was in favour of women with 4.7, that were 82 % women ($p < 0.05$). The most dominant age group was 45–55 years old with 27 % followed by the 55–65 age group with 21 % and the 35–45 age group with 17 %. More than half of the study population were out of school (54 %). In terms of BMI, this population was characterised by a clear dominance of obesity, a very important risk factor in type 2 diabetes. In fact, the results show that more than one third of the population was obese (37 %), of which 16 % suffered from morbid obesity, 22 % from severe obesity and 62 % from moderate obesity. Of the remaining 63 %, 31 % were overweight.

Referring to TT/TH, 59 % of patients had high coronary risk, 10 % moderate and 12 % low. Of the population studied, 17 % were hypertensive and 10 % were type 2 diabetics. In detail, the number of women with diabetes was 19 or 8 % of the female population with 8 newly detected cases. Among the old diabetic cases, 9 women were hypertensive, 3 had developed diabetic retinopathy and 4 had cardiovascular complications. In men, 17 % were obese, 6.6 % were diabetic and 15 % were hypertensive. Our results demonstrate that type 2 diabetes seems to be associated with a lack of physical activity, a lack of regular monitoring blood glucose and a lack of a healthy balanced diet.

Conclusion: Patients followed at the health centers in Oujda Angad prefecture in eastern Morocco constitute a socio-economic vulnerable population with an increased risk for type 2 diabetes and obesity. Diabetes treatment programs in this region should target those who are most exposed to risk factors for type 2 diabetes and obesity, such as poor and elderly people, through the establishment of a multidisciplinary program based on a healthy lifestyle.

P 06

Diabetes and hypertension: epidemiology and treatment reality in a public health care center in rural Brazil

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Rationale and objective: In developing countries – here exemplified by a rural area in Brazil – hypertension and diabetes are becoming increasingly important, but health care systems focus on acute conditions. Strategies to improve disease awareness are suggested to improve outcome despite limitations imposed by socio-economic conditions.

Methods: Records of 988 patient consultations of a public primary health care center in Guaramiranga, a rural community in northeastern Brazil, were analysed from January to August 2019 to assess importance of diabetes and hypertension as well as treatment challenges in this developing-world setting.

Results: 31.2 % of consultations were due to alterations of blood pressure and/or blood glucose. (Other consultations: acute disorders and trauma 37.9 %, screening and prenatal exams 14.8 %, tropical diseases 12.9 % and other chronic diseases 34.4 %). A total of 144 patients with hypertension (68 %), diabetes (6 %) and a combination of both (26 %) were identified. Mean age of these patients was 61.8 years; 67 % were female, 33 % male. Based on an estimated population of 1 000, the prevalence of diabetes is calculated to be between 4.5 and 7.2 %, and that of hypertension between 13.6 and 22 %. Drugs prescribed were generally those provided by the public health care system: for hypertension, 69 % of patients received hydrochlorothiazide, 40 % enalapril or captopril, 39 % losartan, 31 % propranolol, atenolol or metoprolol, 21 % amlodipine, and 6 % other drugs. For diabetes: 77 % metformin, 54 % glibenclamide, 46 % NPH insulin and 12 % regular insulin. No other or newer drugs were available for diabetes treatment. Only 14 % of diabetes patients reported blood glucose self-monitoring, and within the past year, an HbA_{1c} value was registered for only 22 %. In any given month, at least one drug class for treatment of hypertension and at least one drug class for diabetes was not available for dispensation within the public health system, and patients routinely reported not having sufficient resources to buy medication. Dosage adjustments generally had to be based on glucose controls during consultations at the health care center, averaging 4 times per patient per year.

Conclusion: Guidelines published in Brazil by the central government and by professional societies mirror European and North American ones and foresee regular laboratory and specialist consultations. However, chronic underfunding, especially in remote, resource-poor areas and at the municipal level of the public health care system translates into few examinations for disease monitoring and early detection and treatment of complications. Despite a campaign for laboratory values for assessment of cardiovascular risk in 2018, priority for blood sampling was given to pregnant patients, acute conditions and planned surgeries. Various other factors contribute to lack of attention given to diabetes and hypertension. Official figures for Brazil show a doctor density less than half that of most European countries. Globally, the official figure is less than 2 doctors per 1 000 inhabitants with a concentration in urban centers. Residents of rural communities in Brazil frequently face problems with lack of water in the dry season, unsatisfactory or nonexistent water and sewage treatment, and long distances to urban centers. Functional illiteracy is about 30 %. Efforts of the health care system focus on infant mortality and acute conditions. In light of the importance of chronic conditions and lack of resources, the most promising strategy to improve patient outcome appears to be the focus on education and disease awareness. For this purpose, an information and guidance campaign is proposed.

PS 2: Micro- and macrovascular comorbidities

P 07

The state of lipid, carbohydrate metabolism and function of cardiovascular system of patients with non-alcoholic fatty liver disease, overweight and obesity

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Rationale and objective: NAFLD is considered one of the manifestations of the metabolic syndrome. The aim of the study is to determine the relationship between insulin resistance and laboratory-instrumental signs of liver damage in patients with NAFLD.
Methods: We examined 168 patients with NAFLD. The diagnosis of NAFLD was made according to the recommendations of EASL, EASD, EASO 2016. Anthropometric parameters were measured in all patients, ultrasound of the liver was performed, cytolysis and cholestasis markers, lipid metabolism indicators were determined. Glucose, insulin and C-peptide levels were evaluated on an empty stomach and after 2 hours. The presence of insulin resistance was established by the level of the HOMA index. Correlation analysis was used to identify the correlation between different indicators with the calculation of the correlation coefficient (r) and its reliability (Pearson test and Spearman test). The statistical significance level was assumed to be $p < 0.05$.
Results: Among NAFLD patients, 27 % were diagnosed with non-alcoholic steatohepatitis. In 14.7 % of patients BMI values corresponded to excess body weight ($25 < BMI < 30\ kg/m^2$); in 39.7 % of patients obesity of degree I was ascertained, in 27.9 % the obesity of degree II and in 17.6 % degree III. The character of fat distribution corresponded to abdominal obesity. 23 % of patients had a history of coronary heart disease less than 10 years ago; more than 10 years ago in 11 % of patients, a history of myocardial infarction was present in 2 % of patients. Arterial hypertension was detected in 59 % of patients. At the same time, most patients had hypertension of degree II. Disorders of lipoprotein metabolism were detected in 51 patients examined. Hypertriglyceridaemia was more commonly reported, serum total cholesterol concentrations > 5.2 mmol/l were less frequently observed. The atherogenic coefficient was 3.5 units, indicating that there is a high probability of developing atherosclerosis and coronary heart disease. Disorders of carbohydrate metabolism were detected in more than half of patients with NAFLD, including more than 20 % of them with type 2 diabetes. The data obtained indicate that the mean fasting glycaemia in the patients we examined was increased. At the same time, they were characterised by high levels of insulin and C-peptide. A direct significant correlation was found between insulinaemia and body mass index ($r = 0.48$; $P < 0.05$), waist circumference ($r = 0.43$; $P < 0.05$), HOMA index ($r = 0.95$; $P < 0.05$) and serum C-peptide concentration ($r = 0.80$; $P < 0.05$). Serum C-peptide concentration correlated directly with body mass index ($r = 0.41$; $P < 0.05$), waist circumference ($r = 0.38$; $P < 0.05$), mean AT ($r = 0.40$; $P < 0.05$), HOMA index ($r = 0.40$; $p < 0.05$), insulinaemia ($r = 0.80$, $P < 0.05$), and fasting glycaemia ($r = 0.44$; $p < 0.05$). Correlation analysis showed that the left ventricular ejection fraction ($r = -0.43$; $P < 0.05$) and the left ventricular myocardial mass index ($r = -0.40$; $P < 0.05$) had an inverse correlation with the age of the patients. According to the instrumental examination, the dependence of the size of the left atrium, the thickness of the posterior wall of the left ventricle and the thickness of the interventricular septum on the degree of obesity were revealed. Also, the presence of diastolic dysfunction was revealed.
Conclusion: The most prognostically significant risk factors affecting the outcomes of NAFLD are the degree of obesity, the presence of coronary heart disease, the HOMA index value and HDL cholesterol levels.

P 08

Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction – the EMMY trial

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Rationale and objective: Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are established antidiabetic drugs with proven cardiovascular benefit. Although growing evidence suggests beneficial effects on myocardial remodelling, fluid balance and cardiac function, the impact of empagliflozin initiated early after acute myocardial infarction (AMI) has not been investigated yet. Therefore, the impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction (EMMY) trial was designed to investigate the efficacy and safety of empagliflozin in diabetic and non-diabetic patients after severe AMI.
Methods: Within a multicentre, national, randomised, double-blind, placebo-controlled, phase 3b trial we will enrol patients with AMI and characteristics suggestive of severe myocardial necrosis are randomised in a 1 : 1 ratio to empagliflozin (10 mg once daily) or matching placebo. The primary endpoint is the impact of empagliflozin on changes in NT-proBNP within 6 months after AMI. Secondary endpoints include changes in echocardiographic parameters, levels of ketone body concentrations, HbA_{1c} levels and body weight, respectively. Hospitalisation rate due to heart failure or other causes, the duration of hospital stay and all-cause mortality will be assessed as exploratory secondary endpoints.
Results: Results will provide the rationale for the conduct of a cardiovascular outcome trial to test the effect of empagliflozin in patients with AMI.
Conclusion: The EMMY trial will test empagliflozin in patients with AMI regardless of their diabetic status. The EMMY trial may therefore underpin the concept of SGLT-2 inhibition to improve cardiac remodelling, pre- and afterload reduction and cardiac metabolism regardless of its antidiabetic effects.

Grant: The EMMY study is funded by an unrestricted investigator initiated trial grant from Boehringer Ingelheim.

P 09

Acute effects of empagliflozin on hemodynamic parameters in patients with type 2 diabetes

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Rationale and objective: In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial) treatment with the sodium-glucose cotransporter-2 (SGLT-2) inhibitor empagliflozin significantly reduced heart failure hospitalisation (HHF) in patients with type 2 diabetes mellitus (T2D). The early separation of the HHF event curves within the first 3 months of the trial suggest that immediate hemodynamic effects may play a role. However, hitherto no data exist on early effects of SGLT-2 inhibitors on hemodynamic parameters. Thus, this study examined early and delayed effects of empagliflozin treatment on hemodynamic parameters including systemic vascular resistance index (SVRI), cardiac index (CI), stroke volume index (SVI), and pulse rate (PR).
Methods: In this prospective, placebo-controlled, double-blind, randomised, 2-arm parallel, interventional and exploratory study 44 patients with T2D were randomised into 2 groups and received empagliflozin 10 mg or placebo for a period of 3 months in addition to their concomitant medication. We used ClearSight System® (Edwards Lifesciences, Irvine, USA) as a validated non-invasive tool (pulse contour analysis) to examine the effects of empagliflozin on hemodynamic parameters including SVRI, CI, SVI, and PR after 1 day, 3 days and 3 months of treatment.
Results: Baseline characteristics were comparable in the empagliflozin (n = 20) and placebo (n = 22) group. Empagliflozin led to a significant increase in urinary glucose excretion (baseline: 7.3 ± 22.7 g/24 h; day 1: 48.4 ± 34.7 g/24 h, p < 0.001) as well as urinary volume (1 740 ± 601 ml/24 h to 2 112 ± 837 ml/24 h, p = 0.011) already after one day compared to placebo. Treatment with empagliflozin had no effect on the primary endpoint of SVRI (baseline: 1 841 ± 379 dyn * s * cm^{-5} * m^{-2}; day 1: 1 864 ± 373 dyn * s * cm^{-5} * m^{-2}, p = 0.411; day 3: 1 837 ± 376 dyn * s * cm^{-5} * m^{-2}, p = 0.991; month 3: 1 908 ± 451 dyn * s * cm^{-5} * m^{-2}, p = 0.795), nor on CI, SVI or PR at any time point. Over time, blood pressure was reduced in empagliflozin-treated participants but the effect did not reach statistical significance.
Conclusion: Empagliflozin treatment of patients with T2D has no significant effect on hemodynamic parameters after 1 or 3 days, nor after 3 months.

P 10

The role of insulin resistance, endothelial dysfunction and systemic inflammation in the development of vascular complications in patients with NAFLD

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Rationale and objective: Insulin resistance is a key pathogenic factor for type 2 diabetes and NAFLD. The presence of NAFLD increases the risk of developing diabetes type 2 twofold over five years. A large number of studies confirm the relationship between NAFLD and the frequency of cardiovascular events and death. Patients with NAFLD have a high risk of both coronary heart disease and stroke, but the mechanisms are not fully understood yet. Objective was to determine the relationship between systemic inflammation, endothelial dysfunction, and insulin resistance as causes of cardiovascular complications in NAFLD patients.
Methods: The study involved 182 NAFLD patients, normal, overweight, and obese. There were 69 patients in the control group. The stratification of cardiovascular risk was carried by traditional SCORE scale version for countries with high risk. The cognitive deficit was determined using a questionnaire. We determined the level of inflammatory mediators (TNF-α, IL-1, IL-6), markers (C-reactive protein, fibrinogen), endothelin (ET-1), the activity of the Willebrand factor (vWF), the thickness of the intima-media complex, presence atherosclerotic plaque and stenosis of the carotid arteries, and index HOMA-IR for all examined patients. The anthropometric survey, measured levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), the degree of liver fibrosis using elastography (FibroScan), ECG, and echocardiography were conducted.
Results: The patients with NAFLD by obesity showed a reduction in endothelium-dependent vasodilation, indicating the presence of endothelial dysfunction. The concentration of pro-inflammatory cytokines such as TNF-α and IL-6 in patients with NAFLD was 3–7 times higher than the parameters of patients with a similar degree of obesity but without evidence NAFLD. The concentration of ET-1 in the blood plasma of patients with NAFLD has a strong direct correlation with the degree of cardiovascular risk and cognitive deficit in surveyed patients. It is found that many inflammatory mediators (TNF-α, IL-1, IL-6) and markers (C-reactive protein, fibrinogen) highly correlate with the degree of obesity, the concentration of ET-1, vWF and markers of insulin resistance, a predictor for cardiovascular risk.
Conclusion: Endothelial dysfunction in patients with NAFLD contributes to myocardial remodelling and cognitive deficit. Disturbance of endothelium-dependent vasodilation, presence of insulin resistance and high levels of inflammatory mediators are highly correlated with the degree of cerebro- and cardiovascular risk.

P 11

Diabetic microvascular complications in patients with a good glycaemic status and an extremely high lipoprotein(a)

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Rationale and objective: Elevated lipoprotein(a) (Lp(a)) level is a risk factor (RF) for a cardiovascular (CV) disease and has often been considered as a non-modifiable CVRF. An extremely high level of Lp(a) > 150 mg/dl is rare. However, the relationship between Lp(a) and microvascular complication in diabetics with good glycaemic status is unclear.
Methods: Lp(a) levels were measured in 52 898 consecutive patients (pts) who

were admitted to a large cardiovascular and diabetes center. In this population we found 580 pts with Lp(a) > 150 mg/dl. We selected all patients > 18 years with diabetes and HbA_{1c} 6.5–7.5 % and reviewed their diabetes microvascular complications (nephropathy, polyneuropathy and retinopathy). As a control group (c-group) we randomised all diabetics with Lp(a) < 30 mg/dl and HbA_{1c} 6.5–7.5 %.
Results: We found 43 pts with HbA_{1c} 6.5 – 7.5 % and Lp(a) > 150 mg/dl. The duration of diabetes was 9.95 ± 8.41 years (Lp(a) > 150 mg/dl) vs. 10.65 ± 10.03 years (c-group). Diabetic nephropathy has been found in 67.44 % (n = 27) pts with Lp(a) > 150 mg/dl, respectively 41.86 % (n = 18) in c-group. 48.84 % (n = 21) pts with Lp(a) > 150 mg/dl had diabetic polyneuropathy vs. 34.88 % (n = 15), and 34.88 % (n = 15) pts with Lp(a) > 150 mg/dl had diabetic retinopathy vs. 18.6 % (n = 8) in c-group.
Conclusion: Even in a good glycaemic status, diabetics with extremely high Lp(a) may be at high risk of diabetic microvascular complications. Further studies with larger patient collective are needed.

P 12

Benfotiamine and alpha-lipoic acid in the treatment of diabetic cardiovascular autonomic neuropathy

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Rationale and objective: Diabetic cardiovascular autonomic neuropathy (CAN) can affect the daily activities of patients and may invoke life-threatening outcomes. This study aims to analyse the effects of benfotiamine (BFT) and alpha-lipoic acid (ALA) on lipid metabolism and insulin concentration, some markers of chronic inflammation in patients with type 2 diabetes mellitus (T2DM) and definite stage of CAN.
Methods: The study involved 60 patients with T2DM and definite CAN, aged between 50 and 59 yrs, with T2DM duration 1–6 yrs, glycated hemoglobin (HbA_{1c}) 7.1 ± 0.6 %. Patients were comparable in sex, age, BMI and treatment. The study was carried out on four separate arms: traditional glucose-lowering therapy (group A, n = 15, control); patients from group B (n = 15) additionally were prescribed BFT 300 mg/d; group C (n = 15) – ALA (thioctic acid) 600 mg in film-coated tablets/q.d., and group D (n = 15) – BFT 300 mg and ALA 600 mg in film-coated tablets/q.d. The duration of the study was 3 months. We investigated levels of HbA_{1c}, lipid profile, immunoreactive insulin (IRI), tumor necrosis factor alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP). Statistics: ANOVA.
Results: We found that HbA_{1c} was not significantly influenced by the treatment ($p > 0.05$). BFT prescription did not cause significant changes in lipid profile ($p > 0.05$), while it probably helped to reduce IRI (26.7 ± 1.39 mclU/ml [before treatment] and 23.3 ± 0.88 mclU/ml [after treatment], $p < 0.05$), hs-CRP (2.97 ± 0.17 mg/l [before] and 2.51 ± 0.11 mg/l [after], $p < 0.05$), and TNF-α (5.4 ± 0.23 pg/ml [before] and 4.7 ± 0.13 pg/ml [after], $p < 0.05$). Administration of ALA contributed to a significant decrease of lRI (26.6 ± 1.3 mclU/ml [before] and 22.1 ± 0.96 mclU/ml [after], $p < 0.01$), hs-CRP (2.95 ± 0.2 mg/l [before] and 2.42 ± 0.11 mg/l [after], $p < 0.05$), and TNF-α (5.71 ± 0.2 pg/ml [before] and 4.83 ± 0.12 pg/ml [after], $p < 0.001$]; total cholesterol (TC) (6.3 ± 0.39 mmol/l [before] and 5.32 ± 0.3 mmol/l [after], $p < 0.05$), low-density lipoprotein (LDL)-C (LDL-C) (4.1 ± 0.32 mmol/l [before] and 3.2 ± 0.24 mmol/l [after], $p < 0.05$], high-density lipoprotein (HDL)-C (0.75 ± 0.04 mmol/l [before] and 0.9 ± 0.06 mmol/l [after], $p < 0.05$). The combined prescription of BFT and ALA was accompanied by a more pronounced decrease in the IRI (26.3 ± 1.41 mclU/ml [before] and 20.1 ± 1.25 mclU/ml [after], $p < 0.001$), hs-CRP (2.89 ± 0.16 mg/l [before] and 2.31 ± 0.14 mg/l [after], $p < 0.01$), TNF-α (5.64 ± 0.21 pg/ml [before] and 4.72 ± 0.18 pg/ml [after], $p < 0.001$), TC (6.19 ± 0.4 mmol/l [before] and 5.03 ± 0.3 mmol/l [after], $p < 0.01$), LDL-C (4.16 ± 0.31 mmol/l [before] and 3.29 ± 0.26 mmol/l [after], $p < 0.01$), a significantly more marked increase in the HDL-C (0.71 ± 0.05 mmol/l [before] and 0.92 ± 0.04 mmol/l [after], $p < 0.001$).
Conclusion: The administration of BFT and ALA for 3 months promotes the reduction of IRI, chronic inflammation markers concentration, reduction of lipids disorders that allows to recommend this combination to patients with T2DM and definite stage of CAN.

P 13

Effect of alpha-lipoic acid on the arterial stiffness and insulin resistance parameters in type 2 diabetes mellitus patients with cardiovascular autonomic neuropathy

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Rationale and objective: Cardiovascular autonomic neuropathy (CAN) in type 2 diabetes mellitus (T2DM) is one of the independent risk factors for cardiovascular mortality. In this study the influence of alpha-lipoic acid (ALA) on the glycaemic control, the state of arterial stiffness parameters and insulin resistance (IR) in patients with T2DM and definite stage of CAN was studied.
Methods: 36 patients with T2DM and definite stage of CAN, aged between 50 and 59 yrs, with disease duration between 1 and 6 yrs and glycated hemoglobin A_{1c} (HbA_{1c}) level of 6.98 ± 0.15 %, were involved. The study was carried out on two separate arms: traditional glucose-lowering therapy (group A, n = 18, control). Patients from group B (n = 18) additionally were prescribed ALA (thioctic acid) 600 mg in film-coated tablets/q.d. The duration of the study was 3 months. We investigated the level of glucose, HbA_{1c}, immunoreactive insulin (IRI) and homeostasis model assessment (HOMA)-IR (HOMA-IR). Artery stiffness parameters were assessed using the device TensioMed™ Arteriograph (monitor "ABPM-04" ["Meditech", Hungary]) (TensioClinic TensioMed™). We investigated the following parameters: aorta augmentation index (AIxao), brachial augmentation index (AIxbr) and pulse wave velocity (PWV). All tests were performed using the ANOVA (MicroCal Origin v. 8.0) software. Statistical significance was set at $p < 0.05$.
Results: The level of HbA_{1c} in patients with T2DM and definite stage of CAN

did not change significantly after treatment ($p > 0.05$). Prescription of ALA was accompanied by statistically significant reduction in pre-prandial glycaemia (6.68 ± 0.22 mmol/l [before treatment] and 6.01 ± 0.24 mmol/l [after treatment], $p < 0.05$), IRI levels (26.62 ± 1.31 mcIU/ml [before] and 22.17 ± 0.97 mcIU/ml [after], $p < 0.01$) and HOMA-IR parameters (7.9 ± 0.55 [before] and 6.04 ± 0.48 [after], $p < 0.05$). Investigated parameters did not change significantly in group A. ALA prescription to patients with T2DM and definitive stage of CAN contributes to a statistically significant reduction in AIxao (29.8 ± 1.54 % [before] and 24.7 ± 1.17 % [after], $p < 0.05$) and PWV (10.1 ± 0.4 m/s [before] and 8.9 ± 0.34 m/s [after], $p < 0.05$) during active period of day; PWV (10.6 ± 0.39 m/s [before] and 9.4 ± 0.33 m/s [after], $p < 0.01$), AIxao (33.6 ± 1.27 % [before] and 28.6 ± 1.37 %, [after], $p < 0.05$) and AIxbr (–7.8 ± 2.17 % [before] and –12.4 ± 2.29 % [after], $p < 0.05$] during the passive period of day. Investigated parameters did not change significantly in group A.

Conclusion: The combination of the positive effects of ALA on glucose, IRI content, HOMA-IR, and artery stiffness parameters demonstrate the feasibility of its administration in the complex treatment of diabetic CAN. However, further randomised, double-blind, placebo-controlled trials of larger scale are needed; doses and duration may provide evidence for the hidden therapeutic capacity of ALA and its potential properties for other diabetic complications such as diabetic CAN.

PS 3: Experimental cardiovascular, renal and metabolic research

P 14

Evaluation of antioxidant treatment for early diabetic kidney disease using contrast-enhanced ultrasound

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Rationale and objective: Diabetes mellitus is the leading cause of diabetic kidney disease in which oxidative stress has been implicated. However, the effect of antioxidant supplementation in preventing or slowing end-stage renal disease in patients with diabetes has failed to show conclusive benefits. Possible reasons behind this could be that very early diabetic kidney disease cannot routinely be detected by currently used biomarkers. The aim of this study was to test whether modification of oxidative stress status using antioxidant treatment improves kidney blood flow using contrast-enhanced ultrasound (CEUS).

Methods: We studied type 2 diabetic patients at high risk of progressive kidney disease. Patients were randomised to receive either vitamin E and/or selenium (n = 6) versus placebo (n = 3). Scans at baseline and at three months follow-up were performed for both kidneys after intravenous bolus injection of 1 ml SonoVue®. Time-intensity curves (TICs) and quantitative indexes such as the derived peak intensity, the time to peak (TTP), the ascending slope, and the areas under the ascending and descending curves (AUC1 and AUC2) were calculated for both the renal cortex and medulla.

Results: The patients' treatment groups at baseline had similar age, BMI, duration of diabetes, HbA_{1c}, systolic and diastolic blood pressure, estimated GFR (58.67 ± 10.6 vs. 66.33 ± 8.89 years; 31.8 ± 2.8 vs. 33.2 ±5.4 kg/m^2; 18.3 ± 7.0 vs. 12.17 ± 6.9 years; 64 ± 32.9 vs. 60.5 ± 20.2 mmol/mol; 144.7 ± 7.3 vs. 144.8 ± 13.9 mmHg; 81.0 vs. 78.5 mmHg; 95 ± 14.7 vs. 80.3 ± 22.2 ml/min/1.73 m^2, respectively). Also, the patient groups had similar plasma glutathione peroxidase activity, and plasma levels of vitamin E and selenium (381.6 ± 88.9 vs. 323.8 ± 88.6 U/l; 7.5 vs. 7.9 µmol/mmol; and 1.4 ± 0.1 vs. 1.2 ± 0.4 µmol/l, respectively). Mean ± SD total cholesterol was higher in the placebo than in the antioxidant group. In the antioxidant treatment group only, the scan at three months showed improved AUC1 and AUC2 in the cortex of the right kidneys in comparison to the baseline scans (38.52 [22.41 – 90.49] vs. 123 [86.98 – 367.03], $p \leq 0.05$; and 347 [175.88 – 654.92] vs. 928.03 [448.45 – 1683], $p \leq 0.05$, respectively], while there were no changes between the baseline and three months follow-up scans in the placebo group.

Conclusion: In this study, CEUS in real time and dynamic mode showed beneficial effects of antioxidant treatment compared to placebo in patients with early renal microvascular perfusion deficits due to type 2 diabetes. Confirmatory studies in patients with type 2 diabetes with greater power are required.

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P 15

Impact of sex differences and type 2 diabetes on mitochondrial permeability transition and oxidative stress in heart of rats

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Rationale and objective: Cardiovascular risk in people with diabetes mellitus is significantly higher than in those without the disease. However, increasing evidence indicates that sex may modify the effects of diabetes into a risk for cardiovascular diseases. It is well established that oxidative stress and induction of mitochondrial permeability transition in cardiomyocytes are linked with tissue damage and development of diabetic cardiomyopathy. The mitochondrial permeability transition pore (mPTP) plays a crucial role in the initiation of apoptotic and necrotic cardiomyocyte death. The aim of the study was to assess the impact of sex on oxidative stress and mitochondrial permeability transition in the heart of rats with type 2 diabetes.

Methods: Type 2 diabetes was induced in 12 weeks old male and female Wistar rats by intraperitoneal injections of 25 mg/kg streptozotocin twice a week, followed by a high-fat diet for four weeks. All animals were divided into four groups: intact (control) group (male [Cm] and female [Cf], n = 10) and untreated diabetic group (male [Dm] and female [Df], n = 10). Mitochondria were isolated from rat hearts by differential centrifugation. Levels of advanced oxidation protein products (AOPP),

NADPH oxidase, xanthine oxidase and thioredoxin reductase activities were determined in mitochondrial preparations. Ca^{2+}-induced opening of mitochondrial permeability transition pore was measured as the velocity of mitochondrial swelling.

Results: It was established that the oxidative stress, evaluated by the AOPP production in the mitochondria of the intact animals, was higher in males than in females (Cm: 48.7 ± 2.2 vs. Cf: 32.6 ± 2.5 nmol-equivalent of choramine-T/mg protein, $p < 0.05$). Type 2 diabetes increased AOPP levels in the heart mitochondria of both sexes, but it was significantly higher in males (Dm: 80.7 ± 2.8 vs. Df: 61.8 ± 3.4 nmol-equivalent of choramine-T/mg protein, $p < 0.05$). The activity of NADPH oxidase and xanthine oxidase which are main sources of reactive oxygen species production in the heart did not depend on the sex in control animals ($p > 0.05$). However, diabetes increased the activity of both enzymes in males (NADPH oxidase Dm: 1.15 ± 0.06 vs. Cm: 0.63 ± 0.03 nmol/min/mg protein, $p < 0.05$; xanthine oxidase Dm: 1.17 ± 0.08 vs. Cm: 0.71 ± 0.02 nmol/min/mg protein, $p < 0.05$) and did not affect the activity of these enzymes in females ($p > 0.05$). In control animals, the activity of antioxidant enzyme – thioredoxin reductase which plays an important role in apoptosis of cardiomyocytes – was similar in both sexes (Cm: 2.55 ± 0.28 vs. Cf: 3.13 ± 0.26 nmol/min/mg protein, $p > 0.05$). It has been shown that increased oxidative stress in diabetes was accompanied by reduction of thioredoxin reductase activity which was more pronounced in males' heart mitochondria (Dm: 1.34 ± 0.19 vs. Df: 2.31 ± 0.10 nmol/min/mg protein, $p < 0.05$). It was revealed that Ca^{2+}-induced opening of mPTP did not depend on the sex of control animals (Cm: 15.14 ± 2.75 vs. Cf: 15.46 ± 1.10 µU/min/mg protein, $p > 0.05$), but the velocity of mitochondrial swelling was increased by 60 % in heart mitochondria of diabetic male compared to diabetic female (Dm: 36.84 ± 2.89 vs. Df: 23.02 ± 1.42 µU/min/mg protein, $p < 0.05$).

Conclusion: These data demonstrate that type 2 diabetes induces more pronounced oxidative stress and mPTP opening in heart mitochondria of males compared to diabetic females. This may be associated with higher sensitivity of myocardium cells to pro-apoptotic stimuli in diabetic males.

P 16

The relationship of MCP-1 to the severity of erectile dysfunction in patients with type 2 diabetes at high risk of cardio-renal disease

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Rationale and objective: Erectile dysfunction (ED) is associated with cardiovascular disease (CVD). MCP-1 has been suggested as a potential target for diabetic kidney disease, however it is unclear of its role in ED. We aimed to elucidate the relationship between markers of oxidative stress status, MCP-1 and ED severity to aid earlier identification of patients with type 2 diabetes mellitus (T2DM) at risk of developing early cardio-renal disease.

Methods: 67 patients with T2DM free from but at high risk of cardio-renal disease were enrolled. Presence of ED and its severity was assessed using the validated International Index of Erectile Function-5 (IIEF-5) questionnaire. CVD risk was estimated using the Framingham Risk Score Calculator. Plasma activities of glutathione peroxidase (GPx-3) and superoxide dismutase (SOD), as well as Vitamin E and urinary 8-hydroxy deoxyguanosine (8-OHdG) levels were measured to assess oxidative stress status. Plasma MCP-1 was also quantified.

Results: The cohort composed of patients with no ED to moderate (n = 39) and moderate to severe ED (n = 28). The patient groups had similar age, body mass index, sitting systolic blood pressure and HbA_{1c} (57.82 ± 8.0 vs. 60.6 ± 7.5 years; 30.0 ± 4.0 vs. 30.4 ± 4.8 kg/m²; 142.0 [131.0 – 152.0] vs. 139.5 [133.0 – 150.3] mmHg, and 48.0 [45.0 – 58.0] vs. 55.0 [44.3 – 60.8] mmol/mol, respectively). Patients with severe ED had higher 10-years estimated CVD risk (27.4 [18.4 – 42.0] vs. 29.6 [25.0 – 39.8] %, $p \leq 0.05$), and MCP-1 levels (117.6 ± 55.5 vs. 164.93 ± 57.8 pg/ml, $p \leq 0.05$) than patients with mild ED. Also, patients with moderate to severe ED compared to patients without ED or mild ED had higher MCP-1 levels and lower eGFR (169.2 ± 56.8 vs. 139.1 ± 61.9 pg/ml, $p \leq 0.05$; 89.5 [77.8 – 97.5] vs. 96.0 [82.0 – 102.0] ml/min/1.73 m²), $p \leq 0.05$, respectively). Oxidative stress status was similar in the subclasses of ED patients. In an ordinal regression modelling, MCP-1 was a significant predictor of having moderate to severe ED (1.1012 [95 % CI 1 – 1.024], $p < 0.05$).

Conclusion: In this study of patients with T2DM at increased risk of cardio-renal disease, those with severe ED have increased 10-years CVD risk, lower eGFR and increased MCP-1 levels. Also, MCP-1 was a predictor of the severity of ED. This findings show a relationship between ED, MCP-1 and CVD risk, however it remains unclear if early ED could be an early predictor of CVD.

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P 17

Melatonin ameliorates diabetic heart injury via antioxidative and antiinflammatory capacity in experimental type 2 diabetes mellitus

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Rationale and objective: Diabetic heart injury is an important health problem and protection against heart injury in type 2 diabetes is a main challenge worldwide. Cardiomyopathy occurs as a consequence of hyperglycaemia induced oxidative stress. Several antioxidants showed great modality in treatment of diabetic cardiomyopathy. Melatonin is secreted from the pineal gland and exerts significant protection in diseases characterised by elevated oxidative stress. Not only is melatonin a remarkable antioxidant but also able to up-regulate endogenous antioxidants. This study aimed to evaluate the protective effect of melatonin on experimental cardiac injury in type 2 diabetes mellitus.

Methods: Streptozotocin (55 mg/kg)/nicotinamide (100 mg/kg) were used to induce T2DM in male Wister rats. Melatonin (10 mg/kg) was orally administered.
Results: The treatment with melatonin significantly ameliorated HbA_{1c}, and improved lipid profile and tissue insulin resistance in diabetic rats. Melatonin also protected the histological structure of the heart and the islet of Langerhans in pancreas. Heart function was also normalised, evidenced by normalisation of troponin T and CK-MB and maintaining of satisfactory level of antioxidants in the heart. A positive expression of insulin was demonstrated in the islet of Langerhans of melatonin-treated rats compared with diabetic rats, indicating protection of beta cells that was confirmed by sustaining adequate insulin levels. Moreover, melatonin prevented the formation of perivascular and interstitial fibrosis in heart as shown by Masson's trichrome stain. Melatonin also ameliorated inflammatory cytokines in type 2 diabetic rats.
Conclusion: Melatonin is a good therapeutic modality for oxidative cardiomyopathy and protects β-cells in islet of Langerhans in case of type 2 diabetes through its antioxidative and antiinflammatory potential. It is recommended that melatonin is a safe natural chemotherapeutic adjuvant to overcome diabetic complications after a clinical trial in human.

P 18

Cardioprotective effect of succinate derivative phensuccinal in rats with type 2 diabetes

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Rationale and objective: Dysfunction of cardiac mitochondria appears to play a substantial role in cardiomyopathy and is a promising therapeutic target for many cardiovascular diseases. Persistent hyperglycaemia and hyperlipidaemia are believed to be the main causes of increased oxidative stress, mitochondrial dysfunction, fibrosis, and apoptosis of cardiomyocytes in diabetes. We have previously shown that the low-toxic succinate derivative (beta-phenylethylamide-2 hydroxy-succinanylic acid) phensuccinal (Ph) possesses antioxidant and antiinflammatory properties. The aim of the study was to assess the effects of Ph on mitochondrial functions and oxidative stress in the rats' heart with type 2 diabetes.
Methods: Type 2 diabetes was induced in 12 weeks old male Wistar rats by a single intraperitoneal injection of streptozotocin 50 mg/kg followed by a high-fat diet during four weeks. All animals were divided into three groups: intact (control) group (C, n = 8), untreated diabetic group (D, n = 8) and diabetic rats treated with Ph (D + Ph, n = 8) for four weeks (50 g/kg/day per os) after diabetes induction. Mitochondria were isolated from rat hearts by differential centrifugation. The activity of mitochondrial respiratory enzymes – cytochrome c oxidase, succinate dehydrogenase and aconitase – was measured. Levels of reactive oxygen species (ROS) and reduced glutathione (GSH) and activity of antioxidant enzymes – glutathione reductase (GSSG-reductase), glutathione peroxidase (GSH-Px), and manganese superoxide dismutase (Mn-SOD) were determined as biomarkers of oxidative stress in mitochondrial preparations.
Results: A significant increase in ROS production (D: 0.377 ± 0.037 vs. 0.171 ± 0.018 nmol H_2O_2/min/mg of protein, $p < 0.01$) was accompanied by a 2-fold reduction of GSH level and compensatory elevation of antioxidant enzymes GSSG-reductase (D: 6.02 ± 0.28 vs. 4.42 ± 0.29 µmol/min/mg protein, $p < 0.05$), GSH-Px (D: 28.01 ± 3.22 vs. C: 11.32 ± 1.12 µmol/min/mg protein, $p < 0.01$), Mn-SOD (D: 29.49 ± 1.94 vs. C: 16.97 ± 1.10 U/mg protein, $p < 0.02$) activity in diabetic heart mitochondria. In addition, mitochondrial matrix aconitase, a ROS sensitive enzyme, was inhibited by 50 % in the diabetic rats' heart. The activity of mitochondrial respiratory enzymes – succinate dehydrogenase (Complex II) – was significantly decreased (D: 14.65 ± 1.13 vs. C: 23.70 ± 2.04 nmol/min/mg protein, $p < 0.02$), while activity of cytochrome c oxidase (Complex IV) did not change in diabetic rats in comparison with intact animals. Administration of Ph provided reduction in ROS production (D + Ph: 0.151 ± 0.025 nmol H_2O_2/min/mg of protein, $p < 0.01$), GSH-Px (D + Ph: 12.94 ± 1.62 µmol/min/mg protein, $p < 0.02$), Mn-SOD (D + Ph: 16.27 ± 1.70 U/mg protein, $p < 0.02$) activity and increased GSH level (D + Ph: 5.37 ± 0.29 vs. D: 2.89 ± 0.29, $p < 0.05$) and aconitase activity (D + Ph: 269.61 ± 38.38 vs. D: 138.52 ± 13.50, $p < 0.01$) in heart mitochondria compared to untreated diabetic group. In addition, Ph also normalised succinate dehydrogenase activity (D + Ph: 25.05 ± 2.20) in heart mitochondria of diabetic rats.
Conclusion: These data demonstrate that novel succinate derivative phensuccinal can protect against mitochondrial dysfunction and oxidative stress in the heart of diabetic rats. We suggest that the use of phensuccinal may contribute to the amelioration of cardiovascular risk in type 2 diabetes.

P 19

Severity of oxidative stress in patients with type 2 diabetes mellitus and cardiovascular autonomic neuropathy

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Rationale and objective: Oxidative stress, defined as an imbalance between reactive oxygen species production and antioxidant defense, is closely associated with type 2 diabetes mellitus. Oxidative stress is a known risk factor for cardiovascular disease and microvascular complications of diabetes mellitus. It seems that the activity of cellular antioxidants such as the enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) may be crucial to this process. However, there are limited data regarding the expression of oxidative stress in patients with diabetes and cardiovascular autonomic neuropathy (CAN). Therefore, the aim of this study was to evaluate the severity of oxidative stress by measurement of enzymatic and non-enzymatic biomarkers in patients with diabetes mellitus and CAN.
Methods: Ten healthy volunteers (aged 43.9 ± 1.7 years); 10 patients

with type 2 diabetes mellitus (T2DM) without CAN (aged 45.4 ± 1.1 years), HbA_{1c} 8.4 ± 1.3 %; and 10 patients with type 2 diabetes mellitus and CAN (aged 48.4 ± 1.2 years), HbA_{1c} 8.9 ± 1.4 %, participated in the current study. CAN was diagnosed by examining the variability of R-R intervals and conduction of cardiovascular tests. Neuropathy was diagnosed using the following scales – NSS, TSS, NIS-LL, and Toronto. The patients studied did not have a history of cerebrovascular diseases and did not take any medications affecting measured substances in blood. The superoxide dismutase and catalase activities, the level of lipid peroxidation (LPO) in plasma as well as content of H_2O_2, reduced glutathione and activity of glutathione peroxidase in erythrocytes were measured.
Results: We found that the indices of the oxidative stress development increased significantly in both groups of diabetic patients compared to the healthy participants. But this increase was more pronounced in patients with type 2 diabetes mellitus and CAN than in diabetic patients without CAN. Thus, the levels of LPO and H_2O_2 were higher in T2DM with CAN by 32 and 40 % (P< 0.05), respectively, than in healthy persons, these indices in T2DM without CAN were increased by 26 and 27 % (P< 0.05), respectively. A significant increase in the SOD activity (by 24 %, P< 0.05) and CAT (by 85 %, P< 0.05) was registered in T2DM patients with CAN in comparison with control healthy group. No significant differences were found in the SOD activity in diabetic patients without CAN. We found that diabetic patients with and without CAN demonstrated significantly lower values of GSH (by 36 % and 31 %, P< 0,05) and activity of glutathione peroxidase (by 25 and 16 %, P< 0,05) than control subjects. So, our findings suggest that diabetic patients with CAN have more severe oxidative stress than diabetic patients without CAN. We suggest that the increase in total SOD and CAT activities may serve as a possible compensatory mechanism in response to the increased production of the superoxide anion, which would lead to an augmentation in the production of H_2O_2. However, the increase in the activity of these antioxidant enzymes in type 2 diabetes mellitus is not sufficient to protect cells against oxidative stress, because increased LPO level, depleted GSH and decreased GPx activity indicate that oxidative damage has already occurred.
Conclusion: Our results confirm the hypothesis that oxidative stress plays a significant role in the development and progression of CAN in patients with diabetes mellitus.

PS 4: Diagnostic approaches, technologies

P 20

An innovative, non-invasive medical device for assessing sudomotor function – relevance in the screening of cardiac autonomic neuropathy in diabetic patients

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Rationale and objective: The main objectives of this study were to assess the prevalence of peripheral and autonomic neuropathy in a population of diabetic patients, as well as to analyse in a real life, outpatient unit scenario, the feasibility of performing Sudoscan (Impeto Medical; Paris, France) tests together with consecrated tests for neuropathy.
Methods: A total of 33 patients were included in the study. The Toronto Clinical Neuropathy Score (TCNS), as well as the Neuropathy Disability Score (NDS) and the Neuropathy Symptom Score (NSS) were applied to record diabetic neuropathy (DN), while the Sudoscan medical device was used in order to assess the sudomotor function, to detect diabetic autonomic neuropathy and screen for cardiac autonomic neuropathy (CAN).
Results: According to the assessment of the sudomotor function performed by Sudoscan, 15 (45.5 %) patients had sudomotor dysfunction. The Sudoscan CAN risk score was positively correlated with the hands electrochemical sweat conductance (ESC), diastolic blood pressure (DBP), the level of the glycated hemoglobin, as well as with the TCNS, NDS, and NSS.
Conclusion: A high prevalence of sudomotor dysfunction was found in the studied group of patients. Performing Sudoscan tests together with other tests for DN proved to be a feasible approach that could be used in daily clinical practice in order to screen for DN, as well as for the early screening of CAN, before more complex and time consuming tests apply.

P 21

Mathematical analysis and modelling of blood glucose levels for a diabetic patient

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Rationale and objective: Patients with diabetes are confronted with two major problems, the first one related to long term complications, and the other one linked to hypoglycaemia which can lead to seizures, loss of consciousness, and sometimes can even be fatal. That is why it is a requirement to prevent low or high blood glucose levels. The purpose of our study is to model blood glucose levels in order to predict the values in advance which will allow the patient to react before reaching hypoglycaemia or hyperglycaemia, thus protecting the body from the dangerous effects of blood glucose fluctuations outside the body's normal range.
Methods: Using a time series of a diabetic patient's blood glucose level selected from a device that allows self-monitoring of the patient's blood glucose, the measurements were performed over nearly 67 days every 15 minutes, for a total of 6 404 observations. Stochastic modelling techniques were used to model the time series of blood glucose levels where the data were divided into a learning sample (6 226 observations) and a test sample (138 observations). It should be noted that in the literature and to our knowledge, no attempt to model blood glucose levels has been recorded using time series. In the process of modelling the stationarity of the series was checked, and a descriptive study was carried out, then the spectral characteristics of this time series were examined. The type of the stochastics processes was chosen based on some statistical tests. The lag of the autoregressive model was

identified and its parameters were estimated. Finally, significance of the parameters was tested and the validation of the estimated model was verified.
Results: The results are very interesting, allowing an excellent prediction of the patient's glycaemia based on his previous blood glucose values. The quality of the prediction exceeds 95 % and the largest increase and decrease in the series are successfully detected.
Conclusion: We believe that it is possible to model the blood glucose levels of any diabetic patient using a stochastic model. For this reason, we would like to announce a project that will allow the generalisation of these results, which will make a big difference for a large class of people with diabetes.

P 22

Reference values of septal-lateral early and late tissue Doppler velocities ratio in subjects with normal diastolic function

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Rationale and objective: Tissue Doppler imaging (TDI) detects early signs of left ventricular dysfunction. Diastolic dysfunction also is an early sign of heart disease. The aim of this study was to define the range of left ventricular septal and lateral TDI velocity ratio in subjects with normal diastolic function.
Methods: We prospectively studied 50 adult outpatients with normal diastolic function and normal LVEF. They underwent 2D echo, including septal-lateral tissue Doppler e'/a' ratio. Standard TTE examinations were performed on a commercially available system Epiq7.
Results: The values of septal e'/a' ratio among the studies varied from 0.9 to 2.4 (mean 1.33). The values of lateral e'/a' ratio among the studies varied from 1 to 2.0 (mean 1.75). The values of E/A ratio varied from 1 to 2.1 (mean E/A 1.38). Age of patients varied from 17 to 51 (mean age 31 years), n = 50%, 25 were male (50 %), 25 were female.
Conclusion: 1) We have found that septal/lateral mean e'/a' ratio was > 1 in subjects with normal diastolic function. 2) Values of tissue Doppler e'/a' ratio in patient with diastolic dysfunction require further investigations. 3) This study determined values of septal-lateral tissue Doppler e'/a' ratio in subjects with a normal heart.

P 23

Design and synthesis of gliclazide tabletted microspheres using hydrophilic alginate polymer

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Rationale and objective: Gliclazide, 1-(3-aza bicyclo [3,3,0] oct-3-yl)-3-(P-tolyl sulphonyl) urea is an oral hypoglycaemic second generation sulphonyl urea drug which is useful for the treatment of non-insulin dependent diabetes mellitus. Gliclazide absorption rate from gastrointestinal tract is slow and varies among the subjects. The slow absorption of gliclazide is due to its poor dissolution and solubility. Incorporation of gliclazide in control release formulation would control the dissolution rate of the drug and consequently its rate of absorption from the gastrointestinal tract and improves the pharmacokinetic profile of gliclazide. The aim of this work was to improve the oral absorption and bioavailability of gliclazide by incorporating it into controlled released tabletted microspheres prepared using alginate polymer.
Methods: In first stage of the study, gliclazide loaded alginate microspheres were prepared using ionic gelation method. The microspheres were characterised for drug loading, micromeretics properties, surface texture and morphology using scanning electron microscopy and in vitro drug release. In the second stage of the study, tablets containing gliclazide microspheres were prepared by direct compression technique. Two types of directly compressible diluents namely Avicel and Emcompress were used in the formulations to prevent rupture and damage of the microspheres during compression and to investigate the effect of their presence on the compression behaviour and the physicochemical properties of the tabletted microspheres. The prepared tabletted microspheres were evaluated for their weight variation, hardness, friability, thickness, disintegration time and in vitro drug release.
Results: Alginate microspheres had an average size of 1,303 ± 2 µm and encapsulation efficiency of 96.4 %. The flow properties of the microspheres was excellent as indicated by the angle of repose (23.25 ± 0.404) and Hausner ratio (1.050 ± 0.01) values. Surface textures and morphology studies revealed that the microspheres were nearly spherical but with very rough surface covered with drug particles that were loosely attached. The in vitro drug release studies of alginate microspheres were performed in phosphate buffer pH 7.4 and showed prolonged drug release, which was completed in 6 hours. Presence of Avicel or Emcompress have improved the compressibility characteristic of the microspheres into tablets as indicated by the increase in the tablets hardness values (10.416 ± 0.510 Kg for tabletted microspheres containing Avicel and 6.791 ± 0.188 Kg for tabletted microspheres containing Emcompress). Tabletted microspheres compressed without diluent were the least strong (hardness 4.041 ± 0.188 Kg). The disintegration studies showed that microspheres compressed without diluent disintegrated within 8 minutes and that addition of Avicel or Emcompress to the formulations has decreased the disintegration time to 5 minutes and 3 minutes, respectively. The in vitro drug released from tabletted microspheres containing Avicel diluent were compared with those containing Emcompress and the results showed a slower release rate for gliclazide from tablets containing Avicel and the effect was pronounced as the concentration of Avicel increased in the formulations. A cross-sectional SEM photograph of gliclazide tabletted microspheres showed presence of nearly spherical shaped particles in the tablet, suggesting that presence of directly compressible vehicle provided cautioning effect to protect the microspheres within the tablet during compression. Since this requirement for producing the tabletted microparticles, the procedure used in this research is suitable for tabletting.
Conclusion: Therefore, the present study concluded that incorporation of gliclazide into alginate microspheres has improved the tabletting properties of the drug and may improve its absorp-

tion and the bioavailability by sustaining the drug release from the formulations.

P 24

Budget impact of improved diabetes management by utilisation of glucose meters with a color-range indicator-comparison of five European healthcare systems

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Rationale and objective: Diabetes is a major burden not only for those affected but also for healthcare systems and costs for the treatment of diabetes and its comorbidities have become a major global issue. A recent randomised clinical trial (RCT) revealed that the introduction of color range indicator (CRI)-based glucose meters (GMs) positively affects the glycaemic control (HbA_{1c}) of patients with type 1 and type 2 diabetes, when compared to GMs without a CRI. This budget impact analysis aimed at translating this beneficial effect of CRI-based GMs, notably OneTouch Verio Flex and OneTouch Verio, into potential monetary impact for the healthcare systems of five European countries, Germany, Spain, Italy, France, and the United Kingdom.
Methods: Data from a RCT evaluating the effect of CRI-based GMs were used to estimate the ten-year risk of patients for fatal myocardial infarction (MI), as calculated by the UK Prospective Diabetes Study (UKPDS) risk engine. On the basis of assessed risk for MI, the potential monetary impact for the healthcare systems in five European countries was modelled.
Results: Based on a mean clinical HbA_{1c} reduction of 0.36 %, as demonstrated in the corresponding RCT, the UKPDS risk engine estimated a reduction of 2.4 % of the ten-year risk of patients for fatal MI. When applied to our economic model, substantial potential cost savings for the healthcare systems of five European countries were calculated: 547 472 € (France), 9.0 million € (Germany), 6.0 million € (Italy), 841 799 € (Spain), and 421 069 € (United Kingdom) per year.
Conclusion: Improving metabolic control in patients with diabetes by the utilisation of CRI-based GMs may have substantial positive effects on the expenditure of the healthcare systems of several European countries.

P 25

Cardiovascular diseases in patients with diabetes are associated with advanced glycation end products accumulation and sudo-motor dysfunctions

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Rationale and objective: The association between micro- and macrovascular diabetes complications is a "time honoured" observation, implying common pathomechanisms (e.g. glycation), but also screening and diagnosis particularities. Measurement of skin accumulation of advanced glycation end products (AGEs) and of the sudo-motor dysfunctions with non-invasive and accessible devices are two relative recently introduced methods. The aim of our study was to evaluate the association between the presence of cardiovascular diseases and the intensity of the glycation process (measured with AGE Reader®) and of the sudo-motor dysfunctions (evaluated as electrochemical skin conductance with Sudoscan®) in patients with diabetes.
Methods: Based on their expressed informed consent, 174 consecutive patients with diabetes were included in a single-center follow-up observational study. We are presenting some of the results of their initial evaluation, stratified by the presence or not of previous diagnosed cardiovascular diseases (ischaemic heart disease, IHD, or peripheral arterial disease, PAD, or cerebrovascular disease, CVD). 9 (5.2 %) patients had type 1 diabetes, 165 (94.8 %) had type 2 diabetes; 89 (51.1 %) were male; mean age was 66.68 ± 8.69 years and mean duration of diabetes was 16.03 ± 6.92 years. The patients were clinically evaluated and, in the same day, the skin autofluorescence (SAF; with AGE Reader®, Groningen, The Netherlands) and the sudo-motor function (Sudoscan®, Impeto Medical, France) were measured. Descriptive and inferential analysis was carried out using SPSS 20.00 package.
Results: 78 (40.6 %) patients were included in the strata "with cardiovascular diseases" (having IHD or PAD or CVD). There were more men in this group (57.7 % vs. 42.3 %) and the mean age, diabetes duration and body mass index (69.15 ± 7.50 yrs vs. 64.68 ± 9.09 yrs, 31.94 ± 5.11 kg/m^2 vs. 30.08 ± 5.14 kg/m^2) were significantly higher in comparison to the group without cardiovascular diseases. In the univariate analysis, assuming equal variances, the value of SAF (arbitrary units) was significantly higher (2.59 ± 0.62 vs. 2.34 ± 0.59, p = 0.09) and the value of skin conductance in hands and feet was significantly lower (63.16 ± 14.57 vs. 70.00 ± 11.92 µS, p = 0.001, respectively 71.90 ± 12.46 vs. 75.01 ± 11.71 µS, p = 0.094) in the group with cardiovascular disease. These significant differences were present also in the multivariate logistic regression (that included, as independent variables, age, diabetes duration and BMI).
Conclusion: In our study the skin accumulation of AGEs and decreased electrochemical skin conductance were associated with the presence of cardiovascular diseases suggesting that these two relative simple and accessible methods can offer valuable information in the process of global evaluation of the patients with diabetes.

PS 5: Treatment approaches

P 26

Glucagon-like peptide-1 receptor agonist on top of sodium-glucose cotransporter-2 inhibitor treatment compared to sodium-glucose cotransporter-2 inhibitor alone: a systematic review and meta-analysis of randomised controlled trials

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Rationale and objective: Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have now evolved as key players in the treatment of type 2 diabetes mellitus (T2DM). The purpose of

this meta-analysis was to provide precise effect estimates regarding the safety and efficacy of the addition of a GLP-1RA on top of SGLT-2i treatment.
Methods: MEDLINE and CENTRAL, along with grey literature sources, were searched from their inception to May 2019 for randomised controlled trials (RCTs) with a duration ≥ 12 weeks, evaluating the safety and efficacy of addition of a GLP-1RA on a SGLT-2i compared to SGLT-2i alone in patients with T2DM.
Results: We identified three eligible RCTs (AWARD-10, DURATION-8, SUSTAIN-9), pooling data retrieved from 1 042 patients with T2DM in total. Administration of the maximum dose of a GLP-1RA on top of SGLT-2i treatment compared to SGLT-2i alone resulted in a significant decrease in HbA_{1c} by 0.91 % (95 % CI: –1.41 to –0.42), in body weight by 1.95 kg (95 % CI: –3.83 to –0.07), in fasting plasma glucose by 1.53 mmol/l (95 % CI: –2.17 to –0.88) and in systolic blood pressure levels by 3.64 mmHg (95 % CI: –6.24 to –1.03). No significant effects on diastolic blood pressure and lipid profile were demonstrated. However, a significant increase in the odds for any hypoglycaemia and gastrointestinal adverse events was shown. No other safety issues were identified.
Conclusion: This meta-analysis confirms that a GLP-1RA/SGLT-2i combination, if tolerated, exerts significant beneficial effects on glycaemic control and body weight loss, however increasing the odds for any hypoglycaemia and gastrointestinal adverse events. Large RCTs are required, in order to investigate the cardiovascular implications of these beneficial metabolic effects and whether a GLP-1RA/SGLT-2i combination provides additive cardioprotection in clinical practice.

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The influence of inappropriate insulin therapy on diabetes complication in patients with diabetes type 2

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Rationale and objective: Until 2017 no oral diabetes drugs were available free of charge, in contrary to insulin. It caused increase in number of patients injecting insulin. This gave us an unique opportunity to observe the influence of inappropriate insulin therapy and chronic overdose of insulin on diabetic complications.
Methods: We have selected 147 patients with T2D. There was no statistically significant difference between following parameters: Age (57 ± 6.7 years), T2D (9.4 ± 5.4 years), HbA_{1c} (10.2 ± 3.1 %), C-peptide (2.1 ± 1.3 ng/ml), BMI (30 ± 5.7 kg/m²) and waist circumference (104.6 ± 14.1 cm). The patients were divided in 3 groups depending on treatment method: N1 combination of metformin with sulfonylureas (SU) or insulin (daily dose of insulin 36.3 ± 5.7 U) (n = 57), N2 only SU (n = 36), N3 just insulin (n = 54), daily dose of insulin 60.7 ± 8.7 U. Duration of treatment were 7.9 ± 3.1 years. (Patients were treated with hydrochlorothazide/ACE inhibitor, no statin.) We compared metabolic parameters, vascular and neurological complications.
Results: Incidence of myocardial infarction (MI) was significantly higher in the insulin group (N3) compared to SU (N2) and metformin combination (N1) groups (N3 22.7 % vs. N2 14.8 %, and vs. N1 –8.1 %). The metformin combination group (N1) appeared to have significantly lower incidence of MI compared to insulin (N3), as to SU (N2) (N1 8.1 % vs. N2 14.8 %). Also incidence of diabetic angiopathy of lower extremities was significantly higher in insulin group (N3), compared to metformin combination (N1) and SU group (N2). (N3 54.2 % vs. N1 29.6 %, and vs. N2 –38.5 %). Total cholesterol was found to be lower in the metformin combination group (N1) than the other groups (N1 226.6 ± 38.5 vs. N2 SU 248.1 ± 36.9, P = 0.043; vs. N3 251.6 ± 34.7, p = 0.019). The T/A level was higher in insulin group (N3) compared to metformin combination group (N1) (syst. N3 140.4 ± 18.8 vs. N1 128.9 ± 19.1, p = 0.036; diast. N3 84.4 ± 8.3 vs. N1 78.1 ± 10.8, p = 0.025). Difference between incidence of diabetic neuropathy and stroke was not statistically significant among groups.
Conclusion: Our results suggest that unreasonable insulin therapy has increased number of CVDs. Insulin has both proatherogenic and antiatherogenic effects. We think that inappropriate insulin and chronic overdose of insulin can lead to detection of its proatherogenic characters. Therefore, the indication for the insulin therapy should be strictly documented. Since 2018, patients have been given metformin and SU for free in Georgia. DPP-4 inhibitor medication is much more concessionary nowadays.

P 28

The importance of lifestyle and treatment changes in diabetic patients with CVD

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Rationale and objective: Patient N. M., Caucasian, male, age 53 years, type 2 diabetes (T2DM), diabetes duration 7 years. At diagnosis (2011): weight 112 kg, height 179 cm, BMI 31 kg/m²; weight reduction was recommended. Six months weight loss and exercise attempts were unsuccessful. Glycaemic control poor: HbA_{1c} > 7.5 %, glycaemic profile variations 7.5 mmol/l – 9.5 mmol/l. Metformin 1000 mg (1 tablet twice daily) was prescribed. In 2016, percutaneous coronary interventions with drug-eluting stents for acute myocardial infarction (AMI) were performed. At the hospital, insulin therapy was started (Actrapid and Insulatard). After discharge metformin (1000 mg twice daily) was added. Rosuvastatin (10 mg) was initiated, but stopped when he observed no positive results.
Methods: About a year ago he applied to our clinic: weight 121 kg, BMI 33 kg/m², latest HbA_{1c} 9.5 %, C-peptide 1.5 nmol/l, fasting blood glucose (BG) 11.5 mmol/l, post-breakfast 2.8 mmol/l, pre-lunch 11.3 mmol/l, post-lunch 4.9 mmol/l, pre-dinner 17 mmol/l, at bedtime 3.6 mmol/l. Lab tests: total cholesterol 221 mg/dl, LDL-C 148 mg/dl, HDL-C 36 mg/dl, triglycerides 268 mg/dl; creatinine 98 mmol/l, eGFR 97.5 ml/min, Cockcroft-Gault 145.2 ml/min, microalbuminuria 20 < 30, glucosuria 50 mg/dl; sodium

141 mg/dl – normal, potassium 4.3 mg/dl – normal; ALT 27 U/l; AST 39 U/l; ABP 130/85 mmHg, EF 43 %. Heart: left ventricular hypertrophy, hypokinese of septum, periodically angina pectoris attack. Eye check normal. Foot check normal. Treatment: Actrapid 32 IU/daily (3 injections), Insulatard 18 IU/daily (2 injections), metformin 1000 twice daily; perindopril/indapamide (05/1.25/1 tablet/daily), Plavix 75 mg/1 tablet.

Results: Diagnosis: uncontrolled T2DM (HbA_{1c} > 9.5 %), obesity (BMI 33 kg/m^2), hyperlipidaemia (uncontrolled), hypertension, previous AMI. Treatment regimen/lifestyle were changed. Previously, patient received no dietary recommendations, he was currently obese. Patient realised that excessive carbohydrate intake influences his glucose control and agreed to improve eating habits and to walk 15–20 minutes twice a day. Patient was on combination therapy (metformin and insulins). As patient had hypoglycaemia episodes and pronounced glycaemic variability and his body weight increased, it was decided to withdraw fast-acting insulin and replace intermediate-acting insulin with insulin glargine – long-acting insulin analogue (26 U/in the evening). Two weeks later: BG – fasting: 11.3 mmol/l, post-breakfast 13.3 mmol/l, pre-lunch 11.1 mmol/l, post-lunch 12.2 mmol/l, pre-dinner 9.2 mmol/l, at bedtime 10.5 mmol/l. Dapagliflozin (10 mg/once daily/2 pm) was initiated. Two months: BG – fasting 6.2 mmol/l, post-breakfast 6.3 mmol/l, pre-lunch 6.8 mmol/l, post-lunch 6.3 mmol/l, pre-dinner 7.5 mmol/l, at bedtime 6.0 mmol/l; HbA_{1c} 8,7 %; glucosuria 1000 mg/dl; ketone bodies negative. Insulin dose decreased to 22 U. Glycaemic profile and other parameters showed positive dynamics, insulin dose was further reduced to 16 U. Six months: BG – fasting 6.2 mmol/l, post-breakfast 5.6 mmol/l, pre-lunch 6.8 mmol/l, post-lunch 6.3 mmol/l, pre-dinner 5.8 mmol/l, at bedtime 6.0 mmol/l; HbA_{1c} 7,1 %; glucosuria 500 mg/dl; ketone bodies negative.

Conclusion: Patient feels better. HbA_{1c} decreased by 2.4 %. Glycaemic targets are reached. His weight decreased by 16 kg. No complains on cardiac pain; EF 49 %. Combination therapy with long-acting insulin and dapagliflozin shows to be effective in patients with T2DM and documented CVD.

P 29

Low metformin dose and its therapeutic serum concentration in prediabetes

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Rationale and objectives: When prescribing the lowest dosage of metformin (3 x 500 mg) to patients with prediabetes (pre-DM), we strongly believe that the drug reaches the therapeutic concentration and thus e.g. protects them from diabetes. To check the metformin concentration, blood samples from healthy people or patients with type 2 diabetes were analysed. The therapeutic concentration for metformin is not well defined, and based on few studies could be found as a range from 0.1–20.7 (median 4.5) µmol/l, if kidney function is not disturbed, for the median drug dose of 1500 mg/day. Aim was if patients with pre-DM reach the therapeutic concentration of the metformin after 6 and 15 weeks of the therapy of 1500 mg/day regimen.

Methods: To assess serum concentration of metformin, using liquid chromatography-mass spectrometry technique, in people with pre-DM and long-term treatment random blood samples from 20 patients treated with regimen 3 x 500 mg were taken at 6 and 15 weeks of the treatment. Analysis of the impact on BMI and patients' weight of the metformin serum concentration was also done.

Results: The mean metformin concentration was: 4.65 ± 2.41 µmol/l and 5.41 ± 3.44 µmol/l (p = 0.27); median: 4.4 (1.5–9.5) and 4.75 (1.2–15.1) after 6 and 15 weeks of the treatment, respectively. There was a positive correlation between the body mass (but not BMI), and the serum concentration of metformin in 15th week of the therapy (R Spearman 0.45, p = 0.04).

Conclusion: 1. All patients reached the proposed therapeutic concentration after only 6 weeks of therapy. 2. None of the patients with prediabetes who used 1500 mg/day of the metformin reached the concentration of the drug upper the therapeutic limit, assigned to patients with diabetes in previous studies. 3. To define if the obtained concentration is beneficial to the patients with prediabetes, there is a clinical effect and thus could be constituted as a therapeutic concentration. Plasma glucose and other parameters describing patients' metabolic status should be assessed as effectiveness biomarkers. 4. Longer duration of the treatment can have an impact on the correlation between body mass and metformin serum concentration.

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P 30

A pilot study on the cardiac effects of low-dose empagliflozin in STZ-induced diabetic rats

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Rationale and objective: Long term diabetes causes cardiac dysfunction. The EMPA-REG Outcome trial has demonstrated that empagliflozin, a sodium-glucose cotransporter-2 inhibitor, decreased major cardiovascular events and death from any cause in type 2 diabetic patients compared to placebo. Its beneficial effects on cardiac structure and function have been reported in diabetic animal models. Thus, we aimed to investigate the effects of empagliflozin on cardiac function in streptozotocin (STZ) diabetic rats.

Methods: 11–12 week old male Sprague Dawley rats were randomly divided into 4 groups; control (C, n = 7), diabetic (D, n = 7), empagliflozin-treated control (CE, n = 6), empagliflozin-treated diabetic (DE, n = 9). Diabetes was induced by STZ injection (40 mg/kg, i.p.). After 12–16 weeks, some of the diabetic and control rats were treated with empagliflozin (10 mg/kg/day, oral gavage, once daily). Pressure-volume (PV) loop analysis and papillary muscle experiments were done after 8 weeks of empagliflozin treatment.

Results: STZ injection resulted in decreased body weight and increased blood glucose level, as expected. Although empagliflozin lowered glucose levels in diabetic rats (C, 95 ± 3; D, 466 ± 72; CE, 95 ± 5; DE, 188 ± 60 mg/dl), it did not improve weight loss (C, 428 ± 20; D, 346 ± 23; CE, 410 ± 24; DE, 345 ± 41 g). PV loop analysis demonstrated that most of the in vivo hemodynamic parameters were impaired in group D. Empagliflozin slightly increased end systolic pressure (ESP) and rate of relaxation (–dp/dt) (ESP; C, 107.00 ± 6.53; D, 87.13 ± 15.79 *; CE, 104.00 ± 5.92; DE, 96.74 ± 16.52; –dp/dt; C, –5 972 ± 833; D, –3 936 ± 722 ***; CE, –5 473 ± 399; DE, –4 532 ± 999 *, * P < 0.05 C vs. D). It did not improve decreased rate of contraction (+dp/dt) or increased isovolumic relaxation constant (Tau) (+dp/dt; C, 6 790 ± 655; D, 4 771 ± 669 ***; CE, 6 472 ± 398; DE, 5 276 ± 674 ***; Tau logistic; C, 18.5 ± 1.2; D, 22.3 ± 3.0 **; CE, 19.5 ± 1.3; DE, 22.2 ± 0.9 **, ** P < 0.01, *** P < 0.001 C vs. D). End diastolic pressure (EDP), ejection fraction (EF), end diastolic volume index (EDVI), end systolic volume index (ESVI) did not differ between the groups (EDP; C, 10.5 ± 2.1; D, 8.4 ± 2.6; CE, 9.9 ± 3.5; DE, 9.7 ± 1.7; EF; C, 49.8 ± 7.4; D, 45.7 ± 5.2; CE, 55.9 ± 3.2; DE, 51.5 ± 4.7; EDVI; C, 0.9 ± 0.1; D, 1.1 ± 0.2; CE, 0.9 ± 0.2; DE, 1.1 ± 0.2; ESVI; C, 0.5 ± 0.1; D, 0.6 ± 0.1; CE, 0.4 ± 0.1; DE, 0.6 ± 0.1, n.s.). Preload independent parameters were also not changed in diabetic or treated groups (PRSW; C, 53.2 ± 8.1; D, 57.1 ± 9.6; CE, 57.7 ± 10.7; DE, 52.9 ± 6.3; ESPVR; C, 0.3 ± 0.1; D, 0.3 ± 0.1; CE, 0.3 ± 0.2; DE, 0.3 ± 0.1; EDPVR; C, 0.005 ± 0.003; D, 0.008 ± 0.005; CE, 0.006 ± 0.003; DE, 0.008 ± 0.006, n.s.). Isoprenaline-induced beta adrenergic responsiveness was reduced in group D to some extent, however it was not statistically significant (C, 192 ± 40; D, 170 ± 30; CE, 200 ± 40; DE, 158 ± 20, n.s.).

Conclusion: Our results show that low-dose empagliflozin improved blood glucose level in STZ diabetic rats. However, the drug was ineffective on improving cardiac impairment. This could be related to the treatment dose as other studies have also demonstrated that the beneficial effects of empagliflozin is more obvious with higher doses. Thus, new studies with a higher dose of empagliflozin could help to clarify its cardiac benefits in STZ diabetic rats.

P 31

Effects of DPP-4 inhibitors on the inflammation and macrophage M1-M2 polarisation

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Rationale and objective: A critical component of T2DM is chronic, low-grade inflammation (LGI); accumulating evidence is being provided regarding the role of LGI in the blood glucose control and development of diabetes-induced complications. Endothelial cells, macrophages and their interaction play a key role in LGI; macrophages have distinct functional phenotypes that range from a proinflammatory (M1) to an antiinflammatory phenotype (M2) and regulation of subtype is important for this phenomenon. DPP-4 inhibitors are used extensively in clinical practice and have not only a glucose lowering effect but also antiinflammatory effects. Furthermore, in addition to high-glucose induced chronic inflammation in T2DM, DPP-4 itself also induced inflammation, suggesting a role of DPP-4 in LGI. However, drug-intrinsic differences among DPP-4 inhibitors have been suggested and the mechanism of antiinflammatory effects remains to be unknown. The aim of the work was to characterise the antiinflammatory effect of DPP-4 inhibitors: we investigate the effect of the DPP-4 inhibitors teneligliptin and sitagliptin on inflammation and macrophage polarisation induced by high glucose and/or DPP-4.

Methods: The stably differentiated THP-1 cells by phorbol 12-myristate 13-acetate (PMA) were treated with 10 ng/ml LPS or 10 ng/ml IL-4 for 2 hours for activation of M1 and M2 macrophage phenotype, respectively, in the presence of DPP-4 (0.1, 0.2, and 0.5 µg/ml) and/or teneligliptin/sitagliptin at 3.0 µmol/l. To test the effects of DPP-4 inhibitors on endothelial inflammation and macrophage polarisation induced by high glucose conditions, HUVEC or co-culture of HUVEC and differentiated THP-1 cells were exposed to three different experimental glucose conditions: continuous normal glucose (NG), continuous high glucose (HG), and metabolic memory (HM, continuous HG, followed by NG). Teneligliptin and/or sitagliptin added directly to the culture medium at 3.0 µmol/l every 24 hours and the expression of inflammatory cytokine and adhesion molecules or activation of M1 and M2 macrophage phenotype were evaluated.

Results: Exposure of macrophages to different concentrations of DPP-4 increased mRNA expression for M1 markers and reduced mRNA expression of M2 markers upon stimulating with the LPS and IL-4, respectively. ROS production was also induced by both stimulants. Teneligliptin reduced the macrophage M1 polarisation and induced M2 polarisation, reducing ROS production, but not sitagliptin at the same dose. The HUVEC exposed to HG and HM induced inflammatory cytokine and adhesion molecules such as TNF-α, IL-6 and VCAM-1 compared to NG conditions. Treatment with teneligliptin, but not with sitagliptin, ameliorated these inductions. In the macrophage-EC co-culture model, HG and HM conditions induced M1 macrophage polarisation compared to NG. Teneligliptin suppressed M1-polarised activation and induced M2-polarised activation in this co-culture model. Teneligliptin also restored eNOS expression in this model. To investigate the role of eNOS in macrophage polarisation, we introduced siRNA of eNOS to EC and found that induction of M1 markers was enhanced in eNOS depleted HUVEC, suggesting the eNOS signaling is required for polarisation from M1 to M2 macrophage population.

Conclusion: In conclusion, we provided the first evidence that the DPP-4 inhibitor teneligliptin can promote a switch from M1 toward M2 polarisation, probably by enhancing eNOS expression, and attenuating hyperglycaemia-induced inflammation in endothelium.

P 32

Changes in β-adrenoceptor mediated responses and protein expression in dapagliflozin treated HFD and low dose STZ diabetic rat heart

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Rationale and objective: DECLARE-TIMI 58 trial has demonstrated that the use of dapagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT2i), reduces CV outcomes in patients with type 2 diabetes mellitus (T2DM), including mortality and hospitalisation due to heart failure. However, the exact mechanism how dapagliflozin decreases CV outcomes has not been completely understood. Recently, we have found that dapagliflozin treatment improved beta 1 adrenoceptor (β1-AR) contractile responses and the maximal rate of contraction in diabetic rats. However, this did not affect most of the in vivo basal hemodynamic parameters. In this study, we aimed to explore the effects of dapagliflozin on β-AR mediated cardiac contractility and expression of intracellular Ca^{2+}-regulatory proteins.
Methods: 6-week-old male Sprague Dawley rats were divided into 4 groups: control (C, n = 7), dapagliflozin-treated control (CT, n = 7), diabetic (D, n = 6), and dapagliflozin-treated diabetic group (DT, n = 6). Diabetes was induced by high-fat diet (35 % fat w/w) and low dose streptozotocin injection (25 mg/kg, i. p.). Some of the diabetic and control rats were treated with dapagliflozin (1 mg/kg/day, orally) for 12 – 15 weeks. After the treatment, β-AR mediated positive inotropic effect was evaluated on papillary muscle preparation by using fenoterol (0,1 nM – 10 µM) and norepinephrine (0,1 nM – 10 µM) in the presence of prazosin (1 µM) and desipramin (10 µM). The expression of sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a), phospholamban (PLN), phosphorylated PLN (p-PLN) and glucose-regulated protein 78 kDa (GRP78) were determined by western blot experiments using left ventricular cardiac tissue. Quantitative analysis of blots was performed using ImageJ. All data analysed using GraphPad Prism (8.2.0) and expressed as means ± SD. Multiple comparisons were performed using one-way ANOVA followed by Bonferroni post-hoc test and $p < 0.05$ was considered for significance.
Results: Blood glucose levels were significantly higher in D compared to C. Dapagliflozin treatment restored blood glucose levels (C: 111 ± 6, CT: 104 ± 10, D: 400 ± 95, DT: 173 ± 18 mg/dl). The fenoterol mediated positive inotropic effect tended to be higher in D vs. C, but it was not found statistically significant (C: 71.8 ± 29.0, CT: 83.0 ± 61.9, D: 137.1 ± 73.4, DT: 112.6 ± 28.4). Similarly, there was no significant difference in norepinephrine-mediated contractility between the groups (C: 81.2 ± 31.5, CT: 91.0 ± 55.3, D: 118.6 ± 40.9, DT: 118.9 ± 62.0). In addition, there are no significant changes in protein expression of GRP78, SERCA2a and p-PLN/PLN (GRP78: C: 100 ± 13, CT: 104 ± 24, D: 117 ± 13, DT: 103 ± 11; SERCA2a: C: 100 ± 17, CT: 84 ± 13, D: 85 ± 13, DT: 81 ± 12; p-PLN/PLN: C: 100 ± 35, CT: 93 ± 12, D: 91 ± 21, DT: 82 ± 18). SERCA2a/PLN ratio, on the other hand, was decreased in D and DT (SERCA2a/PLN: C: 100 ± 6, CT: 89 ± 13, D: 81 ± 15, DT: 82 ± 8; $p < 0.05$ D and DT vs. C and CT).
Conclusion: Our results indicate that dapagliflozin treatment significantly attenuated blood glucose level. Despite of a slight increase in β1- and β2-AR-mediated inotropic responses in diabetes, there was no significant difference between the groups. Moreover, dapagliflozin treatment did not alter neither fenoterol- nor norepinephrine-mediated responses. Supporting the functional data, the expression of intracellular Ca^{2+}-regulatory proteins GRP78, SERCA2a and p-PLN/PLN was not changed in diabetic or treated groups. However, SERCA2a/PLN ratio was decreased in diabetic groups, while dapagliflozin treatment did not change this ratio.

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PS 6: Glycaemic variability, clinical aspects

P 33

Hypoglycaemia leads to delayed increase in platelet and coagulation activation markers in subjects with type 2 diabetes – results from a stepwise hypoglycaemic clamp study

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Rationale and objective: Many studies exploring the impact of intensive glucose control on different cardiovascular outcomes have failed to demonstrate beneficial effects and hypoglycaemia is discussed as a potential reason for the lack of benefit. Experimental data investigating the effect of hypoglycaemia on platelet and coagulation activation in type 2 diabetes are limited. The purpose of this study was to determine acute and prolonged effects of clamp induced hypoglycaemia on markers of platelet activity and coagulation.
Methods: This monocentric, open, single-arm, mechanistic trial included 14 subjects with established type 2 diabetes (10 male and 4 female, age 55 ± 7 years, HbA_{1c} 51 ± 7 mmol/mol, diabetes duration 5 ± 4 years) on metformin monotherapy. A stepwise hyperinsulinaemic-hypoglycaemic clamp (3.5 and 2.5 mmol/l, for 30 minutes, respectively) was performed, aiming to investigate parameters of platelet and coagulation activity during predefined plateaus of hypoglycaemia as well as 1 day and 7 days later.
Results: While platelet activation assessed by light transmittance aggregometry did not significantly increase following a hypoglycaemic clamp, flow cytometry based platelet activation showed a platelet activation induced by hypoglycaemia, demonstrating a significant increase 24 hours (PAC1CD62Ppos, PAC1CD63Ppos and PAC1CD62PCD63pos $p < 0.01$) compared to baseline, and 7 days after the hypoglycaemic clamp ($p < 0.001$ for PAC1CD63Ppos, $p < 0.01$ for PAC1CD62Ppos and PAC1CD62PCD63pos) in comparison to baseline. In addition, coagula-

tion markers like fibrinogen, D-Dimer, PAI-1, von Willebrand Factor activity, and factor VIII were also significantly increased, an effect that was most pronounced 24 hours after the hypoglycaemic clamp.
Conclusion: One single event of insulin induced hypoglycaemia led to an increase in markers of platelet activation and coagulation in subjects with early stages of type 2 diabetes on metformin therapy, however, the activation occurred with a delay and was evident 24 hours and 7 days after the actual hypoglycaemia.

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P 34

Identifying the phenotypic determinants of the cellular "glucose variability"

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Rationale and objective: In subjects with diabetes, both type 1 (T1D) and type 2 (T2D), one of the main contributors to the risk to develop short- and long-term complications is identified with the glycaemic variability (GV), a complex phenomenon in which the daily oscillations of glucose might be worse than stable hyperglycaemia. Although several studies showed that deleterious mechanisms attributable to GV are due to increasing DNA double-strand breaks, apoptosis, induction of some regulatory micro-RNAs, as well as the over-generation of reactive oxygen species, the characteristic GV phenotype is scarcely defined. The aim of this study is to define a global landscape about the regulation of the major proteins differentially expressed in a cellular model of GV and the role of microRNAs driving the activation of certain molecular pathways during the in-vitro long-term exposures.
Methods: HUVECs were cultured in i) NG, normal glucose (5 mmol/l), ii) OG, oscillating glucose (5–25 mmol/l) and iii) HG, high glucose (25 mmol/l) for 21 days and subjected to 1) proteomic analyses (2-DE coupled with matrix-assisted laser desorption ionisation-time of flight mass spectrometry [MALDI-TOF/TOF MS]), and 2) miRNA profiling. Univariate analysis and Pearson correlation analyses were performed by SAS software between proteome and miRNome datasets. Annotated pathways linked to proteins found in NG, OG and HG phenotype was obtained by KEGG databases.
Results: Our preliminary data showed 89 proteins and a subgroup of miRNAs significantly expressed ($p < 0.05$) in the aforementioned conditions. The correlations intragroup identified specific protein-protein interaction, suggesting an important role in defining the GV phenotypes. We also found, by univariate correlation that occurred different protein associations in the group of OG than those observed in the group of NG and HG, suggesting a unique and distinct phenotype regulated by OG. The annotated pathways for the proteins significantly found in NG are linked to "carbon metabolism", "glycolysis", "superpathway of conversion of glucose to acetyl CoA and entry into the TCA cycle", "gluconeogenesis", "26S proteasome" and others. In OG, the most relevant biological processes and their co-expression are related with "regulation of insulin growth factor (IGF) activity", "protein processing in endoplasmic reticulum (ER)", "catalysis" and many other. miRNA profiling revealed 5 differentially expressed miRs (miR-146a-5p, miR-155, let-7d, miR-125a-5p and miR-331) between OG and HG.
Conclusion: These data could provide novel clues about the use of novel determinants for defining glucose variability.

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Novel use of abaloparatide to augment spinal fusion in patient undergoing cervico-thoracic revision surgery after failed fusion

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Rationale and objective: To present a case of using abaloparatide (PTHrP 1-34 analogue) to promote spinal fusion s/p revision cervical corpectomy, anterior cervical plate fixation and posterior cervico-thoracic fusion in a patient with history of cervical pain/radiculopathy and instability s/p multiple cervical operations with non-union.
Case presentation: A 66-year-old female with a medical history of multiple sclerosis, obesity, depression, and hypothyroidism was undergoing neurosurgical evaluation for cervical spinal stenosis causing neck pain. She additionally reported radicular sensory and motor deficits and ataxia. The patient underwent an anterior cervical discectomy and fusion in February 2018 for her symptoms. Her neck pain and radiculopathy were initially alleviated by the surgery but eventually she suffered non-union. She underwent a cervical corpectomy (C5–C7) in August 2018 which also failed followed by redo cervical corpectomy and posterior fusion. Her clinical symptoms improved briefly before progressively worsening and now included dysphagia and inability to keep her head upright.
She presented to our facility in November 2018 for further evaluation where initial work up showed unstable cervical spine along with displaced and loosened hardware in the cervical region including a corpectomy cage pressing up against the esophagus. She underwent a revision C4–C7 anterior cervical corpectomy anterior fixation of cervical plate C4–T1 and posterior cervico-thoracic fusion. Post procedure she was seen by our endocrine service inhouse and evaluated for any underlying metabolic bone disease. Initial work excluded common endocrine etiologies like hyperthyroidism, hyperparathyroidism and Vitamin D deficiency. She had no personal or family history of metabolic bone disease, no history of long term steroid usage, and no bone density scan prior to her surgeries. As per discussion with the neurosurgery team, a decision was made to pursue anabolic osteoporosis treatment to attempt to augment spinal fusion and healing post procedure.
The patient had her surgery on January 24th, 2019. She was initiated on abaloparatide 80 µg SQ daily 2 weeks post procedure. Lab work since starting anabolic

therapy is pending but increase in bone turnover markers is expected. Cervical CT scan imaging in April 2019 showed postsurgical cervico-thoracic fusion with instrumentation and hardware in appropriate place.

Discussion: Abaloparatide is a 34 amino acid synthetic analogue of parathyroid hormone-related peptide (PTHrP) which works by selectively activating PTH1 receptor found on osteoblasts. Currently anabolic therapies (including teriparatide) are only FDA approved for treatment of osteoporosis but there is reported off label use in cases of spinal fusions, arthroplasty and fracture healing. Studies have shown that presence of PTH and PTHrP are necessary for fracture healing. Animal studies have also shown that intermittent PTH promotes spinal fusion. The role of PTHrP and its exact mechanism of action in fracture healing remains less well understood. This case represents a novel use for abaloparatide to augment spinal fusion in a human clinical model.

Conclusion: The use of anabolic therapies like abaloparatide should be considered in patients undergoing spinal fusion surgery at high risk for non-union or undergoing revision surgery for failed fusion.

P 36

Nivolumab-induced fulminant autoimmune diabetes presenting as diabetic ketoacidosis in a patient with melanoma

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Rationale and objective: Anti PD-1 antibody immunotherapies like nivolumab and pembrolizumab are newer agents used in the treatment of melanoma and multiple other types of advanced cancers. Immune-mediated endocrinopathies triggered by these drugs are increasingly reported in literature and encountered by endocrinologists in their daily practice. Fulminant diabetes characterised by rapid autoimmune destruction of the pancreatic beta cells is a relatively rare (less than 1 % reported incidence with nivolumab) but a potentially lethal complication associated with anti PD-1 therapies.

Case presentation: A 44-year-old African American man with metastatic melanoma was treated with nivolumab for 3 months as second line therapy after disease progression on standard therapy. After receiving his third dose of nivolumab (doses q4 weeks), patient started complaining of gradually worsening polyuria, polydipsia, dehydration and blurry vision prompting hospitalisation. The patient had no personal or family history of prior diabetes. His outpatient glucose values on office visits 1 month prior to hospitalisation were normal, 80 and 82 mg/dl. Admission labs showed significant hyperglycaemia with serum glucose of 938 mg/dl (nl 70 – 100 mg/dl), elevated anion gap of 24 mEq/l (nl 7 – 17 mEq/l), mild acidaemia with pH 7.35 (nl 7.32 – 7.45), elevated serum osmolality at 335 mOsm/kg (nl 281 – 304 mOsm/kg), ketonuria and glucosuria. HbA_{1c} at the time was 9.1 % (nl 3.1 – 6.5 %). A diagnosis of diabetic ketoacidosis was made, and the patient was admitted to the medical ICU for intravenous fluids and insulin therapy. Additional work up showed undetectable levels of C-peptide when blood glucose was 215 mg/dl. The patient was tested positive for islet cell antibodies and had undetectable titers of anti-GAD antibodies. The patient was medically stabilised and eventually discharged home on a basal-bolus insulin regimen.

Conclusion: Our patient is a rare case of nivolumab-induced autoimmune diabetes, clinically significant for the rapid onset and profound nature of DKA on presentation. The use of anti PD-1 immunotherapies like nivolumab is likely to become ubiquitous soon given their efficacy in treating advanced cancers. Clinicians should be aware and educated about monitoring for the potential endocrinopathies including fulminant autoimmune diabetes caused by these drugs.

P 37

Weight loss can be really disturbing, both for the patient and the clinician

Zaidi MS, Al-Rubeaan K; Riyadh, Saudi Arabia

Rationale and objective: Diabetes has been associated with heart failure without hypertension and coronary artery disease, which is being termed as diabetic cardiomyopathy. Our patient had both systolic and diastolic ventricular dysfunction. He developed profound weight loss and had normal coronaries on evaluation.

Case presentation: A 76-year-old Saudi gentleman with type 2 DM for 20 years, dilated cardiomyopathy for ≥ 6 years, was admitted between 1st – 20th April, 2017 for the management of decompensated biventricular failure. In 2016 he was admitted for the work up of profound weight loss of 14 kg in the preceding 6 months. Appetite was normal. He was on strict diet and regular, daily exercise.

Systemic review: Early satiety after meals, chronic constipation, right inguinal hernia, erectile dysfunction. NYHA Class I, shortness of breath (SOB) only (no orthopnea, paroxysmal nocturnal dyspnoea [PND]).

Past history: Pilonidal sinus excision 30 years ago. He had normal coronary angiogram in 2009 and had declined the option of biventricular ICD then. Cataract extraction left 5 years ago, ischaemia right upper limb during Ramadan, 1436H.

Family history: unremarkable.

He was a non-smoker with no addictions or allergies.

He was on metformin 750 mg and furosemide, both twice daily, and on daily gliclazide 120 mg/d, sitagliptin 100 mg/d, acetylsalicylic acid 81 mg, carvedilol 25 mg, enalapril 10 mg/d, spironolactone 25 mg, simvastatin 10 mg and omeprazole 20 mg.

Elderly man of medium height and built, well oriented and co-operative. Vitals – blood pressure 110/74 mmHg, pulse 70/min, regular, respiratory rate 20/min, temperature 37 °C, O_2 sat 96 % on room air. Weight 81.8 kg. No pallor, jaundice, cyanosis, clubbing, muscle wasting or lymphadenopathy. Moderate bilateral pitting edema at ankles and lower calves. Jugular venous pressure (JVP) raised up to earlobes. Thyroid not enlarged. Cardiorespiratory S1 and S2 with S3 gallop. NVB with bilateral fine basal crepts. Abdomen: soft, non-tender, non-pulsatile hepatomegaly (span – 19 cm in medioclavicular line). Hepatojugular reflux and no

other viceromegaly. Abdominal girth 127 cm. Shifting dullness and PR exam normal. Right direct inguinal hernia and neurology: non-focal exam. Eye exam: Left moderate non-proliferative diabetic retinopathy. No macular edema.
CBC (Hb% 10 g/l (MCV 73.1 fl), PLTs 243 000/cumm) ESR 20 mm/1st h. Renal functions normal apart from serum creatinine 121 µmol/l. LFTs, TFTs bone profile and lipids-normal. Ferritin 29 µg/l, BNP 6 661 pg/ml. HbA_{1c} 11.7 %. PSA 0.69 µg/l. ECG-LAD, LBBB and poor R wave progression. CXR enlarged cardiac shadow and bilateral redistribution of upper lobe pulmonary vessels and degenerative spinal changes. Echocardiogram – severely dilated LV and severe global LV systolic dysfunction and severe diastolic dysfunction. EF – 15–20 %. Moderate RV systolic dysfunction and mild RVH. Mild functional MR. Mild to moderate functional TR. Severe pulmonary HTN (PAP 65–70 mmHg). Autonomic study – positive. USG whole abdomen – hepatomegaly (17.1 cm). No focal lesion. Prominent hepatic veins and IVC, associated and small pocket of sub-hepatic free fluid. Homogeneous, parenchymal hepatic echotexture. Thickened GB. No stones. Both kidneys normal and having one right medullary and two left cortical cysts. Urinary bladder normal. Prostate 14.3 ml and a post-void volume of 18.4 ml. Urine analysis normal. Stool OB X3-negative. Our patient was treated with fluid restriction, O_2, diuretics, antibiotics along with the previous medication. His vitals, O_2 sat, weight, abdominal girth, I/O and serum glucose were closely monitored. His medication was optimised and he was referred to the heart failure clinic in another hospital.
Conclusion: One should be aware of the possibility of diabetic cardiomyopathy in people with diabetes and heart failure. This can also manifest with cardiac cachexia, as happened with our patient.

P 38

A man with diabetes and palpitations

Zaidi MS, Al-Rubeaan K; Riyadh, Saudi Arabia

Rationale and objective: Diabetes is known to be a coronary artery disease equivalent and so the mainstays of treatment in this condition are optimal glycaemic control and addressing risk factors for ischaemic heart disease. We present a case having subtle cardiac symptoms, who was ultimately diagnosed to have ventricular arrhythmia with non-ischaemic heart failure.
Case presentation: A 59-year-old Saudi gentleman had routinely visited the preventive cardiology clinic with mild dyspnea on alighting 30–40 flight of stairs (NYHA Grade I) and palpitations. He had had type 2 diabetes for 17 years, hypertension, hypogonadotrophic hypogonadism, benign prostatic hyperplasia, dyslipidaemia, obstructive sleep apnea and previous history of lumbar disc prolapse. He had a history of undocumented arrhythmia, 4 years back, which had settled without any treatment. There was no associated chest discomfort, orthopnea or paroxysmal nocturnal dyspnea. Rest of the systemic review and the family history were unremarkable.
He had been on glimepiride (6 mg/d), sitagliptin-metformin combination twice daily (50/1 g), insulin glargine (14 units [PM] daily), bisoprolol (5 mg/d), valsartan (80 mg/d), amlodipine (5 mg/d), and simvastatin (20 mg HS). The patient was on regular continuous positive airway pressure (CPAP) machine for the sleep apnea. On exam our patient was fully alert and was not distressed. Blood pressure 130/68 mmHg, pulse 42/min, small volume with intermittent missed beats. respiratory rate 20/min, O_2 sat 96 % at room air. He had flushed facies with bilateral peri-orbital edema. Apart from mild, bilateral, pitting ankle edema, pallor, cyanosis, jaundice, clubbing, lymphadenopathy were absent. Jugular venous pressure (JVP) was not raised. Cardiovascular exam: Muffled S1, S2 interspersed with ectopic beats. No gallop, murmurs or basal crepitation. Rest of the systemic exam was normal.
Results: The biochemical workup revealed normal blood cell counts, hemoglobin (15 g/dl), renal, liver, and thyroid functions. His HbA_{1c} was 8.4 % (<7), PSA 1.33 µg/l (0–4), serum total testosterone 3.89 nmol/l (9.9–27.8), LH 3 U/l (1.7–8.6), FSH 3.2 U/l, prolactin 200.6 mU/l (86–324).
The electrocardiogram showed a sinus rhythm with a heart rate of 66/min. There was right bundle branch block, left axis deviation, scattered premature atrial complexes with aberrant conduction vs. premature ventricular complexes. The patient's last ultrasound abdomen had shown enlarged fatty liver, few renal cysts and an enlarged prostate (96.2 ml) with a post-void volume of 47 ml.
The patient was immediately referred to a higher center for further cardiac assessment and management. Subsequently, he visited the ER of a tertiary care, military hospital and was admitted. His echocardiogram showed depressed LV systolic function (EF 35 %). The coronary angiography showed massive coronary ectasia and moderate non-obstructive coronary artery disease. Continuous Holter monitoring revealed frequent premature ventricular contractions (PVCs), accounting for 31 % of total recorded beats, along with baseline sinus bradycardia. The PVCs did not show any improvement with beta-blockade therapy. The PVCs seemed to originate from the right ventricular outflow tract. So, the consent for radio frequency ablation through 3-D mapping was obtained from the patient. The 3-D mapping demonstrated that the earliest activation site was in the mid posterior part of right ventricular outflow tract. At that location the local ventricular activation during the PVC seeded the QRS on the surface ECG by approximately 42 ms. The paced mapping at that location also showed a 99.3 % match. So the radiofrequency was delivered at the afore-mentioned activation site with an immediate elimination of the PVCs. The patient was safely discharged home on medical therapy. Bisoprolol was stopped.
Conclusion: All people having diabetes with other co-morbidities need periodic surveillance for the development of coronary artery disease. At the same time the possibility of non-ischaemic cardiovascular problems e.g. arrhythmias, non-ischaemic heart failure should not be ignored.

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