**Atherosclerotic Cardiovascular Disease in Austria 2010**

**Oncostatin M-enhanced vascular endothelial growth factor expression in human vascular smooth muscle cells involves PI3K-, p38 MAPK-, Erk1/2- and STAT1/STAT3-dependent pathways and is attenuated by interferon-γ**


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Basic Res Cardiol. 2010 Dec 21. [Epub ahead of print] The pleiotropic cytokine oncostatin M (OSM), a member of the glycoprotein (gp)130 ligand family, plays a key role in inflammation and cardiovascular disease. As inflammation precedes and accompanies pathological angiogenesis, we investigated the effect of OSM and other gp130 ligands on vascular endothelial growth factor (VEGF) production in human vascular smooth muscle cells (SMC). Human coronary artery SMC (HCASMC) and human aortic SMC (HASMC) were treated with different gp130 ligands. VEGF protein was determined by ELISA. Specific mRNA was detected by RT-PCR. Western blotting was performed for signal transducers and activators of transcription1 (STAT1), STAT3, Akt and p38 mitogen-activated protein kinase (p38 MAPK). OSM mRNA and VEGF mRNA expression was analyzed in human carotid endarterectomy specimens from 15 patients. OSM increased VEGF production in both HCASMC and HASMC derived from different donors. OSM upregulated VEGF and OSM receptor-specific mRNA in these cells. STAT3 inhibitor WP1066, p38 MAPK inhibitors SB-202190 and BIRB 0796, extracellular signal-regulated kinase1/2 (Erk1/2) inhibitor U0126, and phosphatidylinositol 3-kinase (PI3K) inhibitors LY-294002 and PI-103 reduced OSM-induced VEGF synthesis. We found OSM expression in human atherosclerotic lesions where OSM mRNA correlated with VEGF mRNA expression. Interferon-γ (IFN-γ), but not IL-4 or IL-10, reduced OSM-induced VEGF production in vascular SMC. Our findings that OSM, which is present in human atherosclerotic lesions and correlates with VEGF expression, stimulates production of VEGF by human coronary artery and aortic SMC indicate that OSM could contribute to plaque angiogenesis and destabilization. IFN-γ reduced OSM-induced VEGF production by vascular SMC.

**Complement in atherosclerosis - friend or foe?**

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J Thromb Haemost. 2010 Dec 14. doi: 10.1111/j.1538-7836.2010.04172.x. [Epub ahead of print] Atherosclerosis is a chronic inflammatory disease and the complement system plays a central role in innate immunity. Increasing evidence exists that the complement system is activated within atherosclerotic plaques. However, the role of complement in atherogenesis is not fully understood. Whereas complement activation by the classical and lectin pathway may be protective by removal of apoptotic cells and cell debris from atherosclerotic plaques, activation of the complement cascade by the alternative pathway and beyond the C3 convertase with formation of anaphylatoxins and the terminal complement complex may be proatherogenic and may play a role in plaque destabilization leading to its rupture and the onset of acute cardiovascular events. In this review article we present evidence for complement activation within atherosclerotic plaques and we discuss recent data derived from experimental animal models that suggest a dual role of complement in the development of the disease. In addition, we summarize the role of complement components as biomarkers for cardiovascular disease.
**Evidence of carotid atherosclerosis in orthopantomograms and the risk for future cardiovascular events.**

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Vasa. 2010 Nov;39(4):298-304. Background: Evidence of carotid atherosclerosis can be detected in 3 to 5 % of orthopantomogram (OPG) investigations. The clinical impact of these findings is unknown. We investigated the association of OPG findings of carotid atherosclerosis with the occurrence of future cardiovascular adverse events. Patients and methods: We randomly selected 411 of 1268 participants with pre-existent cardiovascular disease from the prospective Inflammation in Carotid Arteries Risk for Arthrosclerosis Study (ICARAS) and assessed their OPGs for the presence of calcified atherosclerotic lesions or indirect signs of atherosclerosis, such as surgical clips or intravascular stents. The degree of carotid stenosis was measured by duplex ultrasound investigations. Patients were then followed for median 39 months (interquartile range 33 to 44 months) for the occurrence of major adverse cardiovascular events (MACE) including myocardial infarction, coronary revascularisation, stroke and death. Results: We found no statistically significant association between the presence of carotid atherosclerosis detected on OPGs and the presence of a significant carotid stenosis (left carotid artery kappa = 0.08; right carotid artery kappa = 0.12), or the degree of carotid stenosis (P = 0.20). Furthermore, the presence of OPG signs of carotid atherosclerosis was not statistically significant associated with future MACE (adjusted hazard ratio 0.92, 95 % confidence interval 0.59 to 1.42; P = 0.70). Conclusions: Evidence of carotid plaque revealed by OPGs in patients with previously known cardiovascular disease is no useful prognostic marker for MACE. Detection of carotid atherosclerosis by OPGs in these patients therefore has no clinical consequence.

**Inflammation, adiponectin, obesity and cardiovascular risk.**

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Curr Med Chem. 2010;17(36):4511-20. The development of atherosclerotic lesions leading to myocardial infarction (MI) or stroke encompasses a cascade of cellular and molecular events that can well be characterized as a chronic immune-mediated inflammation occurring preferentially in the biologic surrounding of the so called metabolic syndrome. Adipokines, chemokines, cytokines, and their receptors are critically involved in the initiation and perpetuation of atherosclerosis, and they play important roles at all levels in the pathogenesis of this disease. Metabolic risk profiles associated with sedentary lifestyle, obesity, especially intra-abdominal fat accumulation, insulin resistance, and dyslipidemia pave the way for a chronic, immunemediated vascular inflammation around vascular lipid deposits. In the present article, the impact of adiponectin, monocyte and T-cell associated cytokines (with emphasis on Neopterin), individual adipose tissue - distribution and pleiotropic drug effects on the individual course of atherosclerosis and associated cardiovascular disease are reviewed.

**The versatility of HDL: a crucial anti-inflammatory regulator.**

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Eur J Clin Invest. 2010 Dec;40(12):1131-43. doi: 10.1111/j.1365-2362.2010.02361.x. BACKGROUND: Low levels of plasma high-density lipoprotein (HDL) represent a major cardiovascular risk factor and therefore raising HDL has been proposed to positively affect patients with atherosclerotic heart disease. However, the current evidence that raising HDL per se will reduce atherosclerosis and thereby cardiovascular events still remains controversial. AIMS: In this review, we discuss the diverse anti-atherogenic and anti-inflammatory properties of HDL in the light of recent findings indicating that the quality rather than the mere quantity of HDL determines its beneficial effects against atherosclerosis. More specifically, we will focus on the conspicuous anti-inflammatory properties of HDL as this might contribute to the overall beneficial effects of HDL in diseased patients such as modulation of costimulatory/adhesion molecule expression, cytokine production and inhibition of the prototypical proinflammatory transcription factor NF-κB. RESULTS: A range of clinical disorders share permanent inflammation as a characteristic hallmark including coronary artery disease, chronic kidney disease, diabetes mellitus or rheumatoid arthritis and also display distinct
qualitative changes in the HDL compartment. Loss of anti-inflammatory functions of HDL is emerging as an important risk factor for disease progression and survival in these clinical entities. **CONCLUSIONS:** It will be important to define the anti-inflammatory effects of HDL at the molecular level and to dissect the manifold functional implications to develop both novel functional assays that enable meaningful outcome studies and foster new therapeutic concepts in patients with altered HDL function.

**Long-term results of thoracic endovascular aortic repair in atherosclerotic aneurysms involving the descending aorta.**


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*J Thorac Cardiovasc Surg.* 2010 Dec;140(6 Suppl):S179-84; discussion S185-S190. Epub 2010 Jul 21. **OBJECTIVE:** This study evaluated long-term results of thoracic endovascular aortic repair for atherosclerotic aneurysms involving descending aorta. **METHODS:** One hundred thirteen patients underwent thoracic endovascular aortic repair for this indication from 1996 to 2009. Mean follow-up was 54 ± 38 months (5-144 months). In-hospital mortality, neurologic injury, need for rerouting, occurrence of endoleaks and their treatment, and survival were recorded. **RESULTS:** In-hospital mortality was 5.3%. Transient neurologic injury rate was 2.6%. Previous rerouting was performed in 51%. Assisted early and late type I and III endoleak rates were 7.9% and 5.7%, respectively. Five percent of patients required late surgical conversion. Actuarial survivals were 86%, 60%, and 42% at 1, 5, and 10 years, respectively. Aorta-related actuarial survivals were 94%, 90%, and 83% at 1, 5, and 10 years, respectively. Cox regression analysis revealed higher number of prostheses as independent risk factor for early (hazard ratio, 5.38; 95% confidence interval, 1.68-42.37) and late (hazard ratio, 8.49; 95% confidence interval, 1.09-66.06) endoleak formation. Female sex (hazard ratio, 0.35; 95% confidence interval, 0.13-0.99), no arch involvement (hazard ratio, 0.21; 95% confidence interval, 0.05-0.08), and higher number of prostheses (hazard ratio, 7.95; 95% confidence interval, 1.36-46.58) affected survival. **CONCLUSIONS:** Aorta-related survival is excellent among patients undergoing thoracic endovascular aortic repair for atherosclerotic aneurysms involving the descending aorta. Lifelong surveillance remains mandatory, with early and late failure uncommon but still needing consideration. Thoracic endovascular aortic repair in this group of patients remains attractive and has now proven durability.

**The effects of endurance and recreational exercise on subclinical evidence of atherosclerosis in young adults.**

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*Am J Med Sci.* 2010 Apr;339(4):332-6. **BACKGROUND:** This study set out to identify the effects of recreational and endurance exercise on subclinical evidence of atherosclerosis in young adults. **METHODS:** Cardiovascular disease risk factors and intima-media thickness determination by B-mode ultrasonography of 150 subjects were correlated to endurance exercise, recreational exercise, and sedentary lifestyle. The subjects comprised 20- to 40-year-old men and women without cardiovascular disease. This cross-sectional, case-control study analyzed data on the laboratory parameters and information collected from a risk factor questionnaire. **RESULTS:** The athletes, both endurance and recreational groups, have significantly superior values with respect to physiognomy, lipid profile, and inflammatory markers in relation to the nonexercising study population (all P < 0.05). Detailed analysis showed markedly reduced values for relative body fat (relative reduction 14.3%), low-density lipoprotein (10.6%), and triglycerides (13.5%) and a 50% reduction of hs-C-reactive protein. In the univariate and multivariate comparison of athletic (n = 100) and nonathletic (n = 50) groups, exercise did not show to exert a significant influence on vascular wall parameters (for all, P > 0.05). **CONCLUSION:** Exercise, in recreational and endurance form, between the ages of 20 and 40 years exerts a preventive influence on cardiovascular risk factors but seems to fail to affect early, atherosclerotic vascular wall changes.
**Pregnancy-associated plasma protein-A as a marker for long-term mortality in patients with peripheral atherosclerosis: inconclusive findings from the Linz Peripheral Arterial Disease (LIPAD) study.**

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Clin Chem Lab Med. 2010 Apr;48(4):537-42. PMID BACKGROUND: Pregnancy-associated plasma protein-A (PAPP-A) has been associated with peripheral artery disease (PAD). The aim of this study was to evaluate the utility of PAPP-A as a marker for long-term mortality in patients with atherosclerotic PAD. **METHODS:** PAPP-A serum concentrations were measured using an enzymatically amplified two-step sandwich-type immunoassay in 487 consecutive patients admitted to a tertiary care hospital with symptomatic PAD. The main outcome measure was all-cause mortality at 5 years. **RESULTS:** During follow-up, 114 patients died and 373 survived. The median PAPP-A concentration was higher among decedents compared with survivors (0.96 vs. 0.78 mU/L, p=0.024). The area under the receiver operating characteristic curve for the prediction of 5-year mortality by PAPP-A was 0.57 [95% confidence interval (CI), 0.53-0.61; p=0.026]. Survival probability was not significantly associated with PAPP-A concentrations using Kaplan-Meier curve analysis. However, univariate Cox proportional-hazards regression analysis revealed that PAPP-A was associated with 5-year mortality [risk ratio 1.25; 95% CI, 1.05-1.50; p=0.013 per one standard deviation (SD) increase in log transformed values]. In the multivariate model using a bootstrapping method, the predictive value of PAPP-A remained significant (risk ratio 1.31; 95% CI, 1.01-1.73; p=0.024 per 1 SD increase in log transformed values), even after adjustment for clinical confounders and other biomarkers, such as high-sensitivity C-reactive protein and amino terminal pro-B-type natriuretic peptide. **CONCLUSIONS:** In this study, PAPP-A was an independent predictor of 5-year all-cause mortality in patients with symptomatic PAD. However, based on the weak association between PAPP-A and outcome in our cohort, we consider PAPP-A measurements to not be useful in clinical practice for prognostic purposes in patients with PAD.

**In vitro angioplasty of atherosclerotic human femoral arteries: analysis of the geometrical changes in the individual tissues using MRI and image processing.**

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Ann Biomed Eng. 2010 Apr;38(4):1276-87. Epub 2010 Feb 11. Existing atherosclerotic plaque imaging techniques such as intravascular ultrasound, multidetector computed tomography, optical coherence tomography, and high-resolution magnetic resonance imaging (hrMRI) require computerized methods to separate and analyze the plaque morphology. In this work, we perform in vitro balloon angioplasty experiments with 10 human femoral arteries using hrMRI and image processing. The vessel segments contain low-grade to high-grade lesions with very different plaque compositions. The experiments are designed to mimic the in vivo situation. We use a semi-automatic image processing tool to extract the three-dimensional (3D) geometries of the tissue components at four characteristic stages of the angioplasty procedure. The obtained geometries are then used to determine geometrical and mechanical indices in order to characterize, classify, and analyze the atherosclerotic plaques by their specific geometrical changes. During inflation, three vessels ruptured via helical crack propagation. The adventitia, media, and intima did not preserve their area/volume during inflation; the area changes of the lipid pool during inflation were significant. The characterization of changes in individual 3D tissue geometries, together with tissue-specific mechanical properties, may serve as a basis for refined finite element (FE) modeling, which is key to better understand stress evolution in various atherosclerotic plaque configurations.
**Modelling the layer-specific three-dimensional residual stresses in arteries, with an application to the human aorta.**

Holzapfel GA, Ogden RW.

Center of Biomedical Engineering, Institute of Biomechanics, Graz University of Technology, Austria. J R Soc Interface. 2010 May 6;7(46):787-99. Epub 2009 Oct 14. This paper provides the first analysis of the three-dimensional state of residual stress and stretch in an artery wall consisting of three layers (intima, media and adventitia), modelled as a circular cylindrical tube. The analysis is based on experimental results on human aortas with non-atherosclerotic intimal thickening documented in a recent paper by Holzapfel et al. (Holzapfel et al. 2007 Ann. Biomed. Eng. 35, 530-545 (doi:10.1007/s10439-006-9252-z)). The intima is included in the analysis because it has significant thickness and load-bearing capacity, unlike in a young, healthy human aorta. The mathematical model takes account of bending and stretching in both the circumferential and axial directions in each layer of the wall. Previous analysis of residual stress was essentially based on a simple application of the opening-angle method, which cannot accommodate the three-dimensional residual stretch and stress states observed in experiments. The geometry and nonlinear kinematics of the intima, media and adventitia are derived and the associated stress components determined explicitly using the nonlinear theory of elasticity. The theoretical results are then combined with the mean numerical values of the geometrical parameters and material constants from the experiments to illustrate the three-dimensional distributions of the stretches and stresses throughout the wall. The results highlight the compressive nature of the circumferential stress in the intima, which may be associated with buckling of the intima and its delamination from the media, and show that the qualitative features of the stretch and stress distributions in the media and adventitia are unaffected by the presence or absence of the intima. The circumferential residual stress in the intima increases significantly as the associated residual deformation in the intima increases while the corresponding stress in the media (which is compressive at its inner boundary and tensile at its outer boundary) is only slightly affected. The theoretical framework developed herein enables the state of residual stress to be calculated directly, serves to improve insight into the mechanical response of an unloaded artery wall and can be extended to accommodate more general geometries, kinematics and states of residual stress as well as more general constitutive models.
Dendritic cells in atherosclerotic disease.
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Clin Immunol. 2010 Jan;134(1):25-32. Epub 2009 Jun 10. Review. Atherosclerosis has been considered a syndrome of dysregulated lipid storage until recent evidence has emphasized the critical contribution of the immune system. Dendritic cells (DC) are positioned at the interface of the innate and adaptive immune system. Recognition of danger signals in atheromas leads to DC activation. Activated DC regulate effector T cells which can kill plaque-resident cells and damage the plaque structure. Two types of DC have been identified in atherosclerotic lesions; classical myeloid DC (mDC) which mainly recognize bacterial signatures and plasmacytoid DC (pDC) which specialize in sensing viral fragments and have the unique potential of producing large amounts of type I interferon (IFN). In human atheromas, type I IFN upregulates expression of the cytotoxic molecule TRAIL which leads to apoptosis of plaque-resident cells. This review will elucidate the role of DC in atherogenesis and particularly in plaque rupture, the underlying pathophysiologic cause of myocardial infarction.

Role of vitamin D in arterial hypertension.
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Expert Rev Cardiovasc Ther. 2010 Nov;8(11):1599-608. PMID Vitamin D deficiency is highly prevalent and may contribute to arterial hypertension. The antihypertensive effects of vitamin D include suppression of renin and parathyroid hormone levels and renoprotective, anti-inflammatory and vasculoprotective properties. Low 25-hydroxyvitamin D levels, which are used to classify the vitamin D status, are an independent risk factor for incident arterial hypertension. Meta-analyses of randomized controlled trials showed that vitamin D supplementation reduces systolic blood pressure by 2-6 mmHg. However, further studies are needed before drawing a final conclusion on the effect of vitamin D therapy on blood pressure and cardiovascular risk. In our current clinical practice we should take into account the high prevalence of vitamin D deficiency, the easy, cheap and safe way by which it can be supplemented and the promising clinical data suggesting that vitamin D might be useful for the treatment of arterial hypertension as well as other chronic diseases. Therefore, we recommend that testing for and treating vitamin D deficiency in patients with arterial hypertension should be seriously considered.

Impact of CYP2C8 and 2C9 polymorphisms on coronary artery disease and myocardial infarction in the LURIC cohort.
Institute of Medical & Chemical Laboratory Diagnostics, Elisabethinen Hospital, Fadingerstrasse 1, 4010 Linz, Austria.
Pharmacogenomics. 2010 Oct;11(10):1359-65. AIMS: As data on the cardiovascular risk associated with CYP2C8 and CYP2C9 polymorphisms is controversial, we performed a cross-sectional analysis of subjects enrolled in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. MATERIALS & METHODS: CYP2C8 and CYP2C9 genetic polymorphisms were determined with real-time PCR in 2827 patients. Based on angiography, 1052 of these patients had coronary artery disease (CAD) and 615 did not; 1160 patients had signs or a history of myocardial infarction (MI) in addition to CAD. The association of genotypes with CAD and MI was determined by logistic regression analysis, adjusted for age, sex, dyslipidemia, hypertension, diabetes mellitus and smoking status. RESULTS: Frequencies of CYP2C8 and 2C9 variants were neither significantly different between CAD and control patients, nor between MI and control patients. Men carrying the CYP2C9*3 allele had an increased risk of MI (odds ratio [OR]: 1.67; 95% CI: 1.06-2.63; p = 0.03) and women carrying the CYP2C9*3 allele had a decreased risk of CAD (OR: 0.65; 95%CI: 0.42-0.9; p = 0.05). CONCLUSION: Overall, LURIC data confirmed that there is no major cardiovascular risk associated with CYP2C8 and CYP2C9 variants in a cardiovascular risk population of patients having undergone coronary angiography.
Midterm results after endovascular treatment of acute, complicated type B aortic dissection.


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Ann Thorac Surg. 2010 Nov;90(5):1444-8. BACKGROUND: The purpose of this study was to assess the efficacy and midterm results of endovascular treatment of acute, complicated type B aortic dissection. METHODS: Between January 2001 and February 2010, 32 patients (7 women, 25 men) with acute, complicated type B aortic dissection (mean age, 56 years; range, 35 to 83 years), defined as either aortic rupture, malperfusion, intractable pain, or uncontrolled hypertension, underwent endovascular stent graft placement with either the Gore Excluder/TAG device (n = 11), Medtronic Talent/Valiant device (n = 16), Bolton Relay (n = 2), or a combination of these stents (n = 3). Follow-up was 94% complete and averaged 26 ± 23 months. RESULTS: Technical feasibility and success with deployment proximal to the entry tear was 87%, requiring partial or total coverage of the left subclavian artery (LSA) in 9 patients (28%). Hospital mortality was 12% ± 11% (95% confidence limit) with 2 late deaths (17 and 98 months after implant). Causes of hospital death included rupture in 2, retrograde type A dissection in 1, and multiorgan failure in 1 patient. Three patients (11%) experienced new neurologic complications (2 paraparesis and 1 hemiparesis). Six patients with malperfusion required branch vessel stenting. Furthermore, 2 had an early type Ia endoleak. Actuarial survival at 1 and 5 years was 81% and 76%, respectively. Freedom from treatment failure at 1 and 5 years (including reintervention, aortic rupture, device-related complication, and aortic related death) was 78% and 61%, respectively. CONCLUSIONS: Endovascular stent-graft placement in acute, complicated type B aortic dissection proves to be a promising alternative therapeutic treatment modality in this relatively difficult patient cohort. Refinements, especially in stent design and application, may further improve the prognosis of patients in this life-threatening situation.

Coronary artery disease-related genetic variant on chromosome 10q11 is associated with carotid intima-media thickness and atherosclerosis.


Department of Neurology, Medical University Innsbruck, Innsbruck, Austria. Arterioscler Thromb Vasc Biol. 2010 Dec;30(12):2678-83. Epub 2010 Sep 16. OBJECTIVE: To investigate whether chromosome 10q11.21 influences common carotid intima-media thickness (IMT) and atherosclerosis and whether it is associated with stromal cell-derived factor-1α (SDF-1α) plasma levels. METHODS AND RESULTS: Variation on chromosome 10q11.21 has been consistently associated with coronary artery disease. The genetic variant lies upstream of the gene encoding SDF-1α. We genotyped 3 population cohorts (Bruneck [age range, 45 to 94 years; 50.0% men; n=738], Health2000 [age range, 46 to 76 years; 55.4% men; n=1237], and essential hypertension in families collected in the region of Oxford [HTO] [age range, 19 to 88 years; 47.9% men; n=770]) for single-nucleotide polymorphism rs501120 at the 10q11.21 locus and conducted a meta-analysis in these cohorts to ascertain a relationship between the polymorphism and carotid IMT. The analysis showed that individuals with the T/T genotype had a significantly higher carotid IMT than individuals with the C/T or C/C genotype (pooled weighted mean difference, 23 μm [95% CI, 9 to 37 μm], P=0.0014 under a fixed-effects model; and 23 μm [95% CI, 6 to 41 μm], P=0.009 under a random-effects model). In the Bruneck cohort, in which data for carotid atherosclerosis and plasma SDF-1α levels were available, we observed an association of the T/T genotype with a higher burden of atherosclerosis and increased susceptibility to the development of atherosclerosis during a 5-year follow-up (multivariable odds ratio, 1.73 [95% CI, 1.18 to 2.52]; P=0.005 for the recessive model) and an association between the T/T genotype and lower SDF-1α levels (2.62 ng/mL for T/T versus 2.74 ng/mL for C/C or C/T; P=0.023). CONCLUSIONS: The coronary heart disease-related variant at the 10q11.21 locus is associated with carotid IMT and atherosclerosis.
Hypertension in end-stage renal disease: different measures and their prognostic significance.
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Division of Nephrology and Dialysis, Department of Medicine III, University of Vienna, Vienna, Austria.
Nephrol Dial Transplant. 2010 Oct;25(10):3161-6. Epub 2010 Aug 4. Hypertension is a risk factor for cardiovascular morbidity and mortality. Hypertension affects the majority of haemodialysis (HD) patients. However, in the absence of prospective data, accurate assessment of blood pressure (BP) and the level to which BP should be targeted remain still to be defined. A direct relationship between volume status and BP as well as between hypervolaemia and morbidity and mortality in HD patients indicates that normovolaemia is the key therapeutic target. Dry-weight reduction by additional ultrafiltration (even in the absence of clinical signs of volume overload) combined with daily dietary salt restriction or individually lowered dialysate sodium is recommended. Strict volume control allows marked reduction of antihypertensive drug treatment or makes it even unnecessary. Long, slow, home HD or frequent, short HD sessions or nocturnal HD also result in reduction of BP and left ventricular hypertrophy in end-stage renal disease patients. It will be interesting to see which recommendations will come from a conference sponsored by the Kidney Disease: Improving Global Outcomes on optimal BP treatment target in relation to end-organ damage and outcomes in HD patients, on antihypertensive drugs and on non-pharmacological therapies are to be considered in achieving BP targets in this population based on a paucity of prospective data.

[Diuretics-related complications in elderly patients].
Otto R, Roller RE, Iglsereder B, Dovjak P, Lechleitner M, Sommeregger U, Benvenuti-Falger U, Böhmdorfer B, Gosch M.
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Wien Med Wochenschr. 2010 Jun;160(11-12):276-80. Review. German. Diuretics are well studied and evaluated for their beneficial use in geriatric patients. However those drugs are often used without taking care of subjects condition or functional impairment. Known side effects of those substances may be increased by combinations of multiple drugs. Polypharmacy is a strong risk factor for the incidence of adverse drug reactions (ADR). ADRs are frequently found in combination with the use of diuretics. The remodelling of human body in aging process and uncontrolled therapeutic strategies seem to be causal for that finding. This article tries to work out the potential risk of the usage of those drugs in geriatric patients and its clinical relevance by using literature published in PubMed.

Diuretics and diabetes incidence--an appeal against the reluctance to prescribe a medication that is safe and proven.
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Diabet Med. 2010 Feb;27(2):130-5. The publication of the scientific report of the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany on the 'Comparative evaluation of the benefits and harms of different antihypertensive drug classes [diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers and angiotensin II (AT-II) blockers] as first-choice therapy for patients with essential hypertension' raised an enormous public debate, particularly as diabetes incidence was not judged to be a patient-relevant outcome. In this assessment, the overall view of the patient-relevant results was that diuretics can be used as first-line antihypertensive treatment. Diabetes incidence is highest with diuretics, but minimal differences in fasting plasma glucose of approximately 0.28 mmol/l are magnified by the transformation of continuous blood glucose values into categorical data: with the establishment of thresholds, the diagnosis of diabetes depends on being above a certain blood glucose value. The protective cardiovascular effects of diuretics do not seem to be reduced in hypertensive patients who develop new-onset diabetes during treatment. Since blood pressure control is often worse, detection, treatment and control should be urgently improved. The debate on antihypertensive agents is mainly of scientific interest and has only minor clinical relevance for everyday patient care.
Gross proteinuria and subacute renal failure after coronary angiography - a case report of cholesterol crystal embolization.
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Wien Klin Wochenschr. 2010 Apr;122(7-8):251-4. We report on a 55-year-old man who was admitted with increased serum-creatinine (3.4 mg/dl), gross proteinuria (4.6 g/24 h) and arterial hypertension. The medical history included hyperlipidemia, coronary artery disease (CAD) and a recent coronary angiography, but normal serum-creatine and no proteinuria before coronary intervention. Serology and urinary analysis did not show any signs of a systemic disease. A renal biopsy, however, revealed multiple cholesterol crystal emboli in small vessels along with a typical infiltration of eosinophilic granulocytes. The patient was subsequently treated with an angiotensin-receptor-1 (AT1R) blocker and high-dose statins and was then evaluated for LDL-apheresis. Gross proteinuria was largely unaffected by (AT1R) blockade and renal function further declined necessitating, initiation of hemodialysis. Renal CCE with profound proteinuria is an unusual presentation of acute renal failure, potentially misleading and thereby prolonging correct diagnostics of a rare entity. Identification of high-risk patients is of utmost importance as efficient therapeutic strategies do not exist.

Choroidal blood flow and progression of age-related macular degeneration in the fellow eye in patients with unilateral choroidal neovascularization.
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Invest Ophthalmol Vis Sci. 2010 Aug;51(8):4220-5. Epub 2010 May 19 PURPOSE: Cardiovascular risk factors such as smoking, hypertension, and atherosclerosis seem to play an important role in the development of choroidal neovascularization (CNV). Recent studies have also provided evidence suggesting that choroidal and retinal blood flow is decreased in patients with AMD. On the basis of these results, the hypothesis for this study was that lower choroidal blood flow is associated with an increased risk of CNV in patients with AMD. METHODS: Forty-one patients with unilateral choroidal neovascular AMD were included in this observational longitudinal study. The fellow eyes of the patients served as study eyes. Subfoveal choroidal blood flow (FLOW) and fundus pulsation amplitude (FPA) were assessed with laser Doppler flowmetry and laser interferometry, respectively. A multivariate COX-regression model was used to test the hypothesis that low choroidal perfusion parameters are associated with the development of CNV. RESULTS: Of the 37 patients that were followed up until the end of the study, 17 developed CNV and 20 did not. The univariate COX-regression analysis shows that lower FLOW, systolic blood pressure, intraocular pressure, and FPA are risk factors for development of CNV. Moreover, the more advanced the AMD in the study eye, the higher the risk for CNV to develop in the fellow eye. Multivariate COX regression analysis indicated that only FLOW (P = 0.0071), FPA (P = 0.0068), and staging (P = 0.031) had statistically significant influences on the progression to CNV. CONCLUSIONS: The present study indicates that lower choroidal perfusion is a risk factor for the development of CNV in the fellow eye of patients with unilateral CNV.

Serum cystatin C is an easy to obtain biomarker for the onset of renal impairment in heart transplant recipients.
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J Thorac Cardiovasc Surg. 2010 Sep;140(3):688-93. Epub 2010 May 5. OBJECTIVE: With the increasing longevity of heart transplant recipients, the long-term effects of cyclosporine on renal function have become more evident. Highly sensitive, early, and effective monitoring of posttransplant renal function is still being researched. This study aimed to evaluate the prognostic value of cystatin C for patients after heart transplantation. METHODS: Seventy-three long-term recipients of a heart transplant more than 5 years before the study start were included in the analysis with a follow-up of 4 years. Serum creatinine, renal glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula, and serum cystatin C levels were collected, and risk factors for renal dysfunction were assessed. Statistical analysis was performed for all patients. RESULTS: Univariate analysis showed a prognostic impact of antihypertensive medication and onset of diabetes (P < .001) on renal failure after transplantation. Multivariate analysis yielded cystatin C measured at the study start as a superior prognostic parameter for all time
CONCLUSIONS: Our results showed an enormous potential of serum cystatin C as an early prognostic and easy to obtain biomarker for renal dysfunction after heart transplantation.

Aldosterone/relin ratio determines peripheral and central blood pressure values over a broad range.
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J Am Coll Cardiol. 2010 May 11;55(19):2171-80. OBJECTIVES: With the present analysis we intended to investigate the magnitude of the effect of relative aldosterone excess in predicting peripheral as well as aortic blood pressure levels in a well-characterized cohort of patients undergoing coronary angiography. BACKGROUND: The discussion on the relationship between aldosterone concentration and blood pressure has recently gone beyond the role of primary aldosteronism in the genesis of arterial hypertension. METHODS: Plasma aldosterone (pg/ml) and plasma renin concentration (pg/ml) were determined in 3,056 Caucasian patients (age 62.5 +/- 11 years; 31.9% women) scheduled for coronary angiography in a single tertiary care center. We formed sex-specific deciles (D) according to plasma aldosterone/renin concentration ratio (ARR) (pg/ml/pg/ml). RESULTS: Mean peripheral systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the entire cohort were 141 +/- 24 mm Hg and 81 +/- 11 mm Hg, respectively. Mean ARR was 10.2 +/- 15.7 in men and 14.4 +/- 19.9 in women (p < 0.0001). Median SBP and aortic SBP increased steadily and significantly from ARR D1 (126.8 mm Hg and 130.0 mm Hg, respectively) to D10 (151.0 mm Hg and 149.6 mm Hg, respectively; p < 0.0001 for both) after multivariate adjustment for age, sex, body mass index, renal function, antihypertensive medications, and various parameters potentially influencing BP. Adjusted median DBP and aortic DBP also increased significantly from 74.3 mm Hg and 66.5 mm Hg (D1) to 86.9 mm Hg and 76.7 mm Hg, respectively (D10) (p < 0.001 for both). In a multivariate stepwise regression model, ARR emerged as the second most significant independent predictor (after age) of mean SBP and as the most important predictor of mean DBP in this patient cohort. CONCLUSIONS: Our results: 1) underline that the ARR affects BP well below a cutoff used for screening for primary aldosteronism; and 2) illustrate the importance of the ARR in modulating BP over a much wider range than is currently appreciated.

Hypertension in women: the role of progesterone and aldosterone.
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Climacteric. 2010 Aug;13(4):307-13. Review The age-related course of blood pressure and its gender-related difference, as well as the incidence of hypertension, have been the subject of multiple experimental, clinical and epidemiological studies over the past decades. The role of the sex hormones estradiol and testosterone within this gender dimorphism has been investigated without conclusive results. In this review, we provide background information on the gender difference in blood pressure, describe the impact of progesterone and aldosterone, and discuss the pathophysiology of aldosteronism as well as the potential role of drospirenone as a gender-specific agent for the prevention and treatment of hypertension and for cardiovascular protection.

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Wien Klin Wochenschr. 2010 Mar;122(5-6):152-8. OBJECTIVE: The aims of the study were to determine time trends in cardiovascular risk factors among young Austrian males between 1986 and 2005 and to examine socioeconomic and geographic differences. METHODS: Data on Austrian conscripts were derived from the nationwide compulsory medical investigations held at military induction at 18 years of age. Four cohorts (1986-1990: n = 252,799; 1991-1995: n = 209,266; 1996-2000: n = 208,427; 2001-2005: n = 209,168) were examined with respect to their place of residence and level of education. Height, weight, waist circumference, blood pressure, serum total-cholesterol and
triglycerides were measured. Mean body mass index (BMI) was calculated: overweight was defined as BMI between 25 and <30 and obesity as BMI ≥ 30. The Chi-squared test and ANOVA were used to test group differences.

**RESULTS:** During the 20-year observation period the prevalence of overweight increased from 13.3% to 15.7% (p < 0.001) and that of obesity from 2.6% to 5.4% (p < 0.001); in accordance, mean BMI and waist circumference increased significantly. Blood pressure and serum total-cholesterol level decreased (p < 0.001) during the period studied, although triglyceride levels (p < 0.001) increased. A significant east-west gradient was identified for the prevalence of overweight and obesity, waist circumference and mean BMI, with lower values in the urban population compared with those of rural inhabitants. Mean BMI and the prevalence of overweight and obesity were higher in conscripts belonging to lower socioeconomic strata. **CONCLUSION:** Our study demonstrates a clear increase of mean BMI, waist circumference and the prevalence of overweight and obesity in Austrian male adolescents during the past 20 years. Conscripts from rural regions and with lower levels of education showed the highest values. The investigation of conscript health appears to be a useful tool for risk surveillance in the male population.

**Serial decline of kidney function as a novel biomarker for the progression of atherothrombotic disease.**

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Atherosclerosis. 2010 Jul;211(1):348-52. Epub 2010 Mar 1. **OBJECTIVE:** Impaired kidney function is associated with cardiovascular disease. However, from the available data it cannot be discerned which of the two entities presents first and entails the other. If renal dysfunction is first, a dynamic decline in the estimated glomerular filtration rate (eGFR) should predict vascular events and prove a useful biomarker for atherothrombotic disease. We therefore tested the hypothesis that a decrease in kidney function predicts future vascular events in a high-risk population of angiographically characterized coronary patients. **METHODS:** We calculated the eGFR by the Mayo clinic quadratic equation at baseline and after two years in a high-risk population of 400 consecutive men undergoing coronary angiography, of whom 355 had coronary artery disease (CAD). Vascular events were recorded over six years. **RESULTS:** A serial decrease in kidney function from baseline to the follow-up visit two years later significantly predicted vascular events in the subsequent four years independently from the baseline eGFR with a standardized adjusted hazard ratio (HR) of 1.41 (1.13-1.76); p=0.003. This result proved robust after adjustment for age, BMI, hypertension, diabetes, LDL-C, HDL-C, smoking, and high-sensitivity C-reactive protein (HR=1.41 [1.12-1.78]; p=0.004). The predictive power of eGFR loss was confirmed even after further adjustment for the presence of CAD at baseline (HR=1.43 [1.12-1.81]; p=0.004). In this fully adjusted model a 10 ml/min/1.73 m2 decrease in eGFR independently conferred a 31% increase in cardiovascular event risk (p=0.004). **CONCLUSION:** A decline of eGFR over two years strongly, significantly, and independently predicts vascular events over the subsequent four years. Declining eGFR is a readily obtainable and inexpensive candidate new biomarker for the progression of atherothrombotic disease.

**Intimal sarcoma of the pulmonary valve.**


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Ann Thorac Surg. 2010 Apr;89(4):e25-7. Pulmonary artery intimal sarcoma is a rare tumor of the cardiovascular system. Intimal sarcoma of the pulmonary valve itself has not been described. Embolization into pulmonary arteries originating from the pulmonary valve intimal sarcoma can mimic chronic thromboembolic pulmonary hypertension and mislead the diagnosis. We present and discuss a patient initially diagnosed as chronic thromboembolic pulmonary hypertension, treated by pulmonary endarterectomy. After 24 months, a tumor of the pulmonary valve was detected by echocardiography. The patient underwent removal and replacement of the pulmonary valve. Histology revealed pulmonary valve intimal sarcoma.
Advances in understanding the pathogenesis of chronic thromboembolic pulmonary hypertension.
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Br J Haematol. 2010 May;149(4):478-83. Epub 2010 Mar 16. Review. Chronic thromboembolic pulmonary hypertension (CTEPH) comprises organizing thrombotic obstructions in the pulmonary arteries. While roughly 40% of CTEPH cases are not preceded by a venous thromboembolic event, 0.1-5.1% of acute pulmonary thromboemboli evolve into organized obstructions of the pulmonary artery. In patients with predominantly proximal disease, surgical pulmonary endarterectomy provides a potential cure of the disease. For years, the scientific debate of CTEPH was mainly focused around its thromboembolic nature because of striking dissimilarities to classical venous thromboembolism, for example, the lack of risk factors for venous thrombosis, the lack of clinically apparent pulmonary embolism in many patients, the difficulty to reproduce the disease in animal models of thrombosis, and the nature of the pulmonary vascular obstructions that are dissociated from the degree of hemodynamic compromise. Recent studies have confirmed an association between venous thromboembolism and the evolution of CTEPH, and have shed light on disease-modifying conditions.

Cadmium and cardiovascular diseases: cell biology, pathophysiology, and epidemiological relevance.
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Cardiothoracic Surgery, Research Laboratories, Department of Surgery, Medical University of Vienna, Währinger Gürtel 18-20, Vienna, Austria. Biometals. 2010 Oct;23(5):811-22. Epub 2010 Mar 7 Today cardiovascular diseases (CVDs) are the killer number one world wide. In 2004 an estimated 17.1 million people died due to CVDs and this number will further increase to an estimated 23.6 million by 2030. Importantly, currently known risk factors, like hypertension, and hypercholesterolemia, can only be made responsible for about 50-75% of all CVDs, highlighting the urgent need to search for and define new CVD risk factors. Cadmium (Cd) was shown to have the potential to serve as one such novel risk factor, as it was demonstrated-in vitro, in animal studies, and in human studies-that Cd causes atherosclerosis (the basis of most CVDs). Herein, we discuss the molecular and cellular biological effects of Cd in the cardiovascular system; we present concepts on the pathophysiology of Cd-caused atherosclerosis, and provide data that indicate an epidemiological relevance of Cd as a risk factor for CVDs.

Aldosterone and arterial hypertension.
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Nat Rev Endocrinol. 2010 Feb;6(2):83-93. Epub 2009 Dec 22. Review. In the setting of primary aldosteronism, elevated aldosterone levels are associated with increased blood pressure. Aldosterone concentrations within the normal range, however, can also alter blood pressure. Furthermore, the aldosterone-to-renin ratio, an indicator of aldosterone excess, is associated with hypertension, even in patients without excessive absolute aldosterone levels. In this Review we assess the data on the role of aldosterone in the development and maintenance of hypertension. We provide an overview of the complex crosstalk between genetic and environmental factors, and about aldosterone-mediated arterial hypertension and target organ damage. The discussion is organized according to major targets of aldosterone action: the collecting duct in the kidney, the vasculature and the central nervous system. The antihypertensive efficacy of mineralocorticoid-receptor blockers, even in patients with aldosterone values in the normal range, supports the evidence that aldosterone plays a part in blood pressure elevation in the absence of primary aldosteronism.
Rate of cardiovascular recovery to combined or separate orthostatic and mental challenges.
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Post stress neurovascular responses induced by physical and mental stress are poorly understood. We investigated the time course of cardiovascular and autonomic recovery, induced by orthostatic and mental challenge, using passive head up tilt (HUT) and mental arithmetic (MA), respectively, when applied singly (MA, HUT) or in combination (MA+HUT). Fifteen healthy males participated in three protocols: HUT, MA and combined MA+HUT, with sessions randomized and 2 weeks apart. Post stress responses were studied in the first 10 min (early; cardiovascular only) and 30 min (late), in 2.5 min epochs. A detailed analysis of early period was done in 30s epochs. Within the first 2.5 min recovery, time courses of heart rate, stroke volume and cardiac output differed significantly, particularly when comparing HUT vs. MA and MA+HUT vs. MA. Additionally, heart rate response differed in HUT vs. MA+HUT. No differences in hemodynamic recovery were seen during the next 2.5 min. Late responses of heart rate and cardiac output showed significantly lower values as compared to baseline, especially for HUT and MA+HUT. Recovery of hemodynamic responses, either due to single or combined stress challenges, showed stressor- and time-dependent patterns. Our data provide useful information regarding why longer recovery periods must be assessed and provide novel insights regarding recovery of physical and mental stressors. This may have clinical implications in the development of cardiovascular diseases such as hypertension or myocardial ischemia.

Trait and state positive affect and cardiovascular recovery from experimental academic stress.
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As compared to negative affect, only a small number of studies have examined influences of positive affect on cardiovascular stress responses, of which only a few were concerned with cardiovascular recovery. In this study, heart rate, low- and high-frequency heart rate variability, blood pressure, and levels of subjectively experienced stress were obtained in 65 students before, during and after exposure to academic stress in an ecologically valid setting. Higher trait positive affect was associated with more complete cardiovascular and subjective post-stress recovery. This effect was independent of negative affect and of affective state during anticipation of the stressor. In contrast, a more positive affective state during anticipation of the challenge was related to poor post-stress recovery. The findings suggest that a temporally stable positive affect disposition may be related to adaptive responses, whereas positive emotional states in the context of stressful events can also contribute to prolonged post-stress recovery.

Is erectile dysfunction a predictor of cardiovascular events or stroke? A prospective study using a validated questionnaire.
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Erectile dysfunction (ED) is linked to various cardiovascular risk factors and may therefore serve as a predictor of cardiovascular events. To gain further insight into this relationship, we reviewed all data regarding hospital admission for cardial or cerebral vascular disease that occurred until 2008 in a cohort of men who underwent a health investigation in 2001. Erectile function was assessed using the International Index of Erectile Function (IIEF-5) questionnaire. In total, 2506 men with a negative history of cardial or cerebral vascular disease were analysed. During the 6.5-year follow-up, 58 cardiovascular events (2.3%) occurred. Men without ED (IIEF-5 >22; n=1636) at baseline developed a cardiovascular event in 1.9% (n=32) as compared with 2.9% (+52%; n=26) in those with ED (IIEF-5 < or =22; n=670). In contrast to age (hazard ratio (HR): 1.6; 1.2-1.8 for every decade), hypertension (HR: 1.88; 1.1-3.1) and diabetes (HR: 2.6; 1.2-5.8), ED was not an independent risk factor for a cardiovascular event. Although men with ED were at increased risk for future cardiovascular events, ED was not an age-independent predictor of cardiovascular events in our cohort.
Experimental immunotherapeutic approaches for atherosclerosis.

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Clin Immunol. 2010 Jan;134(1):66-79. Epub 2009 Aug 8. Review Therapeutic options in atherosclerosis have largely been limited to the control of risk factors, such as hypercholesterolemia, hypertension, or diabetes. However, atherosclerosis is a chronic inflammatory disease in which dyslipidemia and inflammation are equally involved in disease pathogenesis. Moreover, abundant epidemiological and experimental evidence point to an important modulatory role of innate and adaptive immunity in atherogenesis, providing novel therapeutic targets for this disease. Indeed, there is now accumulating data in animal models demonstrating the potential for immunotherapeutic approaches to treat atherosclerosis. These include both general and antigen-specific ways of modulating immune functions, and they show great promise for the development of alternative and/or adjuvant therapies for atherosclerosis.