

Defense (fight and flight) Reaction a Two Sided Sword of Prehypertension and Hypertension

Stevo Julius

*Active Emeritus Professor of Medicine and Physiology, University of Michigan Medical School,
USA*

The flight and fight reaction (FF reaction) is the preferred term for what was once called defense reaction.

The FF reaction is a complex of physiological changes which prepare the body to efficiently respond to a perceived danger. This response is integrated in the brain and it involves changes of sympathetic and parasympathetic tone in multiple human organs. In this presentation I will focus only on the sympathetic tone. Following changes have been documented in the FF reaction:

A./ Increase of muscle tension which by reflex increases the blood pressure (BP) and prepares the muscles for a quick and effective response.

B./ Increased heart rate, cardiac output and blood pressure which prepares the circulation for the expected increase of physical action.

C./ Increased muscle blood flow which redirects the flow to most the important organ.

D./ Increased blood glucose to provide more fuel to muscles.

E./ Increased hematocrit to ameliorate the consequences of bleeding.

F./ Decreased perception of pain to prevent distraction from the expected task. Taken together these physiologic changes increase the chance of survival in a dangerous environment. Jim Neel, the father of American human genetics, postulated that any trait seen in more than 20% of the present population is likely to reflect a previous survival advantage. I will show that all elements of FF reaction are present in one third of patients with prehypertension.

However survival and longevity are two unrelated aspects of living and what facilitated the survival of the species becomes detrimental to a modern individual. I will illustrate the mechanisms by which prolonged increase of sympathetic activity facilitates the acceleration of blood pressure, as well as the development of obesity and insulin resistance. Furthermore prolonged tachycardia mechanically induces vascular damage.

Implications of these finding for clinical practice and research will be discussed.

Perivascular Fat and Hypertension: The Missing Link?

Anthony M. Heagerty, Robert Aldous, Neil Bodagh, Charlotte Bussey, Ben Clark, Sophie Saxton,
Sarah Withers

The University of Manchester, Core Technology Facility, Manchester, UK

The majority of small arteries that contribute to peripheral vascular resistance is surrounded by a layer of perivascular adipose tissue. Previously it was believed that the adipocytes were inert reservoirs of excess energy but it is now realised that they are capable of secreting a large number of cytokines and proteins, all of which could contribute to vascular tone and the profile of which is dependent upon the phenotype of the individual. Healthy lean normotensives appear to produce a variety of vasodilator adipokines in response to various stimuli and cause a reduction in vascular tone. The consequence of this is a reduction in blood pressure. In obese patients with glucose intolerance there is adipocyte hypertrophy, inflammation and a loss of the bioavailability of vasodilator adipokines with an increase in peripheral vascular resistance leading to higher blood pressure and impaired glucose uptake in skeletal muscle. The restoration of a normal perivascular environment in obese subjects leads to a fall in pressure and a normalisation of blood glucose. This can be achieved using weight reducing surgery or strict dieting but also there is evidence that interference with the inflammatory process can be effective and maybe the key to new therapeutic approaches to the complications of weight gain and obesity.

What is new?

Perivascular adipose tissue is producing a large number of vasodilator adipokines which are lost during weight gain, obesity and the development of the metabolic syndrome.

What is the learning objective?

The learning objective is to introduce the delegates to the new concept of adipose tissue depots being highly metabolically active and manipulatable by exercise, diet or surgery.

Endothelial Cells – The Interface between Risk Factors and Vascular Disease

Hermann Haller

Department of Nephrology and Hypertension, Hannover Medical School, Germany

The road from risk factors to vascular disease is in most patients long and complicated. Most of the cardiovascular risk factors are circulating substances such as metabolic factors as iGlucose or hypocholesteremia or uric acid. Others are hemodynamic factors such as hypertension. All these risk factors exert injury onto the vascular wall and lead to acute and chronic vascular changes. The first surface they encounter when acting on the vascular system are the endothelial cells. Endothelial cells cover all blood vessels and display a large surface area. The cardiovascular risk factors therefore firstly damage the endothelial cells. Since endothelial cells have a variety of physiological functions to keep our blood vessels active and healthy the damaging effects of the risk factors alter endothelial cell function. The most important of the endothelial cell functions are vasoconstriction/vasodilation, regulation of transport from the circulating blood into the vascular wall and interaction with circulating blood cells i.e. inflammation. All these functions are influenced by cardiovascular risk factors. Endothelial cells in patients with diabetes show an exaggerated permeability and allow circulating substances to enter the vascular wall in high concentrations. In addition, the vasodilatory function of endothelial cells is impaired via a downregulation of eNOS. At the same time the production of superoxide from endothelial cells is increased. Thirdly, the inflammatory activity of the endothelial cells is altered by cardiovascular risk factors. The endothelial cells change their glycosylated surface molecules (glycocalyx) and expose adhesion molecules which bind circulating leukocytes and platelets. In addition, the binding sites for inflammatory molecules on the glycocalyx are altered and enhances interaction with inflammatory molecules. Lastly, the coagulation cascade and complement cascade are influenced by cardiovascular risk factors and are more active. After the injury of the endothelium the behavior of the vascular wall changes, vascular smooth muscle cells proliferate and subsequent changes are induced. However, for a long time in of the life of a patient the endothelial cell dysfunction as described above is the major vascular alteration. It is a challenge to analyze endothelial cell function in patients. Although endothelial mechanisms have been observed for more than two decades, we are still in the infancy of the assessment of endothelial cell function. Circulating markers of endothelial cell damage, assessment of the glycocalyx and measurement of microinflammation are targets for future research. Only a better understanding of the endothelial cell function in our patients will help us to delineate novel treatment strategies in the patients who most need it.

Treatment of Hypertension and CMS: New Algorithm for Hypertension Diagnosis and Treatment

Reuven Zimlichman

Sackler Faculty of Medicine, Tel Aviv University, The E. Wolfson Medical Center, Holon, Israel

Increased longevity during the last decades caused changed significantly the proportions of different types of hypertension, their therapeutic and diagnostic aspects.

Aging of the population increases the proportion of patients with stiff arteries and changes our approach to evaluation, diagnosis and treatment of hypertensive patients. With increasing age arterial stiffness increases, a process that causes increase in systolic pressure and decrease in diastolic pressure, the mechanism of which will be discussed. These demographic changes are the reason why the majority of patients with hypertension today have isolated systolic hypertension and their treatment should be guided by this finding. These facts should cause to change of diagnosis, evaluation and treatment of patients with hypertension and should lead us to different algorithms and treatment modalities.

Obesity Hypertension: Weight Reduction and Pharmacological Approach

Efrain Reisin

Department of Medicine, Louisiana State University Health Science Center, New Orleans, USA

There is an increasing global prevalence of the metabolic syndrome and obesity. Both conditions are associated with higher prevalence of hypertension, cardiovascular and renal disease.

The potential underlying mechanisms by which obesity and the metabolic syndrome promote hypertension include changes in cardiovascular and renal physiology induced by leptin, the sympathetic nervous system, insulin resistance, free fatty acid, natriuretic peptides and proinflammatory cytokines.

Obesity has been associated with increase in left ventricular wall thickness, and a high prevalence of left ventricular hypertrophy and left ventricular mass. Obese subjects also show a high incidence of focal segmental glomerulosclerosis.

Weight reduction induced by hypocaloric diet or bariatric surgery has been effective in decreasing hypertension and improving cardiovascular and renal risks.

Few prospective trials have been conducted in the search of the ideal antihypertensive regimen for obese hypertensive subjects; but the optimal antihypertensive drug therapy in these patients has not been defined.

Angiotensin converting enzyme inhibitor and angiotensin receptor blockers are considered the best initial approach in the treatment of hypertension in subjects with obesity and the metabolic syndrome, because they do not worsen the insulin sensitivity.

Calcium channel blockers are supported by some national and international recommendations to be used as second line therapy.

Controversy has long existed about the safety of using thiazide diuretics to improve the antihypertensive efficacy in the subjects with obesity and the metabolic syndrome.

Aldosterone antagonist may have a role in the treatment of obesity hypertension.

A pilot study with a small number of obese patients have shown that aldosterone antagonist decreases blood pressure and improves metabolic parameters, but more studies are necessary to prove the safety of this approach.

Epigenetic Changes, Oxidative Stress and Vascular Disease in Obesity and Diabetes

Francesco Cosentino

Cardiology Unit, Dept. of Medicine, Karolinska University Hospital, Solna, Sweden

Type 2 diabetes mellitus (T2DM) is associated with increased risk of micro- and macrovascular complications and approximate two-fold greater risk of mortality as compared with the general population. Advances in therapy have reduced morbidity and mortality in patients with T2DM. However, cardiovascular risk is far to be eradicated and mechanism-based therapeutic approaches are needed. In patients with obesity and diabetes endothelial inflammation, mitochondrial oxidative stress and reduced availability of nitric oxide, a key effector of vascular health are common features. This chain of events favors the development of coronary atherosclerotic lesions as well as vascular disease. Although the link between elevated cardiometabolic risk and atherosclerosis is well established, a better comprehension of the underlying mechanisms is of utmost importance to identify novel molecular targets. Adverse chromatin remodeling is emerging as a key driver of vascular damage and may play a role in this setting.

Stimulating the Protective Arm of the Renin-Angiotensin System: A Novel Approach to Cardio-Metabolic Prevention and Organ Protection

Thomas Unger

CARIM - School for Cardiovascular Diseases Maastricht University, Maastricht, The Netherlands

The renin-angiotensin system (RAS) plays an important role in the initiation and progression of tissue injuries in the cardiovascular and nervous systems. The detrimental actions of the AT₁ receptor (AT₁R) in hypertension and vascular injury, myocardial infarction and brain ischemia are well established. In the past twenty-five years, protective actions of the RAS, not only in the cardiovascular- but also in the nervous system, have been demonstrated. The so-called protective arm of the RAS includes AT₂- and Mas receptors (AT₂R and MasR) and is characterized by effects different from and often opposing those of the AT₁R. These include anti-inflammation, anti-fibrosis, anti-apoptosis and neuroregeneration that can counterbalance pathological processes and enable recovery from disease. The recent development of novel, small-molecule AT₂R agonists offers a therapeutic potential in humans with a variety of clinical indications which will be discussed.

Microalbuminuria and Renal Function as Indicators of Cardiovascular Risk

Bruno Watschinger

Department of Internal Medicine / Nephrology, Medical University of Vienna, Austria

Since the description of an elevated albumin excretion rate i.e. microalbuminuria as predictor for the development of nephropathy in diabetic patients, it has become evident that an elevated albumin excretion rate also reflects disturbances of the cardiovascular system. Through its close association with endothelial dysfunction, microalbuminuria serves as an early indicator of changes in the vascular system and subsequent cardiovascular risk.

Evidence suggests that cardiovascular risk and the albumin excretion rate follow a continuous relationship, with increasing risk in patients with higher levels even in the “normoalbuminuric range”. Likewise a reduced kidney function with a decreased glomerular filtration rate is an important risk factor for cardiovascular events and cardiovascular mortality.

Many observational studies have identified

- Microalbuminuria as predictor of the development of hypertension
- An association between microalbuminuria and/or GFR reduction with subsequent cardiovascular (e.g. myocardial infarction, stroke) as well as renal events,
- A predictive power of microalbuminuria for the development of renal functional impairment in the general population and in patients with renal disease, as well as
- An association between microalbuminuria and/or GFR reduction with increased cardiovascular mortality in diabetic and in non-diabetic subjects.
- Thus the preservation of renal function and the reduction of microalbuminuria have recently become important treatment targets.

Pre-levels of CV Risk Factors: Boosting Risk of Events and deciding who should be treated

Uday Jadhav

Cardiology Department., MGM New Bombay Hospital, India

Coronary heart disease risk in asymptomatic patients is based on Framingham risk criteria which estimate the risk of developing CHD within a 10-year time period. Low risk will correlate with a 10-year absolute CHD risk less than 10%. “Low-risk” risk estimate <5% does not necessarily mean “no risk,” as there is always a lifetime risks for CVD, even in absence of significant risk factors at a younger age. European Systematic COronary Risk Evaluation (SCORE) algorithm predicts only fatal cardiovascular events and the Prospective Cardiovascular Munster (PROCAM) model has a larger number of covariates.

Risk factor assessment tools only predict 60%–65% of cardiovascular risk, leaving many individuals to have cardiovascular events in the absence of traditional risk factors for atherosclerosis. Subclinical disease imaging is of utility to identify those with premature atherosclerosis.

Coronary arterial calcification (CAC) is pathognomonic of atherosclerosis. CAC occurs less frequently before the third decade of life but becomes extremely relevant with advancing age and does not require the use of contrast dye. CAC is also a measure of overall cardiac plaque burden. Patients without detectable calcium (CAC score = 0) have a very low rate of CHD death or myocardial infarction (0.4% over 3-5 years). Coronary calcium score is superior to conventional risk factors, highly sensitive C-reactive protein (CRP) and carotid intima media thickness (IMT) as a predictor of cardiovascular events. Coronary calcium score has a strong predictive value as has been shown in the recent Multi-Ethnic Study of Atherosclerosis (MESA) study and the Heinz Nixdorf Recall (NHR) study. Coronary calcium score will reclassify more than 50% of intermediate-risk patients into the high-risk or low-risk category. Absence of calcification indicates a very low likelihood of significant coronary artery stenosis in patients at low to intermediate risk and an event rate less than 2%. Calcification scoring is safe, reproducible, and inexpensive and helps individualize treatment in asymptomatic patients at low risk. Doses of radiation less than 0.7mSv makes calcium scoring an effective tool in assessment of premature atherosclerosis

Renal function by CKD in the elderly disease or not disease

Alexander Rosenkranz

*Medical University Graz, Department of Internal Medicine, Clinical Division of Nephrology, Graz,
Austria*

Nephrologists consider glomerular filtration rate of less than 60 ml/min/1,73m² as a significant impairment of renal function. Based on epidemiological data the cardio-vascular morbidity and mortality increases with eGFR <60 ml/min/1,73 m² and even more at 45 ml/min/1,73 m² or less. It is also well established that persons older than 70 years of age commonly suffer from impaired renal function (approximately >40%). As we know, starting with the 5th decade of life, renal function decreases at an average by 1 to 2% per year (Baltimore Longitudinal Study). Therefore, it is questionable whether an elderly person with an eGFR of 50 ml/min or less really suffers from renal disease. This overview discusses the possibility whether there are markers which could discriminate between “real” nephropathy or “age-induced” impaired renal function. One of the markers could be FGF23, which has been lately linked not only to be increased in patients with chronic kidney disease but also as a cardiovascular risk marker.

Renal Complications of Diabetes: Glomerular vs Tubular Genetic Implication

Pavel Hamet, Paul Simon, Francois Harvey, François-Christophe Marois-Blanchet, Mounsiif Haloui, Michael Phillips, Stephen Harrap, Mark Woodward, John Chalmers, Michel Marre, Johanne Tremblay

University of Montreal, Dept. of Experimental Medicine at McGill University, Canada

While renal complications of diabetes are a well-recognized health economic burden, the fact that two distinct components i.e. glomerular and tubular are playing a role is less known. eGFR is a standard measurement of glomerular function and albuminuria, (urinary albumin creatinine ratio, UACR) is becoming an accepted marker of tubular reabsorption dysfunctions. In ADVANCE trial, we have demonstrated that eGFR decline and increase in albuminuria contribute independently and additively to renal and cardiovascular (CV) outcomes including CV death (*Ninomiya et al, J Am Soc Nephrol 2009; 20: 1813-21*). A recent large meta-analysis confirmed a significant improvement of discrimination in cardiovascular outcomes (including death) even beyond traditional risk factors by addition of eGFR and UACR, the improvement being even better with UACR (*Matsushita et al, Lancet Diabetes Endocrinol 2015;3:514-25*). This led us to hypothesize that GFR and albuminuria have distinct genetic determinants in conformity with CKDgene reports which included ADVANCE data (*Pattaro et al. Nat Commun. 2016 Jan 21;7:10023 and Teumer et al. Diabetes. 2015 Dec 2. pii: db151313*). We have performed GWAS analysis on 3500 T2D patients of Caucasian origin from ADVANCE trial. We used Affymetrix 5.0 and 6.0 followed by SNP imputation and analysed separately eGFR decline and UACR increase during the five year follow-up of the trial. Subjects who had an eGFR decline faster than expected by age despite standard therapy showed the strongest association with uromodulin gene (UMOD) : in subjects bearing A allele for the rs9922248 ($p = 3.9 \times 10^{-7}$). UMOD is the best known marker of nephropathy. GWAS of albuminuria increase despite standard therapy identified the strongest associations with SPOCK3 gene ($p= 6.8 \times 10^{-7}$), a calcium binding proteoglycan and with PALLD gene (1.6×10^{-7}) previously shown to be associated with risk of myocardial infarction in GWAS Catalogue. The establishment of genetic risk scores (GRS) for GFR and UACR separately will help us to modulate the capacity of personalized therapeutic tools for attenuation of GFR decline and albuminuria increase in subject according to their individual risks. We propose that such tool will serve as complementary diagnostics in selection of most appropriate individualized prevention of renal function decline in diabetic patients.

Early Kidney Impairment and Prehypertension

Bojan Jelaković

School of Medicine, University of Zagreb, Croatia

A strong association between hypertension, chronic kidney disease (CKD) and cardiovascular (CV) disease was observed. CKD is a silent global epidemic, and high prevalence of CKD is considered a major public health issue. It is of utmost importance to determine predictors of development to CKD. Hypertension is an important risk factor for renal impairment, progression of CKD and a predictor of development to ESRD. However, the link between prehypertension (PHT) and risk of CKD and ESRD remains controversial. This is probably due to the fact that PHT is not a homogeneous group consisting of susceptible subgroup(s) which faster transfer to HT. There is no consensus which factors predict progression to hypertension and consecutively, or independently, to CKD. Furthermore, relationship between CKD and PHT is a chicken-egg situation, and early renal impairment, mostly through sympathetic overactivity, could be predisposing factor for PHT. Glomerular hyperfiltration (GHF) was associated with progression of kidney disease and hypertension (HT). It was reported that GHF increases risk of developing albuminuria in hypertension stage 1, but we failed to find data on association of GHF and clinical course in PHT.

Trying to answer some of controversial topics, data on 5162 subjects (m 2387 w 2775) from BrEna cohort formed from original cohorts of Brisighella Heart Study (Italy) and ENAH study (Croatia) were analyzed. Out of them 3389 (m 1456 w1933) were eligible for further analyses, and 1335 (m 541 w 794) were followed up for average period of 100 months (IQ84-120); 11.337 person years of follow-up. CKD was defined as eGFR<60 ml/min, HT as BP \geq 140/90 mmHg and/or taking antihypertensive drugs, and PHT according to JNC-7 (PHTJ) and ESH stratification (PHTE). Our aims were to determine prevalence of PHT in European rural continental population; to determine incident hypertension (IHT) in PHT subjects; to analyze predictive value of various risk factors; and finally to analyze effect of glomerular hyperfiltration on progression to hypertension and kidney function.

Prevalence of PHTJ was 25.8% (m vs. w 28.4vs.23.9%; $p<0.05$), PHTE 7.8% (m vs.w 8.5vs.7.2; $p>0.05$). Prevalence of CKD in the whole group was 12.1% (m vs. w. 8.1 vs.15.2; $p<0.01$). In the whole group prevalence of CKD increases across BP categories in both gender. However, at baseline, in logistic regression adjusted risk (OR) for CKD was not significant comparing PHT vs. NT, and at the end of follow up PHT was not an independent predictor of new-onset CKD even in obese. IHT was diagnosed in 57.7% PHT subjects (no gender difference), incidence rate of 6.8% per year; 28.5% were treated and 41%controlled. Subgroup of PHT who developed IHT were older, had higher systolic BP, metabolic abnormalities and higher values of leptin and albuminuria.

PHT was not found to be an independent risk factor for new- onset CKD (3a stage) even in subjects with BMI > 30 kg/m². Probably, longer period of follow-up, as it was in HUNT study, is needed this association to become evident. Nevertheless, in PHT, particularly obese, it is prudent to monitor kidney function yearly. High proportion of PHT develop IHT, minority of them are treated and controlled. Diagnostic and prognostic values of albuminuria for IHT in PHT should be further elaborated. According to our results heart rate is positively associated with GHF indicating that increased sympathetic activity might have an important role. In our group of healthy subjects GHF was associated with more rapid decrease of GFR. No impact of GHF on albuminuria and development of IHT in healthy subjects was observed. GHF has less prominent effect on hypertension and albuminuria in apparently healthy subjects and PHT than in those with HT and metabolic disorder.

Coronary Microvascular Dysfunction in Patients with Hypertension, Metabolic Syndrome and Diabetes

Salvatore Novo, V Sucato, A Quagliana, S Evola, G Novo
*Chair of Cardiovascular Disease, Department of Sciences for promoting Health (PROSAMI),
University of Palermo, Italy*

In patients undergoing coronary angiography to evaluate chest pain, 20 percent about has normal coronary angiograms but coronary microvascular dysfunction (CMD). However, the specific role of cardiovascular risk factors (RFs) in CMD still unclear. Our studies aimed to clarify this aspect in different sets of patients, with hypertension, metabolic syndrome (MetS) and diabetes, using two indexes described by Gibson, the Timi Frame Count (TFC) and by Yusuf, the Myocardial Blush Grade (MBG), and the sum of these two indexes in the three main coronary arteries, the LDA, the Cx and the CDx arteries, i.e the total TFC (TTFC) and the total MBG (TMBG).

- We compared 120 patients with essential hypertension with 63 normotensive people which had blood pressure levels under optimal control (140/90 mmHg for three consecutive supine measurements) without any medical therapy. Both normotensive and hypertensive patients had normal coronary arteriograms and angina. The comparison between TFC and MBG values, as well as TTFC and TMBG showed remarkable and significant differences between hypertensives (TTFC longer and TMBG lower) and normotensives
- In 233 patients, whose 109 with MetS, defined according to the Consensus Statement published by Albert K et al, on Circulation 2009 and 124 without, all the values of TFC (longer) and MBG (lower) were significantly different in patients with MetS in comparison with controls, as well as the TTFC and TMBG (p 0.002).
- Finally, recently we studied 310 patients, divided into two groups: diabetics without hypertension (164 patients) and hypertensives without diabetes (146 patients). We found a worse CMD in diabetic-non hypertensive patients with higher values of TFC and TTFC and lower values of MBG and TMBG (p=0.02), compared with non-diabetic hypertensives.

So, in conclusion, patients with chest pain, normal coronary angiograms and RFs such as hypertension, MetS and diabetes show a CMD as evaluated by TFC/TTFC and MBG/TMBG; these alterations are particularly evident in the set of diabetic patients.

Metabolic Syndrome - Clinical Significance and Treatment

Giuseppe Mancia

University of Milano, Bicocca, Italy

This presentation will address pathophysiological and clinical aspects of the condition termed “metabolic syndrome “. Although believed by some to lack pathophysiological unity (and thus be only the coexistence of a number of cardiovascular risk factors by chance) emphasis will be given to the fact that 1) regardless the above criticism, the metabolic syndrome is easily diagnosed, thereby representing a useful tool to identify a high cardiovascular risk condition in medical practice 2) it underscores that the risk factors operate interactively, making the cardiovascular risk high also when individually their modification from normality is only modest and 3) glucose, lipid and blood pressure components of the metabolic syndrome are related in more than a casual fashion, thereby having a pathophysiologic link. The prevalence, risk and abnormalities accompanying the metabolic syndrome will then be described, based on the population data of the PAMELA study. It will be shown that 1) the metabolic syndrome is extremely common in the middle age and elderly fraction of the population; 2) its blood pressure and glucose components are those most frequently found;) there is in this syndrome a much higher prevalence of asymptomatic organ damage than in the control condition and 4) there is also a much higher risk of developing diabetes (in those non diabetic at the start), in and out-of-office hypertension, and cardiovascular events. Treatment should address primarily the required lifestyle changes plus antihypertensive, antidiabetic and lipid lowering drugs if hypertension, diabetes or frank dyslipidemia is present. Antihypertensive drugs should avoid medicaments that may increase the risk of developing diabetes.

The Prognostic Impact of Blood Pressure at Rest and During Ergometer Exercise through 35-yr of Follow-Up in 2014 Apparently Healthy Middle-Aged Men

Sverre E Kjeldsen

Dept. of Cardiology, University of Oslo, Ullevaal Hospital, Norway

Exercise systolic blood pressure (SBP) predicts coronary heart disease in the general population. We tested if changes in exercise SBP through seven years predict coronary heart disease (CHD) and death over the following 28 years. Peak SBP at 100W workload (5.5 METS) was measured among 1,392 men, apparently healthy in 1972-75 and at re-examination 1979-82. All completed the initial workload 100W during bicycle exercise-ECG test at both examinations. The men were divided into quartiles (Q1-Q4) of change in exercise SBP. Relative risks of CHD (angina pectoris, non-fatal myocardial infarction and coronary death) and mortality, between quartiles were calculated using Cox proportional hazard regression adjusting for age, smoking status, resting SBP, peak SBP at 100W and cholesterol at first examination (model 1) and further for physical fitness and change in physical fitness (model 2). Mean change in peak SBP at 100W was +3 mmHg. The highest quartile, Q4, was associated with 1.54-fold (95% CI; 1.17-2.02) adjusted risk of CHD and 1.91-fold (1.23-2.99) risk of CHD death compared to the lowest, Q1. Q4 remained associated with a 1.39-fold (1.05-1.84) risk of CHD and a 1.70-fold (1.08-2.67) risk of CHD death when further adjusted according to model 2. Q4 was associated with increased risk of cardiovascular- and all-cause death compared to Q1 in model 1, but fell short of statistical significance in model 2.

Our results indicate that an increase in exercise SBP at 100W over seven years is independently associated with increased long-term risk of CHD. These findings substantiate our previous finding that that high exercise SBP is an important risk factor for CHD in healthy men.

Prehypertension, Hypertension and Renal Denervation

Guido Grassi

Clinica Medica, Ospedale San Gerardo, University of Milano-Bicocca, Milano, Italy

Evidence collected during the past thirty years have unequivocally shown that sympathetic activation is a hallmark of the essential hypertensive state, its magnitude being progressively greater from prehypertension to mild, moderate and severe high blood pressure states. Recently, new data have been provided that the neuroadrenergic activation detectable in the prehypertensive and in the hypertensive clinical condition appears to be potentiated in the true resistant forms of high blood pressure. These findings, coupled with the evidence that in experimental animal models radiofrequency ablation of bilateral renal nerves reduce blood pressure, have represented the pathophysiological background for the several clinical studies, including those known under the acronym "SIMPLICITY".

This presentation will first examine the evidence that sympathetic overdrive is an important pathophysiological feature of essential hypertension, and specifically of resistant hypertension. It will then examine the "sympathetic effects" of the procedure, discussing both the short- and the long-term effects of the intervention on sympathetic function as well as their relationships with blood pressure changes. Finally, the impact of the procedure on short-term as well as long-term clinic and ambulatory blood pressure values will be discussed, analyzing the possible factors responsible for the negative results reported in recent clinical studies. The ongoing clinical studies carried out in the field of mild and more severe resistant or non-resistant hypertension will be also reviewed.

Influence of Prehypertension and Hypertension on the Progression of Coronary Artery Atherosclerosis: Results of the Heinz Nixdorf Recall Study

Raimund Erbel, Nils Lehmann

Institute of Medical Informatics, Biometry and Informatics, University Hospital Essen, University Duisburg-Essen, Germany

Hypertension belongs to the great four risk factors identified by the Framingham study for more than 50 years. A lot of efforts have been undertaken in order to improve the detection and treatment of this disease, which is leading to atherosclerosis manifesting as coronary heart disease as well as cerebro-vascular events including disabling strokes. In the elderly hypertension is found in > 50 % of the population, but only treated in about 50% and reaching recommended thresholds in only 30%. Multiple guidelines have been presented in order help physicians in the correct decision related to selection of antihypertensive agents and treatment options.

Blood pressure is classified as normal, prehypertension, hypertension stage 1 and stage 2 according to the JNS 7 guidelines. Despite many hints of epidemiological and clinical studies the treatment of prehypertension is still controversial, particularly related to primary prevention. Prehypertension is leading to target organ damage including changes of endothelial function, left ventricular hypertrophy, diastolic left ventricular dysfunction as well as extra-cardiac diseases. Coronary atherosclerosis can now, non-invasively, be detected using computed tomography (CT) visualizing coronary artery calcification (CAC) in the whole coronary tree (1). CAC can not only be detected but also quantified, which is a great advantage. However, CAC is currently not accepted as a method for detection of target organ damage despite the fact that the rate of coronary as well as cardiovascular events is strongly related to the level of blood pressure (2). Even in prehypertension higher rates of coronary and cardiovascular events compared to normotensives was reported (2). Meanwhile, also CAC progression, measured by repeated CT scans, has been reported (3, 4). CAC progression seems to be inevitable, but can be subdivided in rapid, moderate and slow progression comparing observed values with predicted values. It could be shown that not only hypertension, but also prehypertension is closely related to rapid progression of CAC. Even in the range below 140/90 mmHg each 10 mmHg increase was associated with a higher CAC progression, particularly in women.

Conclusion: Future studies aiming at treatment of patients with prehypertension may concentrate on those who show a target organ damage of the coronary arteries and determine CAC as well as CAC progression as endpoint for further elucidating whether or not antihypertensive agents are indicated outbalancing potential pharmaceutical induced risk.

- Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, Dragano N, Grönemeyer D, Seibel R, Kälsch H, Bröcker-Preuss M, Mann K, Siegrist J, Jöckel KH; Heinz Nixdorf Recall Study Investigative Group. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol*. 2010 Oct 19;56(17):1397-406.
- Erbel R1, Lehmann N, Möhlenkamp S, Churzidse S, Bauer M, Kälsch H, Schmermund A, Moebus S, Stang A, Roggenbuck U, Bröcker-Preuss M, Dragano N, Weimar C, Siegrist J, Jöckel KH; Heinz Nixdorf Recall Study Investigators. Subclinical coronary atherosclerosis predicts cardiovascular risk in different stages of hypertension: result of the Heinz Nixdorf Recall Study. *Hypertension*. 2012 Jan;59(1):44-53.
- Lehmann N, Möhlenkamp S, Mahabadi AA, Schmermund A, Roggenbuck U, Seibel R, Grönemeyer D, Budde T, Dragano N, Stang A, Mann K, Moebus S, Erbel R, Jöckel KH. Effect of smoking and other traditional risk factors on the onset of coronary artery calcification: results of the Heinz Nixdorf recall study. *Atherosclerosis*. 2014 Feb;232(2):339-45.

- Moebus S, Bauer M, Kälsch H, Budde T, Montag M, Schmermund A, Stang A, Führer-Sakel D, Weimar C, Roggenbuck U, Dragano N, Jöckel KH; Heinz Nixdorf Recall Study Investigators. Progression of coronary artery calcification seems to be inevitable, but predictable - results of the Heinz Nixdorf Recall (HNR) study. *Eur Heart J.* 2014 Nov 7;35(42):2960-71.

Subclinical Vascular Damage in Prehypertension

Enrico Agabiti-Rosei

Dept. of Medical and Surgical Sciences, University of Brescia, Italy

The relationship between blood pressure (BP) and cardiovascular events is continuous and therefore the distinction between normotension and hypertension is arbitrary. However, for practical reasons, this distinction is universally accepted, although a number of studies have shown that cardiovascular risk is increased when BP values are in the upper range of normotension. For this reason US Guidelines have proposed a distinction between normal BP and “prehypertension”, the condition in which SBP is between 120 to 139 mm and/or diastolic BP is between 80 and 89 mm Hg. European Hypertension Guidelines define “high normal BP”, as a SBP between 130 and 139 and/or a DBP between 85 and 89 mmHg. Despite the differences in cut-off values, studies have shown that these two conditions are associated with a greater prevalence of organ damage, a higher risk of developing hypertension and an increased risk of cardiovascular events. In a general population in Northern Italy we have evaluated the progression to hypertension and the development of target organ damage in 585 subjects (age 50 ± 8 years, 46% males) who were divided, according to BP values at the baseline visit, into 3 groups: normotensives (NT) (SBP/DBP < 130/85 mmHg); High Normal (HN) (SBP/DBP >130/85 and < 140/90 mmHg) and hypertensives (HT) (SBP/DBP > 140/90 mmHg). In 420 subjects a follow up (FU) visit, laboratory examinations, measurement of carotid femoral pulse wave velocity (PWV) and carotid intima media thickness (IMT) were performed after 9 years. Among patients classified as HN at baseline (30 % of total), 71% developed hypertension at FU, 18% had HN BP, 11% were NT. Among subjects classified as NT at baseline, 34% developed hypertension at FU, 23 % were classified as HN and 43 % were NT. A high prevalence of masked hypertension (44%) was observed in patients with HN BP. At Follow up in HN and in HT, as compared with NT, a significant increase of PWV (11.2 ± 2.1 and 12.4 ± 3.3 vs 10.1 ± 1.9 m/sec, ANOVA $p < 0.01$) and of common carotid IMT (1.00 ± 0.19 and 1.09 ± 0.27 vs 0.93 ± 0.15 mm, ANOVA $p < 0.01$) was observed. In conclusion, high normal BP is a common condition in the general population; patients with BP values in the HN range not only frequently develop hypertension in the subsequent years, but also show a greater progression of preclinical organ damage.

Arterial Stiffness and Physical Activity as an important Modifier of Vascular Health

Arno Schmidt-Trucksäss

Division Sports and Exercise Medicine, Medical Faculty, University Basel, Switzerland

To increase physical activity is one of the most important means to reduce the burden of chronic non-communicable diseases and increase overall well-being and quality of life. In general this statement is true and meanwhile generally implemented in guidelines.

The effect of healthy physical activity is visible as a long-term effect on the prevalence of cardio-vascular events but also is associated with arterial stiffness as one of the emerging surrogates for cardio-vascular health. With regard to public health initiatives it is of great interest to know, whether different types (i.e. strength of aerobic exercise) or volume of physical activity (i.e. from sedentarism to healthy levels or beyond) shall be recommended at every age and gender or for patients with or without hypertension.

Thus, this presentation will aim to give a deeper look inside into the dose-response relationship between physical activity and arterial stiffness to better support the initiation of physical activity and monitor the effect of changes of arterial stiffness over time.

Arterial Aging in Hypertension

Charalambos Vlachopoulos

1st Dept. Cardiology, Athens Medical School, Greece

Tools to stratify the risk of patients at an individual level beyond classical risk scores are biomarkers. A surrogate endpoint is a biomarker that is intended as a substitute for a clinical endpoint. In order to be considered as a surrogate endpoint of cardiovascular events, a biomarker should satisfy several criteria, such as proof of concept, prospective validation, incremental value, clinical utility, clinical outcomes, cost-effectiveness, ease of use, methodological consensus, and reference values.

Arterial biomarkers have the potential to integrate the damage of risk factors on the arterial wall over a long period, together with the impact of genetic background. Thus, they have the ability to predict a person's overall cardiovascular risk above and beyond classical risk factors, fitting within the concept of early vascular aging. On the basis of stringent criteria, arterial biomarkers can be classified in three groups:

- Biomarkers that fulfill most of the criteria and, therefore, are close to being considered a clinical surrogate endpoint are carotid ultrasonography, ankle-brachial index and carotid-femoral pulse wave velocity;
- Biomarkers that fulfill some, but not (yet) all of the criteria are brachial ankle pulse wave velocity and central haemodynamics/wave reflections;
- Biomarkers that do not at present fulfill essential criteria are flow-mediated dilation and endothelial peripheral arterial tonometry.

Given their involvement in the pathophysiology of hypertension, arterial biomarkers have an additional role beyond risk prediction specifically for this condition. This is prediction of the **development of the hypertension** (incident hypertension) in normotensive adults. Of all vascular biomarkers, arterial stiffness most strongly associates with incident hypertension. Arterial stiffness has a bidirectional causal relationship with blood pressure. Endothelial dysfunction, as assessed by FMD, has independent predictive value on the incidence of hypertension although findings are not always independent from baseline blood pressure levels. Scarce data exist for wave reflections and cIMT.

The ESH/ESC guidelines for the management of arterial hypertension encourage the screening for vascular biomarkers (in the context of asymptomatic organ damage) as an intermediate stage in the continuum of vascular disease.

Reference:

Vlachopoulos C, Xaplanteris P, Aboyans V, et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis*. 2015;241:507-32

Aortic Stiffness and Metabolic Syndrome Components

Ian Wilkinson

Clinical Pharmacology Unit, Addenbrooke's Hospital, UK

Background: Aortic stiffness is an important predictor of future morbidity and mortality. Diabetes is associated with accelerated vascular ageing and increased aortic stiffness. However the importance of non-diabetic dysglycaemia as a risk factor for accelerated aortic stiffening is unclear.

Methods and results: We tested the hypothesis that dysglycaemia is associated with accelerated aortic stiffening in non-diabetic individuals, independently of other known risk factors for arterial stiffening. Longitudinal data on carotid femoral pulse wave velocity (cfPWV), glycaemia and other cardiovascular risk factors were drawn from 4386 non-diabetic participants in the Whitehall II Study. The mean age of the cohort at cfPWV baseline was 60 years, and 74% were male. cfPWV increased from (mean±SD) 8.30±1.93 to 8.98±2.39 m/s over 4 years of follow-up. At baseline, cfPWV was associated with fasting and 2-hour postload glucose, HbA1c, and HOMA-insulin resistance (HOMA-IR). HbA1c and HOMA-IR were significantly associated with progression of cfPWV after adjusting for physiological confounders and cardiovascular risk factors. A 1SD higher HbA1c and HOMA-IR were associated with greater increases in cfPWV over 5 years (0.12 (0.04, 0.19) P=0.002 and 0.10 (0.01, 0.18) P=0.02 m/s respectively). Additional adjustment for BMI significantly weakened the association with HOMA-IR but not with HbA1c.

Conclusions: HbA1c is independently associated with accelerated progression of aortic stiffness in non-diabetic individuals. This suggests that impaired long-term glycaemic control is a risk factor for accelerated vascular ageing, and may be an important target for preventative strategies.

Central Blood Pressure and Cardiovascular Outcome: A meta-analysis

Carmel McEniery

Clinical Pharmacology Unit, Addenbrooke's Hospital, UK

Background: Systolic blood pressure (SBP) differs between the brachial artery and aorta. Prospective data suggest that central pressure predicts future cardiovascular events, but it is unclear if it is superior to brachial pressure.

Methods and Results: A systematic review and individual participant data meta-analysis from 15 studies was undertaken. Study-specific associations of central and brachial pressure with cardiovascular outcomes, with and without mutual adjustment, were determined using Cox proportional hazard models, and random effect models to estimate pooled estimates. Of 22,433 participants, 908 had a myocardial infarction (MI) and 641 a stroke. The pooled age, sex, height and heart rate adjusted hazard ratio (HR) [95% CI] per SD increase in brachial SBP was 1.17 [1.03, 1.32] for MI and 1.28 [1.13, 1.46] for stroke and 1.16 [1.02, 1.33] and 1.33 [1.15, 1.53] for central SBP, respectively. Mutual adjustment attenuated the HRs for MI: brachial SBP (1.16 [0.90, 1.48]), central SBP (1.09 [0.87, 1.38]) and stroke: brachial SBP (1.18 [0.97, 1.42]), central SBP (1.19 [0.99, 1.44]). However, associations between central SBP and stroke, after adjustment for brachial SBP, were higher in those aged <61 years than in older individuals (1.83 versus 1.08; p-interaction <0.001).

Conclusion: Brachial and central SBP have similar associations with future CV events. Larger studies are required to test whether central SBP may be a more powerful predictor of stroke risk in younger individuals.

Microvascular Structural Alterations and Tissue Perfusion in Hypertension/Diabetes

Damiano Rizzoni

Clinica Medica, Dept. of Clinical and Experimental Sciences,, University of Brescia, Italy

The presence of structural alterations in the small resistance vessels microcirculation that may be observed both in hypertension and in diabetes mellitus may be considered an important link between hypertension and ischemic heart disease, heart failure, cerebral ischemic attacks and renal failure. It is now widely accepted that structural abnormalities of resistance vessels are common alterations associated with chronic hypertension. An increased arterial wall thickness together with a reduced lumen may play an important role in the increase of vascular resistance, and may also be an adaptive response to the increased haemodynamic load. In the last years, many experimental studies have indicated that changes of small artery structure in hypertension are the consequence of either eutrophic or hypertrophic remodeling (re-arrangement of the same amount of wall material around a narrowed lumen or smooth muscle cell hypertrophy/hyperplasia, respectively). The increased media to lumen ratio was demonstrated to be a powerful predictor of cardiovascular events in a high risk population of patients with primary and secondary hypertension. The prognostic importance of structural alterations of subcutaneous small resistance arteries was extended to patients with essential hypertension at low-moderate cardiovascular risk, and to major cardiovascular events (myocardial infarction, stroke and sudden death).

Hypertension and, at least in part, diabetes mellitus is associated with a reduction in the number of total or perfused capillaries. The phenomenon, called rarefaction, may have pathophysiological consequences in terms of tissue perfusion and, consequently, development of organ damage and/or clinical events. However no data about the prognostic meaning of functional or structural capillary rarefaction is presently available

The possible regression of vascular alterations is an appealing goal of antihypertensive treatment. A complete normalization of small resistance artery structure was demonstrated in hypertensive patients, after prolonged and effective therapy with dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. No effect was observed with beta-blockers and diuretics despite similar blood pressure reduction. Recent data suggest also the presence of a prognostic relevance of the extent of the regression of vascular structural alterations. Also capillary rarefaction may be positively influenced by antihypertensive treatment. However, prospective studies, possibly with less-invasive approaches, are needed in order to clarify whether structural alterations in small resistance arteries may be definitely considered a surrogate endpoint in the evaluation of the effects of antihypertensive treatment. Recently, a non invasive evaluation of retinal arteriolar morphology by Scanning Laser Doppler Flowmetry was proposed. The information provided seems to be similar to those obtained with invasive assessments, thus opening interesting clinical perspectives in terms of risk stratification in hypertensive patients. Even more recently, data about the application of adaptive optics in this regards were made available.

What is new? Non invasive assessment of retinal microcirculation: focus on recent developments

What is the learning objectives? To provide information about the clinical meaning of microvascular changes as well as about therapeutic options.

24 Hour Measurement of Pulsatile Hemodynamics: The Logical Next Step

Thomas Weber

Cardiology Department, Klinikum Wels-Grieskirchen, UK

During the last decades, we have seen huge progress in our understanding of blood pressure in terms of diagnostic workup, prognostic value, and therapeutic options, in 2 main areas: first, the focus has shifted from the steady component of blood pressure to the pulsatile one, which includes brachial pulse pressure, central (aortic) hemodynamics, pulse wave reflections, and aortic stiffness (pulse wave velocity and other measurements). Many of them have been shown to confer additional value, when compared to traditional brachial systolic and diastolic blood pressure, and some of them (pulse wave velocity) have even been included into recent hypertension guidelines, based on meticulous assessment of their added value. The second major step forward was the recognition of blood pressure variability and the incorporation of out-of-office measurements of blood pressure (24 hour blood pressure monitoring, home blood pressure monitoring) into guidelines and daily practice.

Until recently, our ability to perform 24 hour blood pressure monitoring was confined to brachial systolic and diastolic blood pressure. Advancement in technology, however, has enabled manufacturers to build portable devices claiming to measure central hemodynamics and aortic stiffness in the ambulatory setting, most of them using brachial cuffs and dedicated software, some wrist-watch-resembling tonometric systems. Invasive validation studies for these devices have been performed for central systolic blood pressure in patients undergoing cardiac catheterization.

First clinical reports have shown physiological differences between diurnal profiles of brachial versus central systolic pressure, with the difference between both (ie amplification) being smaller during the night. Diurnal changes in heart rate may be the major contributor to these differences.

Recently, 24 hour central systolic blood pressure has been shown to be superior to 24 hour brachial systolic blood pressure for the detection of left ventricular hypertrophy in a single-center study. A multi-center project investigating the same issue will be reporting soon.

In summary, ambulatory pulsatile hemodynamics offer a novel opportunity for mechanistic and clinical cardiovascular research. Its clinical role will ultimately depend on the results of ongoing longitudinal studies.

Effectiveness of chlorthalidone/amiloride versus losartan in patients with stage I hypertension: results from the PREVER-TREATMENT randomized trial

Flávio Danni Fuchs

Division of Cardiology, Hospital de Clínicas de Porto Alegre, Brazil

Background: Angiotensin-receptor blockers (ARB) have been the preferential drugs in the management of hypertension worldwide, despite the absence of any consistent evidence of advantage over older agents, and the concern that they may be associated with lower renal protection (Fuchs FD, DiNicolantonio JJ. *Open Heart*. 2015; 2(1):e000236.). Diuretics are as efficacious as other agents, are well tolerated, have longer duration of action and low cost, but have been scarcely compared with ARBs. The PREVER Treatment trial compared the blood pressure-lowering effectiveness of a chlorthalidone/amiloride combination pill with losartan during initial management of Stage I hypertension.

Methods: Details of methods of this trial were published elsewhere (Fuchs FD, et al. *Trials*. 2011 Feb 24;12:53.). The study was conducted in 21 Brazilian academic medical centers. Trial participants (n=655) were adult volunteers aged 30-70 years with stage I hypertension following three months of a lifestyle intervention. During the trial, 13 (3.9%) patients assigned to chlorthalidone/amiloride and 15 (4.7%) assigned to losartan stopped taking their study medication due to an adverse event. At the end of follow-up, 609 (93%) of those randomized were evaluated. Participants were randomized to 12.5/2.5 mg of chlorthalidone/amiloride (N = 333) or 50 mg of losartan (N = 322). If BP remained uncontrolled after three months, study medication dose was doubled, and if uncontrolled after six months, amlodipine (5 and 10 mg) and propranolol (40 and 80 mg BID) were added as open label drugs in a progressive fashion.

Results: The mean difference in systolic BP during 18 months of follow-up was 2.3 (95% CI: 1.2 to 3.3) mmHg favoring chlorthalidone/amiloride. Compared to those randomized to diuretic, more participants allocated to losartan had their initial dose doubled and more of them used add-on antihypertensive medication. Levels of blood glucose, glycosylated hemoglobin, and incidence of microalbuminuria and diabetes were no different between the two treatment groups. Serum potassium was lower and serum cholesterol and LDL-cholesterol were higher in the diuretic treatment group. ECG indexes of left ventricular mass reduction were no different by treatment arm. Microalbuminuria tended to be higher in patients with diabetes allocated to losartan (28.5 ± 40.4 versus 16.2 ± 26.7 mg, $P = .09$).

Conclusion: Compared to losartan, treatment with a combination of chlorthalidone and amiloride yielded a greater reduction in BP. There was no evidence of superior renal protection by losartan compared to diuretic therapy, particularly in patients with diabetes.

Effectiveness of an Association of Chlorthalidone with Amiloride for the Prevention of Hypertension and end Organ Damage in Patients with Prehypertension: The Prever Prevention Randomized Clinical Trial

Sandra C. Fuchs

Division of Cardiology, Hospital de Clinicas de Porto Alegre, Brazil

Background: Prehypertension increases the risk of cardiovascular events, end organ damage and anticipates the developing of full hypertension. Non-drug interventions have low effectiveness to avert such consequences. Two large clinical trials have showed the effectiveness of drug interventions to prevent the incidence of hypertension, but there is no study investigating the prevention of end organ damage or major cardiovascular events. Our trial was designed to investigate the effectiveness and safety of low dose an association of diuretics for prevention of hypertension and reduction of target organ damage in adults with prehypertension.

Methods: Details of methods of this study were published elsewhere (Fuchs FD, et al. *Trials*. 2011 Mar 5; 12:65). In brief, this is a randomized, double-blind, placebo-controlled, multicenter, clinical trial, with participants aged 30 to 70 years, with prehypertension. Previously to the random allocation to the active drug or placebo interventions, all patients were submitted to a lifestyle intervention phase for 90 days. Participants who did not respond to the lifestyle intervention were randomized to 12.5/2.5 mg of chlorthalidone plus amiloride combination pill or placebo, once-daily, and were evaluated every three months during 18 months of treatment. Randomization was performed centrally, using a web-based automated system, with permuted block, stratified by center. Research team was masked to group assignment. The primary outcome was incidence of hypertension analyzed by intention to treat after a follow-up of 18 months. Development or worsening of microalbuminuria, new-onset diabetes mellitus, and reduction of left ventricular mass (LVM) were secondary outcomes.

Results: Baseline characteristics were similar between the two groups. The incidence of hypertension was significantly lower in 372 study participants allocated to diuretics compared to 358 allocated to placebo (HR: 0.58, 95% CI 0.40 to 0.80%), resulting in a cumulative incidence of 11.7% in the diuretic arm versus 19.5% in the placebo arm (P=0.004). Adverse events, levels of blood glucose, glycosylated hemoglobin, creatinine, microalbuminuria and incidence of diabetes were no different between the two treatment groups. Serum potassium was lower and HDL-cholesterol and uric acid levels were higher in the participants allocated to diuretic therapy. LVM assessed through Sokolow voltage and voltage-duration product decreased to a greater extent in participants allocated to diuretic therapy compared to placebo (P=0.02).

Conclusion: Low dose chlorthalidone and amiloride reduce substantially the risk of incident hypertension and beneficially affect left ventricular mass in individuals with prehypertension

Proneurotensin: Is it the Missing Link between Diet, Cardiometabolic Disease and Cancer?

Alan Maisel

University of California at San Diego, Care Unit and Heart Failure Program Veterans Affairs Medical Center, CA, USA

Cost effective cardiovascular prevention relies on the accurate identification of individuals at risk. However, a large proportion of individuals with cardiovascular events have 1 or fewer of the conventional risk factors, including smoking, diabetes, hypertension, or hyperlipidemia. Studies focusing on high-risk populations often yield favorable estimates of biomarker performance but the greatest need for new risk markers exists in low- to intermediate- risk populations, for whom the data are most conflicting .A common problem with cardiovascular biomarkers is that they correlate closely with traditional cardiovascular risk factors and thus add little incremental value for risk prediction when added on top of such traditional risk factors. Prior studies have demonstrated conflicting results regarding how much information biomarkers add to cardiovascular risk assessment.

Pro-Neurotensin (PNT) is a unique biomarker for CVD/ cancer and diabetes risk prediction and monitoring in female subjects. Because of the known relationship between Neurotensin and nutrition, Neurotensin may be a “treatable” biomarker. This would address the unmet need that new cardiovascular biomarkers can bring about improvements in risk assessment that are not just statistically significant but clinically significant as well. Thus, reclassifying individuals as being at low or high risk could have immediate clinical relevance with regard to identifying candidates for more rigorous nutrition control.

Prehypertension and Metabolic Syndrome in Different Population: Epidemiologic Aspects

Çetin Erol

AnkaraUniversity,, Faculty of Medicine,Dept.of Cardiology, Turkey

What is new? The newest numbers for prehypertension and metabolic syndrome in different population and whether the numbers have changed recently.

What is the learning objectives? To focus on the importance of these two entities worldwide and make aware of the people involving in these entities.

Hypertension remains a major public health problem as a critically important risk factor for cardiovascular and renal disease.Prehypertension as well is considered important for these outcomes.Recently presented and published SPRINT study confirmed the low level of blood pressure should be the target.

Metabolic syndrome which is defined as combination of risk factors is also very important for adverse cardiovascular outcomes and diabetes mellitus.Obesity is increasing worldwide and a pre-requisite for metabolic syndrome.So prevention of metabolic syndrome is crucial to the health of the world population.

Dietitians Taking Action Across Europe: Nutrition in all Health Policies

Anne de Looy

Professor of Dietetics and Hon President of the European Federation of the Associations of Dietitians University of Plymouth, UK

The impact on health through dietary advice and improvement in nutritional status and health has been well documented from cancer patients in dietetic-led clinics (1) to the older person suffering from malnutrition in multidisciplinary teams (2). Within the area of cardiovascular disease, and especially hypertension, recognition of changes in lifestyle as a primary intervention is now being vigorously pursued (4). Sahyoun, writing in 2011 (4), asks dietitians, who have particular insight into lifestyle modifications, to become more involved in policy, to reach out across healthcare and community divides and find ways to improve health and reduce health care spending. She goes on to say that dietitians should take proactive steps *'in incorporating nutrition services as core programs within an integrated health care delivery system'*. These exhortations are reflected in European policies such as, the White paper *'Strategy for Europe on nutrition, overweight and obesity'* (5) and the WHO *European Food and Nutrition Action Plan 2015-2020* (FNAP) (6), which stress policies and approaches which are integrated, cost-effective and preventative. Dietitians through such initiatives as the European Dietitians Action Plan 2015-2020 or EuDAP (7) are able to demonstrate their responsiveness and contribution to European Health improvement.

Dietitians in Europe do already make significant contributions to local, regional and national action plans regarding nutrition and food in some parts of Europe. The expertise of dietitians is used when drafting or implementing policy but dietitians need to be more widely recognised and used by Ministries of Health and local governments across Europe if their own plans, eg FNAP 2015-2020, are to be fully successful.

EuDAP sets out the commitment that dietitians and their NDAs are making to enhance and coordinate dietetic activities across Europe, to make explicit the impact dietitians are having on European nutritional health over the next five years.

Chinese Whispers? How Dietary Research on Hypertension and Metabolic Syndrome are Conveyed in the Print Media

Margo Barker

Dept of Oncology, University of Sheffield, UK

The print media have the potential to powerfully affect public understanding of nutrition, change dietary behaviour and ultimately improve wellbeing, given their role in nutrition education. This paper evaluates portrayal of dietary advice for hypertension and metabolic syndrome in UK print media, particularly men's lifestyle magazines and specialist running magazines. Although advice broadly follows public health recommendations encompassing a Mediterranean diet pattern, there are notable gaps of sodium and energy restriction. Particular emphasis on super-foods, fat-burning, and the efficacy of single nutrients, while covering a cornucopia of nutritional effects, may not lead to cardio-protective dietary behaviour. Despite the widespread use of scientific information to underpin dietary advice, the content, format and scientific basis of dietary content leaves much to be desired. Improved journalistic reporting of emerging nutritional science on hypertension and metabolic syndrome and provision of more nuanced advice is needed.

Effect of High Complex-Carbohydrate Diet on Weight Reduction and the Metabolic and Inflammatory Markers in Postmenopausal Women

O. Raz, O. Rogowski, T. Rosenzveig, I. Shapira

Tel-Aviv Sourasky Medical Center, Ariel University, Israel

Background and aims: There is evidence of increasing rate of obesity, sub-clinical low-grade inflammation, pre-diabetes and diabetes in postmenopausal women. As obesity and metabolic syndrome are among the major risk factors for cardiovascular diseases, weight reduction diets can be beneficial for reducing the acute phase inflammatory response and rate of diabetes and pre-diabetes. It is important to establish a kind of diet that is most beneficial for weight reduction, for improving metabolic markers and for attenuating inflammatory response. The aim of this research was to evaluate the effect of high complex-carbohydrate diet (HCCD) in treating obesity and in attenuating inflammatory and metabolic responses in postmenopausal women.

Results: HCCD had beneficial effect on biomarkers of inflammation as well as on lipid profile. In hyper-insulinemic women only, insulin levels decreased and insulin sensitivity was improved as shown by reduced HOMA-IR, and triglycerides level decreased.

Methods: 57 apparently healthy overweight (BMI of $31.5 \pm 3.8 \text{ kg/m}^2$) postmenopausal women participated in the study. 62% of the participants were hyper-insulinemic.

Participants visited a dietitian weekly for 8 weeks, were weighed, waist and hip circumferences were measured, and detailed dietary guidance was given. Blood samples were taken before and after 8 weeks, following an overnight 12-hour fast, for the following tests: hs-CRP, fibrinogen, ESR, WBCc, insulin, glucose, lipids, IL6, TNF α , VCAM, ICAM and plasma lipids.

Conclusions: Diet high in complex carbohydrates beneficially affected weight reduction and waist and hip circumferences, improved metabolic markers and attenuated inflammatory response, and in hyper insulinemic participants, caused a significant reduction in insulin level and HOMA-R. Concentration of ICAM, initially significantly higher in hyper-insulinemic individuals, was reduced by the diet. Weight reduction of about 4% was sufficient for achieving these results. The diet was easy to follow: adherence to the diet was about 80%.

Heritability of Plasma Triglycerides and Role of Adiponutrin

Fahad Al-Zadjali, S Al-Yahyae, S Albarwani, MO Hassan, RA Bayoumi
College of Medicine & Health Science, Muscat, Oman

Heritability estimates of metabolic syndrome traits vary widely across studies. Some studies have suggested that the contribution of genes may vary with age or sex. Serum lipid levels as well as coronary artery disease (CAD) have been shown to be highly heritable with estimates ranging from 40%–60%. This study, based on families recruited from community is aimed to investigate the mode of inheritance, heritability and shared environmental factors in controlling fasting serum Triglycerides and investigate the mean effect of common variant of adiponutrin (PNPLA3, I148M) on TG heritability. Results: The G allele frequency which codes for methionine position 148 is common in the study population accounting for 26%. Heritability of serum TG in 1200 subjects was 0.24 ± 0.058 (P-Value 0.0000002). Interestingly, age and gender adjusted analysis showed that I148M of PNPLA3 contributes to 70% of TG heritability (P-Value 0.0219). Cross sectional analysis revealed gender specific difference in PNPLA3 association with TG levels. In Male, significant dose effect were shown as GG carriers had higher fasting serum TG levels (P Value 0.00686) which were not shown in female subjects. In conclusion, Adiponutrin, a patatin like phospholipase domain containing protein (PNPLA3), known to regulate the triglyceride (TG) metabolism in adipose and liver tissues. PNPLA3 I148M variant showed gender specific association with fasting serum triglyceride levels and contributes to 70% of total genetic variation of serum triglyceride levels.

New Therapeutic Options to Treat Atherogenic Lipoproteins

Khalid Al-Rasadi

Department of Biochemistry, Sultan Qaboos University Hospital, Muscat, Oman

Despite the modest evidence from interventional studies showing that reduction of plasma triglyceride (TG) levels prevents cardiovascular events, recent data from both Mendelian randomization and epidemiological studies show that TG-rich lipoproteins are indeed pro-atherogenic. Non-high density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (Apo B) are markers not only of low-density lipoprotein (LDL) particles but also of TG-rich lipoprotein concentrations.

Statin is the primary treatment for atherogenic lipoproteins and the efficacy of statin therapy in both primary and secondary prevention has been established. Statin in combination therapy with ezetimibe, fibrates and niacin is more effective in reducing atherogenic lipoproteins although these therapies did not demonstrate benefit in reducing cardiovascular events.

New therapeutic treatments like cholesterol ester transfer protein inhibitors and proprotein convertase subtilisin/kexin type 9 (PCSK9) are promising treatments in reducing atherogenic lipoproteins.

Update in Management of Obesity

Mustafa Al Hinai

Sultan Qaboos University Hospital, Muscat, Oman

The prevalence and severity of obesity has increased markedly in recent decades making it a global public health concern. Since obesity is a potential risk factor in the development of hypertension, type-2 diabetes and cardiovascular diseases. Several therapeutic options are suggested to manage obesity. This includes behavioral, dietary, pharmaceutical and surgical methods. Current challenges exist in different guideline are proposed for each of these methods and many of them have not been evaluated rigorously for a definite recommendation and also lack adequate scientific validation. Therefore, presented talk will cover recent updates on management of obesity and also identify specific guidelines for obesity management associated with co-morbidities. Further importance will be shed toward maintenance of long-term control of body weight.

Sleep Related Disorders and Cardiometabolic Diseases

Mohammed A. Al-Abri

Senior Consultant Sleep Medicine, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman

Sleep is very vital for human physiology and it was suggested that eight hours of night sleep is needed for metabolism to work normally. Chronic sleep loss or disturbances may result in impairment of basic metabolic functions such as processing and storing of carbohydrates or regulating hormones secretions. Obstructive sleep apnoea (OSA) is a common condition that causes sleep disturbances, estimated to occur in 4% of men and 2 % of women. Studies had shown that OSA has an association of type 2 diabetes mellitus (DM). The association had been shown in epidemiological cross-sectional studies and in some prospective cohorts. The pathophysiology of the association between OSA and diabetes is not fully understood. However, type 2 diabetes mellitus and OSA are part of metabolic syndrome which is nowadays is increasing in prevalence worldwide. Furthermore, repetitive hypoxaemia and frequent arousals may both contribute independently in the development of DM in OSA patients. Hypoxaemia may increase sympathetic activities or directly decrease insulin sensitivity and worsen glucose tolerance. Treatment with Continuous positive airway pressure (CPAP) may help in preventing DM and also improving the glycaemic control in patients who already have type 2 DM. sleep deprivation is another risk factor for cardiometabolic diseases with increasing evidence supporting the association between short sleep duration and diseases like obesity, glucose intolerance and hypertension.

Early Recognition of Patient Deterioration on General Wards: The Need for Continuous Monitoring

Eyal Zimlichman

*Sheba Medical Center, Tel Hashomer, Israel
Brigham and Women's Hospital, Boston, MA, USA*

With rising complexity of hospitalized patients, a large proportion of patients experience serious adverse events during their hospital stay, including cardiac arrest, respiratory failure and shock leading to unplanned admissions to the intensive care unit (ICU), and death. For patients with unexpected clinical deterioration, delayed or suboptimal intervention is associated with increased morbidity and mortality. This has prompted many hospitals to implement some form of a rapid response system (RRS) for early detection of clinical deterioration and adequate response through rapid response teams (RRT). Still, evidence suggests that many of these systems are deficient in the detection and/or the response phase and do not lead to the expected outcomes in terms of preventing critical events.

Lately, experts have called for a shift of focus from the response teams to the means of detecting patients at risk and have emphasized the importance of continuous accurate monitoring of vital signs for all hospitalized patients. Evidence has been emerging in the last several years that has demonstrated the value of continuous monitoring in preventing adverse outcomes.

Specifically, an innovative contact less continuous vital signs monitoring system implemented at a general medical-surgical ward has managed to decrease ICU utilization for patients that needed transfer by 47.1% and decrease cardiac arrest rate on the ward by 85.7%. Also, a financial analysis done for the implementation of this specific system has found the return on investment to be 6-9 months following implementation. It is believed that this, and other similar continuous monitoring systems, will play a central role in avoiding preventable in-hospital mortality in the future.

Primary Aldosteronism: The Epidemics of a Channelopathy

Gian Paolo Rossi

Head Clinica dell'Iipertensione Arteriosa, University of Padova, Italy

Primary aldosteronism (PA) is the most common endocrine cause of high blood pressure. A minority of the PA cases are familial and their molecular basis has been recognized to be due to CYP11B2/CYP11B1 chimeric gene or to mutations in the KCNJ5 gene, albeit additional gene mutations remain to be identified. In the most common sporadic cases the mechanisms by which the excess aldosterone production persists in spite of high blood pressure, sodium retention, suppression of the renin angiotensin system and low potassium levels, all factors that by themselves would be expected to shut off aldosterone production, remained puzzling for decades until only recently the discovery of functional mutations and down-regulation of potassium channels provided some explanations. These recent findings and their mechanistic implications indicated that all of these mutations affect mitochondrial calcium, a key regulator of aldosterone synthesis in these organelles. We also proposed a clinical molecular classification of familial hyperaldosteronism, which can be important from the practical standpoint as it considers besides the molecular features also the responsiveness to treatment and the imaging features.

Vitamin K, Calcium and the Vascular Wall

Peter W de Leeuw

Dept of Medicine, Maastricht University Medical Center, The Netherlands

Arterial calcification develops early in the pathogenesis of atherosclerosis and is a strong and independent predictor of cardiovascular disease. Arterial calcification is caused by an imbalance in calcification regulatory mechanisms. An important inhibitor is vitamin K-dependent matrix Gla protein (MGP). Inhibition of the vitamin K-cycle by vitamin K antagonists (VKA) results in uncarboxylated MGP (ucMGP) which subsequently results in extensive arterial calcification. Because of the negative impact of vascular calcification on cardiovascular disease, inhibition or regression of vascular calcification is of clinical importance. The effect of vitamin K supplementation was put forward as treatment option to reduce vascular calcifications.

The VitaK-CAC trial is an ongoing, multicenter, double-blind, randomized, placebo-controlled trial including 180 patients with coronary artery disease (CAD). After obtaining baseline CT scans, patients with a baseline CAC-score between 50-400 Agatston units are randomized to an intervention-group (360 microgram menaquinone-7) or a placebo-group. Treatment duration is 24 months and CT-scans are repeated at 12 and 24 months. The primary endpoint of the study is the difference in CAC-score progression between the intervention group and the placebo group. Secondary endpoints include changes of calcifications in plaques, changes in parameters of arterial stiffness and biomarkers of vascular calcification.

Primary Hypertension in Children and Adolescents – Accelerated Development or Premature Aging?

Mieczysław Litwin

Dept. of Nephrology & Arterial Hypertension, The Children's Memorial health Institute, Poland

Intima-media thickness (IMT) and arterial stiffness increase with age and are accompanied by endothelial dysfunction and rise of blood pressure. It was proposed that premature, early vascular aging (EVA) is the main abnormality leading to early development of arterial hypertension and cardiovascular disease (CVD). Patients with rare progeria syndrome present with EVA and develop CVD already in the second decade of life. Primary hypertension (PH) is much more prevalent and affects up to 10% of adolescents and is recognized to be the early stage of development of CVD. Although cardiovascular events are rare in children with PH, hypertensive children present with increased arterial stiffness, increased carotid IMT and endothelial damage which are typical for EVA. Thus, hypertensive children who usually are not exposed to other cardiovascular risk factors such as diabetes or nicotine, show the first phase of development of CVD. These alterations are accompanied by complex metabolic, inflammatory and immune abnormalities typical for aging. The other abnormality is accelerated biological maturation which also contributes to EVA. Few prospective observational pediatric studies showed that early treatment of PH and other cardiovascular risk factors leads to regression of EVA with subsequent improvement of cardiovascular health. However, although observational studies showed tracking of elevated blood pressure into adulthood and early development of CVD in adults exposed to PH in childhood, there are no data if early treatment reduces cardiovascular risk in adulthood. Future longitudinal studies using vascular function markers should prove this hypothesis

Metabolic Syndrome and Obstructive Sleep Apnea in Pre-Hypertension, Hypertension and Resistant Hypertension

Andrzej Januszewicz

Dept. of Hypertension, Institute of Cardiology, Poland

The strong association between obstructive sleep apnea (OSA) syndrome and hypertension has attracted considerable attention in recent years. OSA is especially frequent in patients with resistant hypertension.

There is growing evidence that OSA represents a major cardiovascular risk and is associated with increased cardiovascular and cerebrovascular morbidity and mortality. Recent studies have shown that patients with OSA and hypertension are more likely to display subclinical organ damage - thickening of the carotid wall or of the intima media, left ventricular hypertrophy and/or pronounced urinary albumin excretion. The importance of the presence of subclinical organ damage as an exponent of high cardiovascular risk is increasingly emphasized in the guidelines of expert's groups from many fields of medicine.

The relationship between OSA, metabolic syndrome (MS) and additionally aldosterone is particularly seen in patients with resistant hypertension. It has been suggested that hyperaldosteronism may contribute importantly to worsening the clinical course of OSA in patients with resistant hypertension and that the positive correlation between plasma and 24h-urinary aldosterone levels and AHI in patients with resistant hypertension is largely attributable to patients with hyperaldosteronism. An interesting finding is also the coexistence of primary aldosteronism (PA) with OSA in patients with resistant HT found in almost 60 % of the subjects included in recent studies. Also in patients with PA severity of OSA tended to be more pronounced as compared with those without PA and correlates with the degree of aldosterone excess. Taken together recent studies showed an important overlapping of MS, OSA and PA what may suggest a common pathological phenotype related with resistant HT.

Reclassification of Cardiovascular Risk by Coronary Artery Calcification in Patients with Prehypertension and the Cardiometabolic Syndrome

Joseph Shemesh

The Grace Ballas Cardiac Research Unit, Sheba Medical Center, Israel

Coronary artery calcification (CAC) is the best surrogate marker of the total burden of coronary atherosclerosis. It is the result of many complex biologic processes. Its presence in asymptomatic subjects indicates the existence of subclinical coronary disease and its quantity reflects the extent and the chronicity of the disease. The absence of CAC indicates an excellent prognosis for cardiovascular (CV) events not only in asymptomatic subject but also in high risk patients as well, such as diabetics, hypertensive, smokers, elderly and even in patients with chronic kidney disease.

In hypertensive patients it seems that CAC is a part of a systemic process that accelerates the development of HTN which in turn promotes coronary and vascular calcification through complex mechanisms. Studies that evaluated the relationships between CAC score in regard to future CV events and/or all-cause mortality in patients with high BP reported independent positive associations. The inclusion of CAC score into prediction models improved risk stratification. CAC testing is likely to be of clinical utility for tailoring the medical management of patients with high BP, particularly among individuals with mild or prehypertension. In a large cohort of asymptomatic hypertensive individuals, higher CAC scores were independently associated with progressively higher rates of all-cause mortality. The strongest evidence for the predictive value of coronary calcium strictly among hypertensive patients comes from the Heinz Nixdorf Recall (HNR) study. Higher CAC scores proportionately predicted increasing risks for combined CV end points. The presence and severity of CAC in that cohort was strongly and independently predictive of future CVD events in patients with prehypertension as well as among individuals at all stages of overt hypertension. Given its high predictive value, CAC testing has the potential to improve overall risk stratification in a manner that could effectively alter treatment decisions among these patients.

CAC screening strongly stratifies CHD and CV event risk in individuals with metabolic syndrome and diabetes. These patients have a wide range of risk based on the extent of CAC. Type 2 diabetic subjects with undetectable CAC had a similar survival to those without diabetes and undetectable CAC. Studies have shown heterogeneity in CV risk from low to high in type 2 diabetic subjects and that not all with type 2 diabetes are at increased cardiovascular risk. Thus the concept that type 2 diabetes is necessarily a coronary equivalent can be challenged.

Individualisation of Target Levels for Blood Pressure Lowering in Relation to Type of Vascular Complication in Diabetes Mellitus

Guntram Schernthaner

Dept. of Medicine I, Rudolfstiftung Hospital, Vienna, Austria

Hypertension (HT), defined as a blood pressure (BP) >140/90 mmHg, is a very common CVD risk factor, affecting more than half of patients with diabetes mellitus (DM). HT is particularly harmful for people with DM because it further increases the risk of CVD morbidity and mortality 2-4 times compared with DM people without HT (1). Despite there is general agreement, that effective treatment of HT is a key element in the management of DM patients, it is debated since years (2-6), which BP target is the best to protect the patients from the increased risk for cardiovascular (CV) morbidity and mortality.

In the ACCORD-BP trial (2) 4733 DM patients were randomized to either an intensive treatment strategy to achieve a target systolic BP (SBP) of <120 mmHg or a standard treatment strategy targeting a SBP of <140 mmHg; achieved BPs were 119 mmHg and 133 mmHg, respectively, during 4.7 years. The primary composite endpoint (non-fatal myocardial infarction, non-fatal stroke, and CVD death) or all-cause mortality were not significantly lower in the intensive arm, however stroke was significantly reduced ((0.32% versus 0.53%, HR 0.59, 95% CI 0.39 – 0.89). Remarkably, intensive therapy did, however, increase the risk of major adverse events including symptomatic hypotension, bradycardia, arrhythmia, and hyper-kalemia, The large meta-analysis by Reboldi et al.(5) confirmed that allocation to more-tight, compared with less-tight, BP control reduced the risk of stroke by 31%, whereas the reduction in the risk of MI did not achieve significance.

In a recent large nationwide cohort study (8) of Swedish patients with T2DM and renal impairment, the risk of CV events (CVEs) and all-cause mortality increased significantly with both high and low BPs. The lowest risks of CVEs and all-cause mortality were observed with a SBP of 135–139 and a DBP of 72–74mmHg. The highest risks were observed for those with SBP intervals 80–120 (CVE HR 2.3 and all-cause mortality HR 2.4,) and 160–230 mmHg (CVE HR 3.0 and all-cause mortality HR 2.0 and DBP intervals 40–63 mmHg (CVE HR 2.0, all-cause mortality HR 2.0) and 83–125 mmHg (CVE HR 2.3, all-cause mortality HR 2.3 [95% CI 2.0, 2.6]).

In a very recent metaanalysis by Emdin et al (6) of >100.000 DM patients each 10–mm Hg lower systolic BP was associated with a significantly lower risk of mortality, CVE, CHD, stroke, albuminuria and retinopathy. Although proportional associations of BP-lowering treatment for most outcomes studied were attenuated below a systolic BP level of 140 mmHg, data indicate that further reduction below 130 mmHg is associated with a lower risk of stroke, retinopathy, and albuminuria, potentially leading to net benefits for many individuals at high risk for those outcomes.

In conclusion, with the currently available very limited trial data on the low attained BP level, it is not possible to set a specific treatment target regarding BP level for all diabetic hypertensive patients, but it is important to use a personalized approach in their antihypertensive treatment in relation to absence or presence of a specific CVD such as stroke, myocardial infarction, heart failure and diabetic nephropathy. Most likely BP levels of about 135/80 mm Hg would have the best CVD preventive effect in most DM patients without increasing the risk for major adverse events.

- Emerging Risk Factors Collaboration. Lancet 2010;375:2215
- ACCORD Study Group. N Engl J Med. 2010;362:1575
- Cooper-DeHoff RM et al. JAMA. 2010; 304:61
- Bangalore S et al. Circulation. 2011;123:2799
- Reboldi G et al. J Hypertens. 2011;29: 1253.
- Emdin CA et al. JAMA. 2015; 313:603-15.
- Ettehad D et al. Lancet 2016 (doi: 10.1016/S0140-6736(15)01225-8).
- Afghahi H et al. . Diabetologia 2015 58:1203

Assessing Antihypertensive Adherence with Therapeutic Drug Monitoring

Brian Rayner

Division of Nephrology & Hypertension, University of Cape Town, South Africa

Objective: The proportion of South African hypertensive patients with controlled blood pressure (BP) is low. Non-adherence may play an important role but monitoring adherence remains difficult. Two commonly used antihypertensives are amlodipine and enalapril. This study aims to determine if monitoring amlodipine levels and inhibition of angiotensin converting enzyme (ACE) are feasible means to determine patient adherence.

Design and Method: Patients attending a referral clinic for resistant hypertension that were prescribed enalapril and amlodipine (\pm other antihypertensives) were enrolled. After informed consent patients underwent BP monitoring; a questionnaire on adherence and blood samples for amlodipine levels and ACE activity. Assessments were repeated. Amlodipine was assayed using liquid chromatography-mass spectrometry. The degree of ACE inhibition was determined by the z-phenylalanine-histidine-leucine and hippuryl-histidine-leucine (zFHL/HHL) ratio.

Results: One hundred patients (age \pm 50.5y and 46% male) were enrolled, with 65 follow-up assessments. There was no difference between the mean BP from visit 1 to 2. Most patients (90%) self medicated, and 24% used pillboxes.

ACE Inhibitor Results: Control data suggest a zFHL/HHL ratio <1.4 to be consistent with no ACE inhibition. Ten patients (17%) were found to be non-adherent at both visits and 12 (20%) at either visit 1 or 2; 38 (63%) were adherent at both visits. Five patients had missing data. There were significant differences in BP between adherent and non-adherent patients: $141\pm22/84\pm15$ mmHg vs. $168\pm30/105\pm18$ mmHg for visit 1, ($p<0.0001$); and $146\pm23/86\pm17$ mmHg vs. $172\pm34/99\pm22$ mmHg for visit 2 ($p=0.002$ for SBP and $p=0.19$ for DBP).

Amlodipine results: An undetectable level of amlodipine was found at both visits in 10 (15.4%) patients and in 4 (6.2%) patients at either visit. Fifty-one (78.5%) patients were adherent at both visits. The BP of patients adherent to amlodipine at visit 1 was $141\pm22/85\pm14$ mmHg vs. $176\pm27/108\pm19$ mmHg in the non-adherent group, $p<0.0001$. At visit 2 the adherent group had a BP of $148\pm29/86\pm17$ mmHg vs. $173\pm21/102\pm22$ mmHg, $p=0.008$ and $p=0.005$ for SBP and DBP. At both visits 67% of those non-adherent to amlodipine were non-adherent to enalapril.

Conclusion: Monitoring antihypertensive adherence through therapeutic drug monitoring is a feasible option at the clinic. Non-adherence strongly predicts the presence of uncontrolled BP.

Antiphospholipid Syndrome as an Independent Risk Factor for Cardiovascular Disease

Ljudmila Stojanovich, Aleksandra Djokovic

Internal Medicine, Bezhanijaska Kosa, University Medical Center, Belgrade University, Serbia

Introduction: A major cause of morbidity and mortality in the context of the antiphospholipid syndrome (APS) is the occurrence of thrombotic events, including cardiovascular involvement, arising from accelerated atherosclerotic changes of the arteries.

Methods: We investigated 559 patients: 331 pts with PAPS followed up for an average of 44.00 ± 12.97 y, and 148 pts with secondary APS (SAPS) in scope of SLE (47.74 ± 14.84 y). Antiphospholipid antibody (aPL) analysis included detection of lupus anticoagulant (LA), aCL (IgG/IgM), β 2GPI (IgG/IgM). Data considering acute myocardial infarction (IM), unstable angina (UA), coronary artery bypass grafting (CABG) or percutaneous coronary artery angioplasty (PTCA). Carotid ultrasound was performed and the intima-media wall thickness (IMT). Traditional vascular risk factors were also analyzed.

Results: Presence of aCL IgG was more common ($p=0.001$) in SAPS, and LA in PAPS patients ($p=0.002$). Highly statistically significant difference was revealed considering presence of $\alpha\beta$ 2GPI antibodies and carotid arteries plaque presence ($p=0.020$), in pts with PAPS and $\alpha\beta$ 2GPI (0.049), as well PAPS pts with smoking ($p=0.008$). PAPS and SLE patients did not differ among themselves with regard to the occurrence of MI ($p=0.102$), and UAP ($p=0.123$) unstable angina pectoris (UAP), but presence more than 2 aPL was a significant risk factor for UA ($p=0.017$). PAPS pts were more often presented with coronary artery disease, although without statistical significance IMT values of left CCA ($r=-0.199, p=0.029$) and right CCA ($r=-0.197, p=0.031$). Multivariate regression analysis showed that among traditional risk factors, age ($p=0.005$) and presence of hypertension were independently associated with significant IMT changes ($p=0.031$).

Conclusion: presence of aPL was an independent risk factor for increased carotid IMT in our APS cohort. This seems to suggest a need for a more aggressive education and prevention considering standard risk factors in this group of patient.

Insomnia and Short Sleep Duration in Prehypertension, Hypertension and Metabolic Syndrome

Aleksander Prejbisz

Dept. of Hypertension, Institute of Cardiology, Warsaw, Poland

Short sleep duration and insomnia, although classically related, are different entities. Insomnia requires dissatisfaction with the quality of sleep and daytime consequences that can be explained or not by a factual reduction in sleep duration. Individuals with short sleep duration do not automatically suffer from insomnia since they can freely restrict their sleep time.

The prevalence of insomnia in the general population ranges between 8-40%. Insomnia is a major public health problem as it is associated with impaired occupational performance, increased absenteeism at work, higher health care costs, and worse quality of life. The connection of insomnia with cardiometabolic risk has been only recently evaluated. It has been shown that insomnia might be a risk factor of hypertension development. Several studies have also shown an association between insomnia and elevated diabetes risk. Therefore it is of importance to discuss insomnia in the background of prehypertension and metabolic syndrome as a possibility for prevention of development both hypertension and diabetes.

Short sleep duration is a substantial problem in modern society, it may result from a voluntary restriction of time spent in bed, thus being related to unhealthy life style. Studies demonstrated the sleep restriction is related to metabolic disturbances linking short sleep duration with the risk of diabetes development. Also the relationship between short sleep duration and hypertension development risk has been shown.

Poor sleep duration and quality emerges as a one of the modifiable metabolic and cardiovascular risk factors. Appropriate life-style measures should be undertaken especially in patients with prehypertension or metabolic syndrome coexisting with short sleep duration or insomnia.