## PP088—NITROSONIFEDIPINE, A PHOTODEGRADATION PRODUCT OF NIFEDIPINE, SUPPRESS THE PROGRESSION OF DIABETIC NEPHROPATHY WITH THE ENDOTHELIAL DYSFUNCTION

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**Introduction:** Oxidative stress and endothelial damage are involved in the development and progression of diabetic nephropathy (DN). In this study, we investigated the effects of nitrosonifedipine (NO-NIF) having antioxidative property on DN with the endothelial dysfunction.

**Patients (or Materials) and Methods:** KKAy mice were used as a model of developing type II diabetes mellitus with the endothelial dysfunction. NO-NIF (30 mg/kg/d) was administrated continuously by intraperitoneally injection for 4 weeks. Histologic changes in the kidney, urinary protein, urinary albumin, oxidative stress, and blood glucose levels were evaluated. Moreover, we also examined whether NO-NIF affected the kidney dysfunction in eNOS knockout mice.

**Results:** In NO-NIF—treated KKAy mice, the urinary protein and albumin were significantly decreased compared with nontreated KKAy mice. The pathologic analysis showed expanded glomerular mesangium in KKAy mice, which was suppressed by NO-NIF administration. However, NO-NIF had no effect on blood glucose in KKAy mice. NO-NIF decreased dihydroethidium staining in the kidney and 8-hydroxy-20-deoxyguanosine in the urine in KKAy mice. The expression of intercellular adhesion molecule-1, an endothelial cell damage marker, was decreased in the kidney by NO-NIF while the podocyte injury marker was not changed. The mRNA expression of TNF-α in kidney was also inhibited by NO-NIF. Furthermore, the administration of NO-NIF also suppressed the expansion of glomerular mesangial area and decreased urinary albumin in eNOS knockout mice.

**Conclusion:** NO-NIF prevents renal dysfunction associated with endothelial dysfunction independently of the blood glucose lowering, and it might be a potential drug for the prevention of DN.

**Disclosure of Interest:** None declared.

## PP090—THE 3.5-YEAR MORTALITY IMPACT OF DRUGS IN SECONDARY PREVENTION OF MYOCARDIAL INFARCTION IN REAL-LIFE (INTERIM ANALYSIS OF THE EOLE COHORT)

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**Introduction:** Few studies have assessed the real-life impact of secondary prevention drugs on all-cause mortality postmyocardial infarction (MI), especially in countries with low incidence of MI. The objective of this interim analysis after 3.5-year of follow-up was to assess the real-life all-cause mortality impact of drugs reimbursed for MI secondary prevention in France: acetylsalicylic acid (ASA), antiplatelet agents (APA), beta-blockers (ß-), angiotensin-converting enzyme inhibitors (ACEI), statins, and omega-3 supplementation (Om3)

**Patients (or Materials) and Methods:** Cohort study of patients with recent (≤3 months) acute MI included by hospital and nonhospital cardiologists, with 6-year follow-up. Vital status was obtained from the National death registry, and failing that by patient/relatives/physicians investigation. Drug exposure was defined using both physician and patient reports at inclusion. Cox proportional hazards model was used to estimate for each drug, mortality hazard ratio (HR) of exposed versus nonexposed patients, adjusted for gender, age, cardiovascular risk factors, other MI prevention drugs, and propensity score to be exposed at inclusion. Results presented concern an interim analysis after 3.5 years of follow-up.

**Results:** Between May 2006 and June 2009, 596 physicians included 5538 patients: mean age, 62.1 years, 77.6% male, 9.6% current smokers, 14.5% diabetic, 44.6% hypercholesterolemic, 43.6% hypertensive, and 8.2% with LVEF <40%. At inclusion, 97.5% were exposed to ASA, 91.0% to APA, 89.7% to ß-, 71.1% to ACEI, 92.0% to statins, and 15.7% to Om3. The 3.5-year mortality was 7.8% (95%CI, [7.1%>8.5%]) with an incidence rate of 23.2 per 1000 patient-years. Adjusted HR were: 0.98 [0.60–1.61] for ASA, 0.86 [0.60–1.24] for APA, 0.84 [0.63–1.11] for ß-, 0.80 [0.61–1.03] for ACEI, 0.67 [0.45–1.00] for statins, and 0.82 [0.58–1.16] for Om3.

**Conclusion:** The 3.5-year interim all-cause real-life death reduction point estimates were close to those of large randomized controlled trials, except for ASA, for which almost all patients were exposed. The study's statistical power will be sufficient to confirm or not these trends at the final 6-year analysis.

**Disclosure of Interest:** None declared.

## PP091—COMPLEX REGULATION OF ALPHA-ADRENOCEPTOR-MEDIATED VASOCONSTRICTION IN HUMAN INTERNAL THORACIC ARTERIES

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**Introduction:** Effective flow through conduit arteries is important both for in situ organ perfusion and for tissue function after surgical and other procedures for revascularization. Membrane-bound, calcium-independent phospholipase A2 (iPLA2β) has been implicated in G-protein coupled receptor-mediated vasoconstriction in experimental studies using Sbromoenolactone (S-BEL) as a probe. However, the role of iPLA2β is unclear with regard to the regulation of vascular tone in humans. S-BEL selectively inhibits iPLA2β. It also inhibits other serine hydrolases, including phosphatidate phosphohydrolase-1 (PAP-1).

**Patients (or Materials) and Methods:** We studied human internal mammary (IMA) arteries obtained during coronary artery surgery and assessed iPLAβ in silico and responses in vitro to S-BEL, its enantiomer R-BEL, and propranolol of vessels preconstricted with phenylephrine (PE) to 80% of maximum response. All patients were undergoing surgery for treatment of ischemic heart disease and gave written informed consent to the study, which was approved by the local research ethics committee. Data are shown as means and standard errors. Data were compared by paired (Wilcoxon) or multi-way (Friedman) nonparametric tests.

**Results:** Compared with PE alone, contraction to PE increased during incubation of IMA segments in the presence of SBEL 25μM (PE alone, 6.9 [2.4 ] [SE] mN; PE with S-BEL, 12.7 [2.5] mN; $P = 0.028$, Wilcoxon] in contrast to time-dependent decreased contraction to

PE during incubation with control solutions (methyl acetate: BEL solvent; Krebs buffer or R-BEL; PE alone: 9.8 [2.5] mN; PE with controls: 7.1 [2.0] mN: $P = 0.012$, Wilcoxon). Incubation with S-BEL had not effect on contraction to KCl 60 mM compared with incubation with controls (methyl acetate, Krebs buffer, or R-BEL]. The post–S-BEL washout contractile response to PE was abolished (PE post–S-BEL: -1.2 [0.7] mN; $P = 0.002$, Friedman test; $P = 0.028$ vs pre–S-BEL PE response). Contraction to PE after washout of controls was similar to initial PE responses. Effects were similar for S-BEL 25 uM versus S-BEL 12.5 uM on contractile responses to PE. Propranolol (50 mM) prevented contraction to phenylephrine alone and the early effect of S-BEL to enhance contractile responses to PE.
**Conclusion:** S-BEL has complex, biphasic, time-dependent effects on PE-mediated arterial constriction. Propranolol is both a beta-adrenergic antagonist and inhibitor of PAP-1. Although S-BEL selectively inhibits iPLA2β, our findings suggest that other targets may also contribute to modulation of PE-dependent arterial contraction.
**Disclosure of Interest:** None declared.

## PP092—CHANGES IN VASCULAR REACTIVITY CAUSED BY ANGIOTENSIN II IN ISOLATED VESSELS OF RAT AORTA IN A MODEL OF HYPERTENSION

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**Introduction:** Hypertension (HBP) is a disease with high morbidity and mortality worldwide and is a major etiological factor in heart and vascular diseases. An important regulatory mechanism of blood pressure (BP) is the **renin angiotensin** system (RAS). In fact, all the first-line drugs for the treatment of hypertension act on some component of the RAS. However, these treatments frequently lead to the development of changes in morphology and physiology characterized by vascular complications. It is therefore necessary to consider adjuvant therapies to improve the outcome of treatments and therefore in the quality of life of patients with HBP. A therapy that has been shown to improve the clinical condition of patients with HBP is hyperbaric oxygenation (HBO), in which the patient is subject to a pressure of 2 atmospheres absolute with an oxygen concentration of 100%. This therapy has been shown to improve vascular smooth muscle relaxation, although the mechanism of action has not yet been specified. The aim of this study is to examine the role of the RAS in the relaxation of vessels in hypertensive rats that is produced by HBO.
**Patients (or Materials) and Methods:** Male Wistar rats were used (340 ± 20 g) at standard conditions (light/dark cycle, water and food ad libitum), and hypertension was induced by a previously described surgical method (PAGE). Stable hypertension was established at 7 days' postsurgery (for plethysmographic method). On the eighth day, HBO therapy began, and was carried out 5 days per week for 4 weeks. Rats were sacrificed at the end of treatment, obtaining thoracic and abdominal aorta. The endothelium was removed by a mechanical method, aortic rings were mounted, and concentration response curves were constructed according to increasing doses of ANG II for all groups with and without HBO. The results are analyzed with 2-way ANOVA and post hoc Von Ferroni.
**Results:** Diastolic pressure was found to be 150 (10) mm Hg, consistent with the definition of hypertension. The angiotesin contractile response was lower in the groups of rats treated with HBO, compared with the 2 control groups (untreated and SHAM animals).
**Conclusion:** HBO therapy reduced vascular reactivity in both segments of the hypertensive rat aorta. This suggests that HBO could possibly be used with hypertensive patients to reduce the use of drugs in therapy.
**Disclosure of Interest:** None declared.

## PP094—TARGETS OF THERAPY OF PATIENTS WITH CONGESTIVE HEART HEART FAILURE CAUSED BY ISCHEMIC HEART DISEASE AND DIABETES

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**Introduction:** Congestive heart failure (CHF), caused by ischemic cardiomyophaty and diabetes II-type, is a devastating clinical problem.The aim of this study was highlight several advances in the understanding of molecular pathways involved in cardiac hypertrophy, inflammatory signaling, and oxidant stress that may play a key role in altering transcriptional regulatory networks regulating adaptation or maladaptation, and consequently, the transition to overt HF.
**Patients (or Materials) and Methods:** A total of 56 patients aged 53 (6) years, with ischemic cardiomyophaties (ICMP) accompanied with the diabetes II-type were included in the study. Entry criteria's were: the left ventricular ejection fraction (LVEF) <40% and mild LV dilatation, symptoms of CHF for the last 2 months, at least. All patients including in the study were randomized into 2 groups; control received standard therapy (digoxin 0.025 mg per day, inhibitor of ACE and a diuretic, n = 29) and the main one (n = 30) an inhibitor of ACE, a diuretic, and Adenocin (2 ampoules diluted in 50-100 mL of saline in infused IV). There were no significant differences in baseline characteristics (demographic and anamnesis) between groups. Plasma levels of cytokines (interleukine-1β [L-1β], tumor necrosis factor [TNF-a]), redox-potential NAD/NADH, superoxide anion production, activities of superoxide dismutase (SOD), and catalase (CT) were determined.
**Results:** It has been shown that in the control group, the functional class (FC) of CHF by NYHA decreased by 12%, the dyspnea by 49%, lung congestion by 78%, hepatomegaly by 70%, and peripheral edema improved by 45%. The total CHF score improved by 52%. In the main group, the FC of CHF improved by 25%, dyspnea and lung congestion disappeared completely, hepatomegaly improved by 74%, peripheral edema -by 88%. The total score improved by 67%. In the group receiving Adenocin, LVEF improved by 16% (from 26% to 42%), stroke volume improved by 28%. Hence, the optimal treatment of CHF would be achieved through increase in the energy supply: redox-potential NAD/NADH increased by 34%, the content of pyridine nucleotide in the plasma by 40%. The activity of the marker of hyperactivation of the system of reactive oxygen production decreased by 48% and activities of SOD and CT increased by 45% and 60%, respectively. Treatment with Adenocin leads to a markedly improve of the state of immune system and as a result the content of proinflammatory cytokines, IL-1 β and TNF-a decreased by 49 and 38%, respectively.
**Conclusion:** The modern approach to treatment of HF is multidisciplinary, given that mandatory multiorgan attention is required to ensure early good outcome in these high-risk patients with ICMP and diabetes II-type. From the present results, it is evident that Adenocin cessates cardiac remodeling during the development of cardiac hypertrophy and resrores functional activity of the myocardium.
**Disclosure of Interest:** None declared.