Atherosclerotic Cardiovascular Disease in Belgium Sept. – Dec. 2010

Ruige JB, Mahmoud AM, De Bacquer D, Kaufman JM. 
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Ghent University Hospital, Ghent, Belgium. johannes.ruige@ugent.be
The literature provides no clear answer as to whether low endogenous testosterone increases risk of cardiovascular disease (CVD) in healthy men. Objective Our purpose was to estimate the predictive value of testosterone for CVD and to identify study features explaining conflicting results. Data Sources Articles were identified by a Medline and Embase search and citation tracking. Study Selection Eligible were prospective population-based cohort and nested case-control studies of testosterone and atherosclerosis, stroke, myocardial infarction, ischaemic heart disease, death from coronary heart disease or mortality. Data extraction Two independent researchers re-expressed associations of testosterone and CVD in a uniform manner to be used in meta-regression analyses for identification of study features explaining conflicting results, and to estimate the predictive value of testosterone for CVD. Results and Conclusions 19 potentially eligible articles were identified. Overall, a weak independent association was found with an estimated summary RR of 0.89 for a change of one standard deviation in total testosterone level (95% CI 0.83 to 0.96). Age of study population and year of publication modified the relationship between testosterone and CVD. The estimated summary RR was 1.01 (0.95 to 1.08) for studies of men younger than 70 years of age, and 0.84 (0.76 to 0.92) for studies including men over 70 years of age. The latter studies showed a particular pronounced association if published after 1 January 2007. Results were largely confirmed by separate analyses of free- and bioavailable testosterone. The systematic review displayed no association between endogenous testosterone and risk for CVD in middle-aged men. In elderly men, testosterone may weakly protect against CVD. Alternatively, low testosterone may indicate a poor general health.

Cardiovascular Safety of QVA149, a Combination of Indacaterol and NVA237, in COPD Patients.
1AZ Sint Jan Brugge-Oostende AV, Campus H. Serruys,Oostende, Belgium. bvba.vandemaele@skynet.be
This study assessed the cardiovascular safety of QVA149, an inhaled, once daily, bronchodilator combination containing two 24-hour bronchodilators, the long-acting β(2)-agonist indacaterol and the long-acting muscarinic antagonist glycopyrronium (NVA237). In this randomised, double-blind, placebo-controlled, parallel-group study, 257 patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) were randomised to receive QVA149 (indacaterol/NVA237) 600/100 μg, 300/100 μg or 150/100 μg, indacaterol 300 μg or placebo, once daily for 14 days. The primary endpoint was change from baseline in 24-h mean heart rate versus placebo on Day 14. 255 patients were included in the safety analysis (mean age 63.8 years, 76.5% male, post-bronchodilator forced expiratory volume in one second [FEV(1)] 53.2% predicted, FEV(1)/FVC [forced vital capacity] 50.0%, mean 24-h heart rate 79.6 bpm). There were no clinically significant differences in the 24-h mean heart rate on Day 14 between the three doses of QVA149 and placebo or indacaterol. The confidence intervals of these treatment differences (contrasts) were within the pre-specified equivalence limit (-5 to 5 bpm). No clinically relevant differences in QTc interval (Fridericia’s) were observed between groups on Days 1, 7 and 14. Once-daily QVA149 was well tolerated in COPD patients with a cardiovascular safety profile and overall adverse event rates similar to placebo.

Bondue A, Blanpain C.
Mesp1: a key regulator of cardiovascular lineage commitment.
Interdisciplinary Research Institute, Université Libre de Bruxelles, 808, route de Lennik, BatC, C6-130, 1070 Bruxelles, Belgium. Cedric.Blanpain@ulb.ac.be.
In mammals, the heart arises from the differentiation of 2 sources of multipotent cardiovascular progenitors (MCPs). Different studies indicated that an evolutionary conserved transcriptional regulatory network controls cardiovascular
development from flies to humans. Whereas in Drosophila, Tinman acts as a master regulator of cardiac development, the identification of such a master regulator in mammals remained elusive for a long time. In this review, we discuss the recent findings suggesting that Mesp1 acts as a key regulator of cardiovascular progenitors in vertebrates. Lineage tracing in mice demonstrated that Mesp1 represents the earliest marker of cardiovascular progenitors, tracing almost all the cells of the heart including derivatives of the primary and second heart fields. The inactivation of Mesp1/2 indicated that Mesp genes are essential for early cardiac mesoderm formation and MCP migration. Several recent studies have demonstrated that Mesp1 massively promotes cardiovascular differentiation during embryonic development and pluripotent stem cell differentiation and indicated that Mesp1 resides at the top of the cellular and transcriptional hierarchy that orchestrates MCP specification. In primitive chordates, Mesp also controls early cardiac progenitor specification and migration, suggesting that Mesp arises during chordate evolution to regulate the earliest step of cardiovascular development. Defining how Mesp1 regulates the earliest step of MCP specification and controls their migration is essential to understand the root of cardiovascular development and how the deregulation of these processes can lead to congenital heart diseases. In addition, these findings will be very useful to boost the production of cardiovascular cells for cellular therapy, drug and toxicity screening.

Endocrinologie, CHU Saint-Pierre, 69, avenue Exposition-Universelle, 1083 Bruxelles, Belgium. nathbakoto@hotmail.com
Cardiovascular and endocrine complications in male or sexually-ambiguous patients carrying a 45,X/46,XY mosaicism are rarely discussed in the medical literature. However, young female patients with a diagnosis of Turner's disease usually benefit from regular cardiologic and endocrine follow-up, in accordance with current international guidelines. We report the case of a male patient, aged 23 years, with an ambiguous phenotype known to harbor a mixed gonadic 45,X/46,XY type dysgenesis. The patient was admitted to the cardiology ward for investigation and management of cardiac failure secondary to both a bicuspid aortic valve and ascending aorta aneurysm. This case report, and the few others, which have been previously reported in the literature, emphasizes the importance of cardiologic and endocrine follow-up in male carriers of 45,X/46,XY mosaicism.

Department of Cardiology, University Hospital Ghent, Belgium. frauke.gorre@ugent.be
Beta-blockers are a heterogeneous group of antihypertensive agents. What they have in common is competitive antagonistic action on beta-adrenoreceptors (B1, B2 and B3). They differ in their receptor selectivity, intrinsic sympathomimetic activity (ISA), vasodilating properties and metabolism. Antihypertensive mechanisms and effect differ according to receptor-specificity and ISA, where differences in duration of action also have to be considered. An unfavourable metabolic profile of beta-blockers was reported based on studies describing the metabolic side effects of weakly-selective or non-selective agents. Newer generation beta-blockers appear to have a metabolic neutral profile. In systolic heart failure, three agents proved to improve survival up to 30%, mainly because of B1-blocking and/or vasodilating properties. The position of beta-blockers in treating diastolic heart failure remains uncertain. Beta-blocker therapy in coronary artery disease also leads to uncontested survival benefit, the cardioprotective mechanism largely due to rate reduction. This paper aims to describe the basis of heterogeneity of the available agents and to translate this into their applicability in different cardiovascular diseases, with focus on the underlying physiopathological mechanisms.

Department of Cardiovascular Medicine, University Hospitals Leuven, University of Leuven, Leuven, Belgium. Hein.Heidbuchel@uz.kuleuven.ac.be
OBJECTIVE: The RE-LY trial has shown that the oral direct thrombin inhibitor dabigatran etexilate is a valid replacement for oral anticoagulation with vitamin K antagonists (VKA) in patients with atrial fibrillation at thromboembolic risk. After a decade of failures, these results signify a breakthrough in anticoagulation management.
This article summarizes the available evidence from the perspective of the practicing clinician: do the results apply to all patients with AF? And what considerations should we make when prescribing this new oral anticoagulant?

METHODS AND RESULTS: We review the trials searching for oral alternatives to VKA therapy, with emphasis on the RE-LY data. We have integrated available interaction data, and data on how to deal with side effects and (bleeding) complications with the direct thrombin inhibitor dabigatran etexilate. CONCLUSIONS: dabigatran etexilate is a viable alternative to VKA, improving efficacy and safety in many respects, for many patients, and likely preferred by most patients themselves. Choosing the dose should be based on patient-specific factors. These include the presence of coronary artery disease (with potential requirement of concomitant aspirin +/- clopidogrel), decreased renal function, age, low body weight, administration of other AF drugs or P-glycoprotein inhibitors, a history of gastrointestinal bleeding, and patient compliance.


*How many measurements are needed to provide reliable information in terms of the ambulatory arterial stiffness index? the Ohasama study.*
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Tohoku University Graduate School of Medicine and Pharmaceutical Sciences, Sendai, Japan [2] Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium. kikuyam@mtains.tohoku.ac.jp

The aim of this study was to investigate how frequent ambulatory blood pressure (ABP) readings need to be obtained to reproduce the ambulatory arterial stiffness index (AASI) and pulse pressure (PP) without loss of information. We compared concordance from full and reduced ABP recordings. We recorded 24-h ABP at 30-min intervals in 1542 residents of Ohasama, Japan (baseline age, 40-93 years; 63.4% women). We randomly excluded up to 16 readings per recording or we selected readings at fixed 1- or 2-h intervals. Using full recordings as reference, we computed for the reduced recordings repeatability coefficient by Bland and Altman's approach. By Cox regression, we also calculated multivariate-adjusted hazard ratios for cardiovascular mortality. The median number of ABP readings per recording was 46. Randomly excluding more readings reduced the concordance of AASI, but not PP. Selecting blood pressure readings at 1- or 2-h intervals produced mean values of AASI and PP, which significantly differed from those in full recordings. During follow-up (median, 13.3 years) 126 cardiovascular deaths occurred. Across quartiles, AASI significantly predicted cardiovascular mortality in a U-shaped manner. AASI lost its prognostic significance when the number of randomly excluded readings increased from 8 to 16 or when the interval between readings was 1 h or longer. Compared with PP, AASI is less reproducible when the number of readings in ABP decreases, but this does not affect the predictive accuracy of AASI for cardiovascular mortality, until the median number of readings per ABP recording is less than ~35. Hypertension Research advance online publication, 2 December 2010; doi:10.1038/hr.2010.240.

De Meyer T, Rietzschel ER, De Buyzere ML, Van Criekinge W, Bekaeart S.

*Telomere length and cardiovascular aging: The means to the ends?*
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Dept. of Molecular Biotechnology, FBE, Coupure Links 653, Ghent University, B9000 Ghent, Belgium. Tim.DeMeyer@UGent.be

Epidemiologic and other evidence clearly indicates that peripheral blood leukocyte telomere length, a systemic marker for biological aging, can be useful as a cardiovascular aging biomarker. Although telomere biology might yield new insights into the underlying molecular biology of vascular aging and even radically improve current cardiovascular risk stratification, the specific nature of the association between telomere length and cardiovascular disease still remains to be elucidated. Here, we review several candidate hypotheses and critically review supporting and contesting scientific evidence for the underlying theories. For each hypothesis, we discuss the potential implications. We conclude that the most promising theory is based on an acceleration of the telomere attrition rate due to cardiovascular aging related factors, possibly complemented by telomere mediated hematopoietic senescence.
for several hours after primary PCI. Regardless of whether PCI or thrombolysis is used, patients with a high risk of bleeding should be treated. To prevent possible thrombotic events after PCI, bivalirudin should be continued after an EMS is recommended as always but bivalirudin is an upcoming alternative, either in the catheterization laboratory or in a nearby non-PCI hospital. The first-line management of STEMI patients often determines if the outcome is life or death. This overview presents the current optimal evidence-based management of STEMI patients as a practice-oriented extract according to the latest ESC guidelines, fully published some weeks ago (http://www.escardio.org). All efforts must be made to keep the respective time intervals between the onset of symptoms and the beginning of reperfusion therapy as short as possible, i.e. best within a dedicated STEMI network. Two of the time intervals are particularly essential: the time delay between the onset of symptoms and the first medical contact (FMC) and the time delay between FMC and the beginning of reperfusion. The time delay between the onset of symptoms and FMC depends on the patient as well as on the organization of the emergency medical service (EMS). Unfortunately, too many patients/bystanders still hesitate to immediately call the EMS. More intense measures must therefore be taken to educate the public. The optimal FMC by medical doctors or paramedics reacts quickly and ideally arrives with ECG equipment for immediate diagnosis of STEMI (persistent ST-segment elevation or presumably new left bundle branch block) before hospital admission. Unfortunately in many cases, the FMC is the emergency room of a hospital. Further decisions can be made without laboratory findings. In Germany, the average time delay between onset of symptoms and FMC is 100 min and therefore longer than in some other European countries. The next critical time interval is that between FMC and the beginning of reperfusion: this interval depends solely on the EMS organization and the distance to the next catheter laboratory with 24 h PCI (percutaneous coronary intervention) availability. The key question for further decisions is whether a primary PCI can be performed within 120 min after FMC. If so, the primary PCI should definitely be preferred. In patients <75 years presenting with a large anterior infarction within 2 h after onset of symptoms, this time interval should not exceed 90 min. For primary PCI an often used measure of quality is the “door-to-balloon” time, which should of course be as short as possible. Therefore, patients with STEMI should be admitted directly to the catheterization laboratory bypassing the emergency room or intensive care unit. In Germany, the average time interval between FMC and start of primary PCI is approximately 120 min just at the upper limit of the guideline recommendations. Some other European countries report a significantly shorter corresponding time delay. If primary PCI is not possible within 120 min (or 90 min) after FMC, thrombolysis must be initiated within 30 min after FMC, either in the EMS ambulance or in a nearby non-PCI hospital. A thrombolytic therapy, however, even if “successful”, is not the final therapy: within 24 h (but not before 3 h) cardiac catheterization has to be performed with PCI, if applicable. Analyzing the overall revascularization rates in Germany, 81% receive primary PCI, 7% thrombolysis and 12% no reperfusion therapy. Regarding any reperfusion in STEMI, Germany holds the third place after the Czech Republic and Belgium. Patients presenting at 12-24 h after onset of symptoms or later may possibly benefit from a PCI, even if already asymptomatic, if signs of ischemia/viability in the infarct artery-related area are demonstrable. If this cannot be shown, PCI in these patients is not indicated. The first-line medication aims at dual antiplatelet therapy (DAPT) and anticoagulation. For DAPT, the combination of ASA with a thienopyridine is mandatory. If primary PCI is feasible, DAPT with prasugrel (loading dose of 60 mg, independent of age and weight) is preferred due to its faster onset of action and superior effectiveness over clopidogrel (loading dose of 600 mg). In patients with STEMI, prasugrel when compared to clopidogrel significantly reduced nonfatal myocardial infarction after 15 months from 9.0% to 6.8% and stent thrombosis significantly from 2.8% to 1.6% (ARC definite/probable). If, however, there are contraindications against prasugrel (s/p stroke or TIA) or if thrombolysis had to be performed, clopidogrel is the choice for DAPT. The i.v. administration of glycoprotein IIb/IIIa inhibitors (GPI) has been limited to only those patients with a high intracoronary thrombus burden. The upstream application of GPI is not recommended. Recommendations for the mechanical treatment of thrombus burden include manual thrombus aspiration (which was upgraded) and a mesh-based protection stent device (MGuard™). For anticoagulation, unfractionated heparin (UFH) is recommended as always but bivalirudin is an upcoming alternative, either in the catheterization laboratory on top after an EMS-delivered UFH bolus or as a possible first-line monotherapy. Bivalirudin may be preferred in STEMI patients with a high risk of bleeding. To prevent possible thrombotic events after PCI, bivalirudin should be continued for several hours after primary PCI. Regardless of whether PCI or thrombolysis was the first-line therapy and
Regardless of whether a stent (BMS or DES) was implanted, DAPT should be continued for 12 months with prasugrel 10 mg/day (or 5 mg/day, if ≥75 years old and/or <60 kg body weight) or clopidogrel (75 mg/day). There is no evidence that higher maintenance doses of clopidogrel may circumvent possible clopidogrel resistance. The usefulness of so far non-standardized in-vitro platelet aggregation measurements or the practice-oriented interpretation of genetic tests for CYP2C19 polymorphism is unknown. With the 12 months DAPT the patient is treated not the stent.

Department of Nephrology and Hypertension, Universitair Ziekenhuis Brussel, Brussels, Belgium.
hemovnnp@uzbrussel.be

Hypertension is a major risk factor for cardiovascular disease, which is the leading cause of death in women. **Aim.** To evaluate blood pressure control, prevalence of concomitant cardiovascular risk factors, subclinical and clinical organ damage, and treatment according to gender. **Methods.** 11,562 patients (49% women) from the cross-sectional I-inSyst survey in primary care were included. **Results.** Blood pressure control in women (21.8%) and men (21.2%) was similar, despite a slightly older age (64.9 vs 63 years, p<0.0001). Women had less concomitant cardiovascular risk factors and organ damage, with the exception of diabetes, cerebrovascular and renal disease, than men. They received more antihypertensive drugs than men (1.7 ± 0.9 vs 1.5 ± 0.9, p<0.0001). Diuretics were more (45% vs 36.5%, p<0.0001), calcium-channel blockers (26% vs 29%, p<0.003) and angiotensin-converting enzyme inhibitors (20% vs 22%, p<0.02) were less commonly prescribed in women than in men. Different clinical factors (i.e. age, duration of hypertension, smoking) in women and men were associated with blood pressure control, but gender itself was not. **Conclusions.** In this group of treated hypertensive patients, blood pressure control in women and men was not different. Women had a lower prevalence of most cardiovascular risk factors, subclinical and clinical organ damage. Antihypertensive drug treatment varied according to gender.

Nephrology Division, Department of Internal Medicine, University Hospital Gent, Gent, Belgium.
Raymond.Vanholder@UGent.be

Chronic kidney disease is considered a major cause of cardiovascular risk and non-traditional risk factors remain largely unknown. The in vitro toxicity of 10 guanidino compounds (GCs) was evaluated via a standardized approach on different cell systems of relevance in cardiovascular disease. The parameters evaluated were production of reactive oxygen species, expression of surface molecules, cell proliferation, cytotoxicity and calcification. Several GCs had a stimulatory effect on monocytes and granulocytes (SDMA, creatine and guanidinobutyric acid (GBA)). Some GCs (guandine (G), guanidinosuccinic acid (GSA) and SDMA) inhibited endothelial cell proliferation or reduced calcification in osteoblast-like human VSMC (ADMA, GSA and SDMA). Stimulation of osteoclastogenesis could be demonstrated for ADMA, G, guanidinoacetic acid and GBA in a RAW264.7 cell line. No compounds were cytotoxic to AoSMC or endothelial cells, nor influenced their viability. GCs, especially SDMA, likely contribute to cardiovascular complications in uremia, mainly those related to microinflammation and leukocyte activation.

Centre de Recherche Public Santé, Centre d’Etudes en Santé, Grand-Duchy of Luxembourg.
alaa.alkerwi@crp-sante.lu

**BACKGROUND:** Despite the remarkable technological progress in health care and treatment, cardiovascular disease remains the leading cause of premature death, prolonged hospitalization and disability in most European
countries. In the population of the Greater Region (Grand-Duchy of Luxembourg, Wallonia in Belgium, and Lorraine in France), the prevalence of cardiovascular risk factors and disease is among the highest in Europe, warranting the need for a better understanding of factors contributing to this pattern. In this context, the cross-border "Nutrition, Environment and Cardiovascular Health-NESCAV" project is initiated by an inter-regional multi-disciplinary consortium and supported by the INTERREG IV A program "Greater Region", 2007-2013, to fight synergically and harmoniously against this major public health problem. METHODS/DESIGN: The objectives of the three-year planned project are to assess, in a representative sample of 3000 randomly selected individuals living at the Greater Region, 1) the cardiovascular health and risk profile, 2) the association between the dietary habits and the cardiovascular risk, 3) the association of occupational and environmental pollution markers with the cardiovascular risk, 4) the knowledge, awareness and level of control of cardiovascular risk factors, 5) the potential gaps in the current primary prevention, and finally, to address evidence-based recommendations enabling the development of inter-regional guidance to help policy-makers and health care workers for the prevention of cardiovascular disease.

DISCUSSION: The findings will provide tools that may enable the Greater Region's decision-makers and health professionals to implement targeted and cost-effective prevention strategies.

Vaes B, Delgado V, Bax J, Degryse J, Westendorp RG, Gussekloo J. Diagnostic accuracy of plasma NT-proBNP levels for excluding cardiac abnormalities in the very elderly. BMC Geriatr. 2010 Nov 11;10:85
Department of General Practice, Université Catholique de Louvain, Avenue Mounier 53, bte 5360, 1200 Brussels, Belgium. Bert.Vaes@uclouvain.be

BACKGROUND: In the elderly the diagnosis of chronic heart failure is often challenging and the availability of echocardiography can be limited. Plasma levels of NT-proBNP are valuable tools to diagnose patients with heart failure. However, the performance of this biomarker to detect cardiac abnormalities in the very elderly remains unclear. The aims of this study were to investigate the relation between NT-proBNP and cardiac abnormalities and to evaluate the use of NT-proBNP to exclude structural and functional cardiac abnormalities in a community-based sample of "well-functioning" nonagenarians. METHODS: A diagnostic cross-sectional study embedded within the Leiden 85-plus Study in the municipality of Leiden, the Netherlands. Plasma NT-proBNP levels were measured and 2-dimensional echocardiography was performed in a subgroup of 80 well-functioning nonagenarians. Linear regression analysis was used to explore the relation between NT-proBNP and cardiac abnormalities and ROC curve analysis was used to assess the performance of NT-proBNP to exclude cardiac abnormalities. The upper limit of the lowest tertile of NT-proBNP was used as a cut-off value. RESULTS: NT-proBNP levels were associated with abnormal left ventricular (LV) dimensions, LV systolic and diastolic function, left atrial enlargement and valvular heart disease. LV mass, E/A ratio and degree of aortic regurgitation were identified as independent predictors of NT-proBNP. NT-proBNP levels were higher with greater number of echocardiographic abnormalities (P < 0.001). A cut-off level of 269.5 pg/mL identified patients with abnormal LV dimensions or depressed LV systolic function (sensitivity 85%, negative predictive value (NPV) 77%, area under the curve 0.75 (95% CI 0.64-0.85)). In addition, high NPV were found for LV systolic dysfunction, left atrial enlargement, severe valvular heart disease and pulmonary hypertension. The test performance of NT-proBNP to exclude any echocardiographic abnormality showed a sensitivity of 82% and a NPV of 65%. CONCLUSIONS: In this convenience sample of well-functioning nonagenarians NT-proBNP was related to a wide variety of functional and structural echocardiographic abnormalities. Moreover, NT-proBNP could be used to exclude echocardiographic abnormalities in well-functioning nonagenarians and might be used to indicate who needs to be referred for further cardiovascular examination.

Department of Pediatric Nephrology, Campus Virchow Klinikum, Germany Center for Cardiovascular Research, Campus Mitte, Charité - Universitätsmedizin Berlin, Berlin, Germany, Department of Pediatrics, University of Rostock, Rostock, Germany, Institute of Nutritional Science, University of Potsdam,
BACKGROUND AND OBJECTIVE: Whether treatment with vitamin D receptor activators contributes to cardiovascular disease in patients with chronic kidney disease is a matter of debate. We studied mechanisms involved in vitamin D-related vascular calcifications in vivo and in vitro. METHODS: Aortic calcifications were induced in subtotally nephrectomized (SNX) rats by treatment with a high dose (0.25 μg/kg per day) of 1,25-dihydroxyvitamin D3 (calcitriol) given for 6 weeks. Likewise, primary rat vascular smooth muscle cells (VSMCs) were incubated with calcitriol at concentrations ranging from 10 to 10 mol/l. Immunohistochemistry revealed that the aortic expression of osteopontin, osteocalcin and bone sialoprotein was significantly increased in calcitriol-treated SNX rats compared to untreated SNX controls. In addition, aortic expression of the transient receptor potential vanilloid calcium channel 6 (TRPV6) and calbindin D9k was significantly up-regulated by treatment with calcitriol. Furthermore, calcitriol significantly increased expression of the osteogenic transcription factor osterix. In-vitro studies showed similar results, confirming that these effects could be attributed to treatment with calcitriol. CONCLUSIONS: High-dose calcitriol treatment induces an osteoblastic phenotype in VSMC both in SNX rats and in vitro, associated with up-regulation of proteins regulating mineralization and calcium transport, and of the osteogenic transcription factor osterix.


Department of Urology, CHU de Charleroi, Hôpital Erasme, Brussels, Belgium. dr.wespes@skynet.be

Erection is a vascular phenomenon under a psychologic control in a hormonal environment. Erectile dysfunction is defined as the inability to obtain and to maintain sufficient erection for satisfactory intercourse. Organic erectile dysfunction results mainly from vascular problems due to atherosclerosis, a process that begins during childhood, and becomes clinically evident from middle age. Endothelial dysfunction is the first step of atherosclerosis. As the endothelial cells recover the sinusoid spaces in the cavernous tissue and because common risk factors for atherosclerosis have been frequently found in patients with erectile dysfunction, it is logical that vascular impotence presents the same pathophysiology of the other vascular diseases. They share a similar pathogenic involvement of nitric oxide pathway leading to impairment of endothelium dependent vasodilatation and structural vascular abnormalities. Circulating markers of endothelial cell damage have been reported in patients with erectile dysfunction while they have not yet presented any other vascular pathology. Endothelial progenitor cells of bone marrow origin that play a role in promoting endothelial repair are also reduced in vascular abnormalities. As penile arteries have the smallest diameter in the vascular network and because atherosclerosis is a systemic disease, erectile dysfunction could be a sentinel symptom of a more generalized vascular pathology. Modifications of reversible causes or risk factors at the base of the pathogenesis of atherosclerosis remain the first approach toward improving endothelial function and associated with chronic exposure to PDE5-I, they could improve or even cure ED and could avoid fatal cardiovascular attacks in the future.


Unité de Réadaptation et de Médecine Physique, Université Catholique de Louvain, Brussels, Belgium. edouard.bouffioulx@helha.be

OBJECTIVE: To investigate clinical changes among the acute, post-acute and chronic phases in stroke patients' satisfaction with activities and participation. The SATIS-Stroke questionnaire's sensitivity to change was investigated with a sample of 45 stroke patients. METHODS: The SATIS-Stroke questionnaire was used to collect data from the 45 patients (mean age 69 years, 64% men) in the acute, post-acute and chronic stroke phases. Responsiveness of the questionnaire was investigated using a sample approach (effect size and standardized response mean indices) and an individual approach (t statistic). The clinical significance of change was also calculated using the empirical rule of effect size and the minimal clinically important difference. RESULTS: Analysis of variance showed a significant difference among evaluations in the 3 phases (F = 13.662; 2 df; p < 0.001). Post-hoc analysis showed a significant change between the acute and post-acute phases, but no significant change between the post-acute and
chronic phases. Effect size and standardized response mean indices showed that the greatest change in satisfaction with activity and participation was between the acute and the chronic phases. Analysis of the clinical significance of change indicated that greater changes in satisfaction were necessary to detect clinically relevant improvement over time than clinically relevant deterioration. CONCLUSION: The SATIS-Stroke questionnaire successfully determined changes in satisfaction among stroke patients.

Wens J, Gerard R, Vandenberghe H. Optimizing diabetes care regarding cardiovascular targets at general practice level: Direct@GP. Prim Care Diabetes. 2010 Oct 26. [Epub ahead of print]

University of Antwerp, Faculty of Medicine, Department of General Practice, Interdisciplinary Health Care, and Geriatrics, Universiteitsplein 1, 2610 Antwerp, Wilrijk, Belgium.

AIMS: The objective of this study was to assess the adherence to national guidelines on cardiovascular (CV) prevention and target attainment for patients with type 2 diabetes mellitus followed-up in general practice.

METHODS: Non-interventional, cross-sectional survey. RESULTS: Type 2 diabetes patients remain undertreated with statins (63% treated), even so those with a cardiovascular history (80% treated). Although more patients received antihypertensive treatment (82%) compared to hypolipidemic medication (69%), the proportion of patients attaining targets for total cholesterol (TC) (35%), HDL-cholesterol (HDL-C) (65%), and LDL-cholesterol (LDL-C) (42%) exceeded far those attaining blood pressure control (13%). The primary endpoint of reaching the goal for LDL-cholesterol (<100mg/dL; 2.59mmol/L) was attained by 42% of patients, of which only 13% reached the more stringent target of LDL-C<70mg/dL (1.81mmol/L). About half of the patients (49%) attained glycemic control (HbA1c<7%) and 55% had triglycerides<150mg/dL (1.69mmol/L). CONCLUSIONS: The majority of type 2 diabetes patients are treated for hypercholesterolemia and hypertension, although, there is still under treatment, especially in patients with CV disease. Only 42% of patients were on target for LDL-cholesterol and 13% for blood pressure. Therefore, wider implementation of process and outcome indicators, which proved to be related, and continuous evaluation of their result, is needed.


Cardiovascular Center, OLV Hospital, Aalst, Belgium. emanuele.barbato@olvz-aalst.be

The aim of the present study was to compare 600- and 300-mg clopidogrel loading doses in patients with ST-segment elevation myocardial infarctions who underwent primary percutaneous coronary intervention (PCI). Two hundred fifty-five consecutive patients presenting with ST-segment elevation myocardial infarctions who underwent primary PCI were enrolled. Patients were divided into 2 groups on the basis of the loading dose of clopidogrel received before the procedure (600 vs 300 mg). Procedural angiographic end points and 1-year major adverse cardiac events were compared between the 2 groups. Major adverse cardiac events were defined as death, nonfatal myocardial infarction, and target vessel revascularization. There were no significant differences in baseline clinical and angiographic features between the 2 groups: 157 (62%) in the clopidogrel 600 mg group and 98 (38%) in the 300 mg group. Patients receiving 600-mg loading dose of clopidogrel showed a significantly lower incidence of post-PCI myocardial blush grade 0 or 1 (odds ratio 0.64, 95% confidence interval 0.43 to 0.96, p = 0.03) and significantly less common no-reflow phenomenon (odds ratio 0.38, 95% confidence interval 0.15 to 0.98, p = 0.04) compared to those in the 300-mg group. Propensity-adjusted Cox analysis showed significantly higher survival free of major adverse cardiac events in patients receiving 600-mg loading dose of clopidogrel compared to those receiving the lower dose (hazard ratio 0.57, 95% confidence interval 0.33 to 0.98, p = 0.04). In conclusion, a 600-mg loading dose of clopidogrel is associated with improvements in procedural angiographic end points and 1-year clinical outcomes in patients with ST-segment elevation myocardial infarction who undergo primary PCI compared to a 300-mg dose.
Inhibition of the calcium-activated chloride current in cardiac ventricular myocytes by N-(p-amylcinnamoyl)anthranilic acid (ACA).

Division of Experimental Cardiac Surgery, Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium. kanigula.mubagwa@med.kuleuven.be

N-(p-amylcinnamoyl)anthranilic acid (ACA), a phospholipase A(2) (PLA(2)) inhibitor, is structurally-related to non-steroidal anti-inflammatory drugs (NSAIDs) of the fenamate group and may also modulate various ion channels. We used the whole-cell, patch-clamp technique at room temperature to investigate the effects of ACA on the Ca(2+)-activated chloride current (I(Cl(Ca))) and other chloride currents in isolated pig cardiac ventricular myocytes. ACA reversibly inhibited I(Cl(Ca)) in a concentration-dependent manner (IC(50)=4.2 μM, n(Hill)=1.1), without affecting the L-type Ca(2+) current. Unlike ACA, the non-selective PLA(2) inhibitor bromophenacyl bromide (BPB; 50 μM) had no effect on I(Cl(Ca)). In addition, the analgesic NSAID structurally-related to ACA, diclofenac (50 μM) also had no effect on I(Cl(Ca)), whereas the current in the same cells could be suppressed by chloride channel blockers flufenamic acid (FFA; 100 μM) or 4,4'-diisothiocyanostilbene-2,2'-disulfonic acid (DIDS;100 μM). Besides I(Cl(Ca)), ACA (50 μM) also suppressed the cAMP-activated chloride current, but to a lesser extent. It is proposed that the inhibitory effects of ACA on I(Cl(Ca)) are PLA(2)-independent and that the drug may serve as a useful tool in understanding the nature and function of cardiac anion channels.

The impact of training modalities on the clinical benefits of exercise intervention in patients with cardiovascular disease risk or type 2 diabetes mellitus.

Jessa Hospital/Heart Centre Hasselt, Hasselt, Belgium. rmeeusen@vub.ac.be

Exercise training intervention represents an effective means to reduce adipose tissue mass, improve glycaemic control and increase whole-body oxygen uptake capacity (VO(2peak)) in obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM) and heart disease patients. In this manuscript, we review the impact of different exercise training modalities on clinical benefits of prolonged exercise intervention in these patient (sub)populations. By changing training modalities, significantly greater clinical benefits can be obtained. Greater training frequency and longer programme duration is associated with greater reduction in adipose tissue mass in obesity patients. A greater training frequency (up to 2 days/week) and a longer programme duration (up to 38 weeks) seems to be associated with greater improvements in VO(2peak) in heart disease patients. Longer programme duration and addition of resistance-type exercise further improve glycaemic control in T2DM patients. The first line of evidence seems to indicate that high-intensity interval exercise training has a greater impact on VO(2peak) in heart disease patients and insulin sensitivity in subjects with metabolic syndrome, but not on adipose tissue mass in obese subjects. However, it remains unclear whether addition of resistance-type exercise and continuous higher-intensity endurance-type exercise training are accompanied by greater improvements in VO(2peak) in heart disease patients. Furthermore, the impact of training session duration/volume on adipose tissue mass loss and glycaemic control in obesity and T2DM patients, respectively, is currently unknown. The impact of training frequency on glycaemic control remains to be investigated in T2DM patients.

What do we know about effects of desert dust on air quality and human health in West Africa compared to other regions?

Department of Geography, FUNDP-University of Namur, Rue de Bruxelles 61, 5000 Namur, Belgium. fdelongu@fundp.ac.be

Review. This study aims to compare, on the one hand, the geographical distribution of the desert dust source areas, their contribution to quantities emitted into the atmosphere, the trajectories and the quantities deposited, with on the other hand the areas of research interest focused on the desert dust impacts on air quality and/or human health. Based on a systematic review of the literature using the ISI Web of Knowledge database, we found 231 articles
published over the last decade on the desert dust impacts on air quality. Of these, 48% concerned Asian dust and 39% Saharan dust, with the remaining 13% divided between the other dust source areas. However, only one of these studies addressed the worsening air pollution in West Africa, even though it is very close to the Sahara, the greatest contributor to the global dust budget. Moreover, there have been very few studies (41) looking at the direct links between desert dust and human health; in this context too, no interest has been shown in West Africa. Yet this region is also among the areas in which morbidity rates have been noted to be far higher than those found in other regions of the world, and where respiratory infections alone account for more than 20% of the causes of infant mortality. This survey highlights a clear imbalance between those areas most exposed to dust and the most studied areas in terms of dust impacts. Given these findings and the often alarming results published about other regions of the world, we advocate a revival of interest in research on West Africa in order to achieve a better understanding of the desert dust impacts on air quality and health among the populations of this region.


Department of Hematology, University Hospital Leuven, Belgium. michael.delforge@uzleuven.be
Introduction of the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide has substantially improved outcomes for patients with multiple myeloma. As a result, these drugs have become cornerstones of current antmyeloma treatment regimens. However, after several years of clinical experience it has become apparent that peripheral neuropathy is the most common and potentially disabling non-haematological side-effect associated with thalidomide and bortezomib. Maximising treatment benefit while preserving quality of life therefore requires a careful balance between achieving optimum activity and minimising toxicity, including neuropathy, to further enhance efficacy. In this review, we discuss all aspects of drug-induced peripheral neuropathy in myeloma, with a particular focus on thalidomide and bortezomib.


Center for Heart Failure Research, Cardiovascular Research Institute, Maastricht, The Netherlands; the Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium and Department of Epidemiology, Maastricht University Medical Center, Maastricht, The Netherlands; Centre de Recherche Public-Santé, Luxembourg, Luxembourg; Maastricht University Medical Center, Maastricht, The Netherlands; and Centre Hospitalier Luxembourg, Luxembourg. b.schroen@cardio.unimaas.nl
Background- Small RNA molecules, called microRNAs, freely circulate in human plasma and correlate with varying pathologies. In this study, we explored their diagnostic potential in a selection of prevalent cardiovascular disorders.

Methods and Results- MicroRNAs were isolated from plasmas from well-characterized patients with varying degrees of cardiac damage: (1) acute myocardial infarction, (2) viral myocarditis, (3) diastolic dysfunction, and (4) acute heart failure. Plasma levels of selected microRNAs, including heart-associated (miR-1, -133a, -208b, and -499), fibrosis-associated (miR-21 and miR-29b), and leukocyte-associated (miR-146, -155, and -223) candidates, were subsequently assessed using real-time polymerase chain reaction. Strikingly, in plasma from acute myocardial infarction patients, cardiac myocyte-associated miR-208b and -499 were highly elevated, 1600-fold (P<0.005) and 100-fold (P<0.0005), respectively, as compared with control subjects. Receiver operating characteristic curve analysis revealed an area under the curve of 0.94 (P<10(-5)) for miR-208b and 0.92 (P<10(-9)) for miR-499. Both microRNAs correlated with plasma troponin T, indicating release of microRNAs from injured cardiomyocytes. In viral myocarditis, we observed a milder but significant elevation of these microRNAs, 30-fold and 6-fold, respectively. Plasma levels of leukocyte-expressed microRNAs were not significantly increased in acute myocardial infarction or viral myocarditis patients, despite elevated white blood cell counts. In patients with acute heart failure, only miR-499 was significantly elevated (2-fold), whereas no significant changes in microRNAs studied could be observed in
diastolic dysfunction. Remarkably, plasma microRNA levels were not affected by a wide range of clinical confounders, including age, sex, body mass index, kidney function, systolic blood pressure, and white blood cell count. **Conclusions** - Cardiac damage initiates the detectable release of cardiomyocyte-specific microRNAs-208b and -499 into the circulation.


Department of Cardiology, Valvar Heart Disease Clinic, University Hospital, CHU Sart Tilman, University of Liège, Liège, Belgium. plancellotti@chu.ulg.ac.be

The aim of this study was to determine the impact of aortic stenosis (AS) on the different components of left atrial (LA) function. The study consisted of a total of 52 consecutive patients with severe AS (aortic valve area < 1 cm²) and 20 normal subjects matched for gender, heart rate, body surface area, and baseline systolic blood pressure. Phasic LA longitudinal function was assessed using tissue Doppler imaging. LA peak systolic (reservoir function), early diastolic (conduit function), and late diastolic (active function) strain rates were measured. During late diastole, LA peak strain (active function) was also measured. Mitral annular systolic, early diastolic (Ea), and late diastolic (Aa) velocities were also measured. Compared with controls, all strain values were significantly reduced in patients with AS. By multivariate regression analysis, mitral E-wave deceleration time (p = 0.033) and E/Ea ratio (p = 0.02, R² = 0.43) emerged as independently associated with LA peak systolic strain rate. Ea was the sole determinant of LA early diastolic strain rate (p < 0.0001, R² = 0.42), whereas LA late diastolic strain rate was independently related to aortic valve area (p = 0.031) and Aa (p = 0.022, R² = 0.51). In conclusion, in patients with severe AS, the 3 components of LA function are reduced. LA reservoir dysfunction is related to left ventricular filling pressures, whereas LA conduit dysfunction depends on left ventricular relaxation. Active LA dysfunction is related to the severity of AS and late left ventricular diastolic function.


Division of Cardiology, University of Antwerp, Wilrijk, Belgium. ilse.van.brussel@uza.be

**OBJECTIVES:** Previous in vivo studies on dendritic cell (DC) enumeration in coronary artery disease (CAD) were not always consistent. Therefore, we investigated by flow cytometry whether this was due to CAD-related differences in expression of subset markers for myeloid (m)DCs (blood DC antigen (BDCA)-1, CD11c) and plasmacytoid (p)DCs (BDCA-2, CD123), before and after in vitro stimulation with Toll-like receptor ligands. **RESULTS:** Our data showed that circulating DCs decline in CAD, irrespective of the DC subset marker that was used for enumeration. Upon in vitro activation, BDCA-2 was downregulated, whereas CD11c and CD123 were upregulated. This implies that the expression ratios CD11c/BDCA1 and CD123/BDCA2 can assess DC activation. Comparing these ratios between controls and CAD patients showed no differences in blood DC activation in both groups. **CONCLUSIONS:** This study suggests that when different DC numbers are found between two study populations, the DC activation status from both groups always needs to be verified, since a decrease in BDCA-2(+) pDCs or an increase in CD11c(+) mDCs or CD123(+) pDCs can be due to the altered expression of these markers during activation. Given that CD11c, BDCA-1, CD123 and BDCA-2 are more abundantly expressed on blood DCs than typical activation markers like CD83, CD86 or CCR-7, the use of the ratios is an easy and reliable way to determine DC activation in whole blood assays.


Center for Health Services and Nursing Research, Katholieke Universiteit Leuven, Belgium. RupparT@missouri.edu

**BACKGROUND AND OBJECTIVES:** Older adults' adherence to antihypertensive medications is far lower than what is considered necessary for clinical effectiveness, despite the risks for adverse cardiovascular events from
uncontrolled blood pressure (BP) in the elderly. This pilot study tested a novel 8-week behavioral feedback intervention to improve antihypertensive medication adherence (MA) and BP control among older adults on existing treatment for hypertension. METHODS: Adults 60 years old, or older taking at least 1 antihypertensive medication were randomized to receive the nurse-delivered adherence intervention or usual care. Medication adherence was monitored continuously using electronic monitoring for 20 weeks. Intervention-group participants received biweekly MA and BP feedback, habit counseling, medication and disease education, a medication instruction card, and were given an electronic medication bottle cap with a digital display that provided daily adherence feedback during the 8-week intervention. Blood pressure was measured by a nurse at 12 and 20 weeks after randomization. Adherence and BP outcomes were described using descriptive statistics and analyzed for between- and within-group differences using Mann-Whitney U tests. RESULTS: Fifteen participants (median age, 71 years; 73% female) were eligible for randomization. Participants took an average of 5.8 prescription medications and 2.93 over-the-counter medications per day. A nonsignificant difference was noted in baseline MA between groups. At the end of the intervention, the treatment group had better antihypertensive MA than did the control group (median MA: 100% vs 27.3%, U = 5.00, P = .013). Systolic BP improved slightly in the intervention group during the study and was significantly different at week 12 (median systolic BP: 130 vs 152 mm Hg; U = 4.50, P = .008). Diastolic BP was largely unchanged over the course of the study. CONCLUSION: The results indicate that the intervention had a positive effect on MA. Additional testing is needed to further evaluate the intervention and its effect on adherence behavior and BP control.


Right ventricular ischemic injury in patients with acute ST-segment elevation myocardial infarction: characterization with cardiovascular magnetic resonance.


Department of Radiology, Medical Imaging Research Center, UZ Leuven, Herestraat 49, Leuven, Belgium. jan.bogaert@uz.kuleuven.ac.be

BACKGROUND: Experimental data show that the right ventricle (RV) is more resistant to ischemia than the left ventricle. To date, limited data are available in humans because of the difficulty of discriminating reversible from irreversible ischemic damage. We sought to characterize RV ischemic injury in patients with reperfused myocardial infarction using cardiovascular magnetic resonance. METHODS AND RESULTS: In 3 tertiary centers, 242 consecutive patients with reperfused acute ST-segment elevation myocardial infarction were studied with cardiovascular magnetic resonance at 1 week and 4 months after myocardial infarction. T2-weighted and postcontrast cardiovascular magnetic resonance scans were used to depict myocardial edema and late gadolinium enhancement, respectively. Early after infarction, RV edema was common (51% of patients), often associated with late gadolinium enhancement (31% of patients). Remarkably, RV edema and late gadolinium enhancement were found in 33% and 12% of anterior left ventricular infarcts, respectively. Baseline regional and global RV functions were inversely related to the presence and extent of RV edema and RV late gadolinium enhancement. At follow-up, a significant decrease in frequency (25/242 patients; 10%) and extent of RV late gadolinium enhancement was observed (P<0.001). With the use of multivariable analysis, the presence of RV edema was an independent predictor of RV global function improvement during follow-up (β-coefficient=0.221, P=0.003). CONCLUSIONS: Early postinfarction RV ischemic injury is common and is characterized by the presence of myocardial edema, late gadolinium enhancement, and functional abnormalities. RV injury is not limited to inferior infarcts but is commonly found in anterior infarcts as well. Cardiovascular magnetic resonance findings suggest reversibility of acute RV dysfunction with limited permanent myocardial damage at 4-month follow-up.

Fremault A, Janssens W, Beaucage F, Celis G, Pérez-Bogerd S, Decramer M.

Modification of COPD presentation during the last 25 years.


University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Belgium. antoine.fremault@uz.kuleuven.ac.be

During the last decades progress has been made in the treatment of Chronic Obstructive Pulmonary Disease (COPD). We compared a random sample of patients admitted for an exacerbation in the period 2001-2005 (n = 101), with a random sample of patients hospitalized for the same reason in the period 1980-1984 (n = 51). Patients of the
Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial.


pierre.boutouyrie@egp.aphp.fr

BACKGROUND: Vascular Ehlers-Danlos syndrome is a rare severe disease that causes arterial dissections and ruptures that can lead to early death. No preventive treatment has yet been validated. Our aim was to assess the ability of celiprolol, a β(1)-adrenoceptor antagonist with a β(2)-adrenoceptor agonist action, to prevent arterial dissections and ruptures in vascular Ehlers-Danlos syndrome.

METHODS: Our study was a multicentre, randomised, open trial with blinded assessment of clinical events in eight centres in France and one in Belgium. Patients with clinical vascular Ehlers-Danlos syndrome were randomly assigned to 5 years of treatment with celiprolol or to no treatment. Randomisation was done from a centralised, previously established list of sealed envelopes with stratification by patients’ age (≤32 years or >32 years). 33 patients were positive for mutation of collagen 3A1 (COL3A1). Celiprolol was uptitrated every 6 months by steps of 100 mg to a maximum of 400 mg twice daily. The primary endpoints were arterial events (rupture or dissection, fatal or not). This study is registered with ClinicalTrials.gov, number NCT00190411.

FINDINGS: 53 patients were...
randomly assigned to celiprolol (25 patients) or control groups (28). Mean duration of follow-up was 47 (SD 5) months, with the trial stopped early for treatment benefit. The primary endpoints were reached by five (20%) in the celiprolol group and by 14 (50%) controls (hazard ratio [HR] 0.36; 95% CI 0.15-0.88; p=0.040). Adverse events were severe fatigue in one patient after starting 100 mg celiprolol and mild fatigue in two patients related to dose titration. INTERPRETATION: We suggest that celiprolol might be the treatment of choice for physicians aiming to prevent major complications in patients with vascular Ehlers-Danlos syndrome. Whether patients with similar clinical presentations and no mutation are also protected remains to be established.


OBJECTIVE: To review our management of mycotic aneurysms involving the abdominal aorta over the past 2 decades to assess the safety and efficacy of in-situ and extra-anatomic repair combined with antibiotic treatment.

MATERIALS AND METHODS: From March 1990 to August 2008, 44 patients with a mycotic aneurysm involving the abdominal aorta were treated at our University Hospital. For all patients, we recorded the aetiology, clinical findings and anatomic location of the aneurysm, as well as bacteriology results, surgical and antibiotic therapy and morbidity and mortality. RESULTS: Twenty-one (47.7%) of the mycotic aneurysms had already ruptured at the time of surgery. Free rupture was present in nine patients (20.5%). Contained rupture was observed in 12 patients (27.3%). Urgent surgery was performed in 18 cases (40.9%). Revascularisation was achieved by in-situ reconstruction in 37 patients (84.1%), while extra-anatomic reconstruction was performed in six patients (13.6%). One patient (2.3%) was treated with a combined in-situ and extra-anatomic reconstruction. In one case (2.3%), endovascular aneurysm repair (EVAR) was performed. In-hospital mortality was 22.7%, 50% in the extra-anatomic reconstruction group and 18.9% in the in-situ repair group. One-third (33.3%) of our patients, who presented with a ruptured mycotic aneurysm died in the peri-operative period. This mortality was 13% in the patient-group presenting with an intact aneurysm. Of the 34 surviving patients, 12 patients (27.3%) of surviving patients died after discharge from our hospital. In half of these patients, an acute cardiac event was to blame. Three patients (8%) showed re-infection after in-situ reconstruction. CONCLUSION: Management of mycotic aortic aneurysms remains a challenging problem. The results of surgery depend on many factors. In our experience, in-situ repair remains a feasible and safe treatment option for patients who are in good general condition at the time of surgery.


Review Numerous clinical, physiopathological and epidemiological studies have underlined the detrimental or beneficial role of nutritional factors in complex inflammation related disorders such as allergy, asthma, obesity, type 2 diabetes, cardiovascular disease, rheumatoid arthritis and cancer. Today, nutritional research has shifted from alleviating nutrient deficiencies to chronic disease prevention. It is known that lifestyle, environmental conditions and nutritional compounds influence gene expression. Gene expression states are set by transcriptional activators and repressors and are often locked in by cell-heritable chromatin states. Only recently, it has been observed that the environmental conditions and daily diet can affect transgenerational gene expression via “reversible” heritable epigenetic mechanisms. Epigenetic changes in DNA methylation patterns at CpG sites (epimutations) or corrupt chromatin states of key inflammatory genes and noncoding RNAs, recently emerged as major governing factors in cancer, chronic inflammatory and metabolic disorders. Reciprocally, inflammation, metabolic stress and diet composition can also change activities of the epigenetic machinery and indirectly or directly change chromatin marks. This has recently launched re-exploration of anti-inflammatory bioactive food components for characterization of their effects on epigenome modifying enzymatic activities (acetylation, methylation, phosphorylation, ribosylation, oxidation, ubiquitination, sumoylation). This may allow to improve healthy aging by reversing disease prone epimutations involved in chronic inflammatory and metabolic disorders.
In anemia of multiple myeloma, hepcidin is induced by increased bone morphogenetic protein 2.

Hepcidin is the principal iron-regulatory hormone and a pathogenic factor in anemia of inflammation. Patients with multiple myeloma (MM) frequently present with anemia. We showed that MM patients had increased serum hepcidin, which inversely correlated with hemoglobin, suggesting that hepcidin contributes to MM-related anemia. Searching for hepcidin-inducing cytokines in MM, we quantified the stimulation of hepcidin promoter-luciferase activity in HuH7 cells by MM sera. MM sera activated the hepcidin promoter significantly more than did normal sera. We then examined the role of bone morphogenetic proteins (BMPs) and interleukin-6 (IL-6), the major transcriptional regulators of hepcidin. Mutations in both BMP-responsive elements abrogated the activation dramatically, while mutations in the IL-6-responsive signal transducer and activator of transcription 3-binding site (STAT3-BS) had only a minor effect. Cotreatment with anti-BMP-2/4 or noggin-Fc blocked the promoter induction with all MM sera, anti-IL-6 blocked it with a minority of sera, whereas anti-BMP-4, -6, or -9 antibodies had no effect. BMP-2-immunodepleted MM sera had decreased promoter stimulatory capacity, and BMP-2 concentrations in MM sera were significantly higher than in normal sera. Our results demonstrate that BMP-2 is a major mediator of the hepcidin stimulatory activity of MM sera.

Cardiovascular determinants and prognostic significance of CC Chemokine Ligand-18 (CCL18/PARC) in patients with stable coronary artery disease.

Chemokines are important mediators of angiogenesis, hematopoiesis and leucocyte trafficking. CC Chemokine Ligand-18 (CCL18)/pulmonary and activation-regulated chemokine (PARC) is a circulating chemokine that plays a role in injury healing, physiological homing of mononuclear blood cells and inflammatory responses. CCL18/PARC is also expressed in atherosclerotic plaques. We prospectively evaluated CCL18/PARC levels and their cardiovascular and biological determinants in a large cohort of 285 patients with stable coronary heart disease who were subsequently followed for 3 years for hard cardiac events. It was found that CCL18/PARC levels were associated with decreased cardiac function, decreased exercise capacity and increased inflammatory parameters including interleukin-6 (IL-6) and hs-CRP. More importantly high CCL18/PARC levels were an independent predictor of future cardiovascular events. Therefore, CCL18/PARC is a potential diagnostic and prognostic parameter in patients with stable coronary artery disease.

Assessment of apical rocking: a new, integrative approach for selection of candidates for cardiac resynchronization therapy.

Apical transverse motion (ATM) is a new parameter to quantify apical rocking as an integrative surrogate of both temporal and functional inhomogeneities within the left ventricle. In this study, we tested the predictive value of apical rocking for response to CRT. METHODS AND RESULTS: Sixty-nine patients eligible for CRT were assessed by echocardiography before and 11 ± 5 months after pacemaker implantation. Response was defined as left ventricular (LV) end-systolic volume decrease >15%. Rocking was quantified (ATM) and visually assessed by four blinded readers. Predictive value for CRT response of both assessments was compared with conventional dyssynchrony...
parameters. ATM in the four-chamber view plane differentiated best between responders and non-responders (2.2 ± 1.5 vs. 0.06 ± 1.9 mm, P<0.0001). Quantified ATM predicted reverse remodelling with a sensitivity, specificity, and accuracy of 75, 96, and 83% whereas visual rocking assessment resulted in 89, 75, and 83%, respectively. The accuracy of conventional parameters was significantly lower. CONCLUSION: Apical rocking is a new marker to assess LV dysynchrony and predict CRT response. It is superior to conventional parameters. Even its simple visual assessment may be sufficiently accurate in the clinical setting.

Effect of creatine supplementation as a potential adjuvant therapy to exercise training in cardiac patients: a randomized controlled trial. 
Cardiovascular Rehabilitation Unit, Department of Rehabilitation Sciences, K.U.Leuven, Leuven, Belgium. 
OBJECTIVE: To investigate the effect of oral creatine supplementation in conjunction with an exercise programme on physical fitness in patients with coronary artery disease or chronic heart failure. 
DESIGN: Single centre double-blind randomized placebo controlled trial. 
SETTING: Cardiac rehabilitation centre. 
SUBJECTS AND INTERVENTION: 70 (4 women) cardiac patients (age 57.5 (8.4) years) were randomized to a placebo (n = 37) or creatine (n = 33) treatment for three months. Combined aerobic endurance and resistance training (three sessions/week) was performed during supplementation. 
MAIN MEASURES: Aerobic power was determined during graded bicycle testing, knee extensor peak isometric and isokinetic strength, endurance and recovery were assessed by an isokinetic dynamometer, and health related quality of life was evaluated with the SF-36 and MacNew Heart Disease questionnaires. In addition, blood samples were taken after an overnight fast and 24 hour urinary collection was performed.
RESULTS: At baseline there were no significant differences between both groups. We observed main time effects for aerobic power, muscle performance, health related quality of life, high density lipoprotein cholesterol and triglycerides (pre vs post; P<0.05 for all). However, changes after training were similar between placebo group and creatine group (P>0.05). Further, no detrimental effect on renal or liver function was observed nor were there any reports of side effects. 
CONCLUSION: Oral creatine supplementation in combination with exercise training does not exert any additional effect on the improvement in physical performance, health related quality of life, lipid profile in patients with coronary artery disease or chronic heart failure than exercise training alone.

Everaert BR, Van Craenenbroeck EM, Hoymans VY, Haine SE, Van Nassauw L, Conraads VM, Timmermans JP, Vrints CJ.
Current perspective of pathophysiological and interventional effects on endothelial progenitor cell biology: focus on PI3K/AKT/eNOS pathway. 
Laboratory of Cell Biology and Histology, University of Antwerp, Antwerp, Belgium.
For more than a decade, endothelial progenitor cells (EPCs) have been implicated in cardiovascular homeostasis. EPCs are believed to reside within the bone marrow in close contact with surrounding stromal cells, and, under stimulation of pro-inflammatory cytokines, EPCs are mobilized out of the bone marrow. Hereafter circulating EPCs home to peripheral tissues, undergoing further proliferation and differentiation. Under certain pathophysiologic conditions this process seems to be blunted, resulting in a reduced capacity of EPCs to engage in vasculogenesis at sites of endothelial injury or tissue ischemia. In this review, we focus on the effects of traditional cardiovascular risk factors on EPC biology and we explore whether pharmacological, dietary and lifestyle interventions can favorably restore EPC mobilization, differentiation, homing and angiogenic properties. Because the PI3K/Akt/eNOS pathway plays a pivotal role in the process of EPC mobilization, migration and homing, we specifically emphasize the involvement of PI3K, Akt and eNOS in EPC biology under these different (patho)physiologic conditions. (Pre)clinically used drugs or lifestyle interventions that have been shown to ameliorate EPC biology are reviewed. These treatment strategies remain attractive targets to restore the regenerative capacity of EPCs in cardiovascular diseases.
Missault L, Witters N, Imschoot J.  
**High cardiovascular risk and poor adherence to guidelines in 11,069 patients of middle age and older in primary care centres.**  
Department of Cardiology, St Jan Hospital, Bruges, Belgium.  
[luc.missault@azbrugge.be](mailto:luc.missault@azbrugge.be)  

**BACKGROUND:** Evaluation of the risk for fatal cardiovascular (CV) disease and adherence to guidelines in ambulatory patients in primary care centres.  
**DESIGN AND METHODS:** Cross-sectional survey of risk factors and 10-year Systematic Coronary Risk Evaluation (SCORE) risk in 11,069 patients aged 50 years or more in primary care.  
**RESULTS:** Three-thousand, seven hundred and thirteen (33.5%) patients were actual smokers. Although 61% of the patients were treated with at least one antihypertensive drug, the mean systolic blood pressure was 141±15 mmHg. Of the treated patients, only 15.9% were at goal. Thirty-six percent of the patients were perceived as normcholesterolemic by the primary care physician. In the group of patients, presumed as hypercholesterolemic, the total cholesterol level was 235±38 mg/dl, suggesting that only very high cholesterol level was considered relevant by physicians. Virtually 0% of the patients (n=2) were treated correctly. Obesity (body mass index >30 kg/m) was found in 41% of the patients and central obesity was found in 50% of the patients. Diabetes was present in 2085 (19%) patients and at least one earlier vascular event was present in 2913 (26.3%) patients, with combined pathologies in 388 (4.5%) patients. In the remaining 6766 (61%) patients (neither diabetes nor earlier CV event), the 10-year fatal CV risk according to the Belgian SCORE table was calculated as follows: 716 (10.6%) patients had a risk of less than 2%; 1680 (24.8%) patients had a risk of 2-4%; 2576 (38%) patients had a risk of 5-9% and 1794 (26.6%) patients had a risk of 10% or more.  
**CONCLUSION:** Despite simple, clear, credible guidelines, despite the existence of a simple tool such as SCORE risk scoring and despite a very accessible health system in Belgium, the CV risk remains very high even in a professional medical environment of daily primary care practice.

**Additional value of quantitative EEG in acute anterior circulation syndrome of presumed ischemic origin.**  
Department of Neurology and Stroke Unit, ZNA Middelheim Hospital, Antwerp, Belgium.  
[peter.dedeyn@ua.ac.be](mailto:peter.dedeyn@ua.ac.be)  

**OBJECTIVE:** The clinical course of acute stroke can be highly variable and for effective management outcome prediction needs to be refined. We investigated whether EEG parameters are of additional diagnostic and prognostic value in the early phase of acute ischemic anterior circulation stroke.  
**METHODS:** Ninety-four patients presenting with acute anterior circulation syndrome (ACS) of presumed ischemic origin were incrementally included. Clinical characteristics were correlated with volume of ischemia and EEG parameters. Predictive values for definite stroke, early neurological deterioration, spontaneous early neurological improvement and death within 1 week after ACS were calculated using ROC curves and logistic regression modelling.  
**RESULTS:** In patients with normal or near normal NIHSS score of 0 or 1, the pairwise derived brain symmetry index (pdBSI) was an independent predictor for definite stroke displaying an overall accuracy of 80%. Early neurological deterioration was independently predicted by pdBSI with a correct classification rate of 95%. In ROC analysis, death was predicted by pdBSI with overall accuracy of 97%. Spontaneous neurological improvement was independently predicted by the delta+theta/alpha+beta - ratio with overall accuracy of 75%. Small-vessel stroke was independently predicted by pdBSI with a correct classification rate of 92%.  
**CONCLUSIONS:** EEG may be of prognostic value for spontaneous neurological improvement, early neurological deterioration and death in the acute setting of acute anterior circulation syndrome of presumed ischemic origin.  
**SIGNIFICANCE:** These findings may have an impact on stroke care.

**Association of cognitive performance with the metabolic syndrome and with glycaemia in middle-aged and older European men: the European Male Ageing Study.**  
Department of Experimental Medicine, Division of Gerontology and Geriatrics, Katholieke Universiteit Leuven, Herestraat 49, Leuven, Belgium.  
[jos.tournoy@uzleuven.be](mailto:jos.tournoy@uzleuven.be)
**BACKGROUND AND AIMS:** Metabolic syndrome has been reported to have adverse effects on cognition although the results are conflicting. We investigated the association between metabolic syndrome and cognitive function in a population sample of middle-aged and older European men and whether any observed association could be explained by lifestyle or other confounding factors. **METHODS:** A total of 3369 men in the 40- to 79-year age group were recruited from population registers in eight centres for participation in the European Male Ageing Study. The subjects completed a questionnaire instrument and several cognitive function tests including the Rey-Osterrieth Complex Figure test, the Camden Topographical Recognition Memory test and the Digit Symbol Substitution Test. Metabolic syndrome data were assessed at an invited visit and metabolic syndrome was defined by the National Cholesterol Education Program's Adult Treatment Panel III criteria. Associations between cognitive performance and metabolic syndrome were explored using linear regression. **RESULTS:** Complete cognitive and metabolic syndrome data from 3152 subjects were included in the analysis, of whom 1007 (32%) fulfilled criteria for metabolic syndrome. After adjustment for putative health and lifestyle confounders, no significant associations were found between any of the cognitive function scores and metabolic syndrome or between cognitive performance and high-sensitivity C-reactive protein. Analysis of the individual metabolic syndrome factors, however, revealed an inverse association between the level of glucose and cognitive performance. **CONCLUSIONS:** Metabolic syndrome was not associated with cognitive impairment in this population. Of the individual components of the syndrome, diabetes was associated with poorer performances in memory, executive functions and processing speed, associations that warrant further investigation.

De Preter V, Hamer HM, Windey K, Verbeke K.
**The impact of pre- and/or probiotics on human colonic metabolism: Does it affect human health?**
Mol Nutr Food Res. 2010 Nov 23. [Epub ahead of print]
Translational Research Center for Gastrointestinal Disorders and Leuven Food Science and Nutrition Research Centre, University Hospital Gasthuisberg, Leuven, Belgium.
Kristin.Verbeke@uz.kuleuven.ac.be

Since many years, the role of the colonic microbiota in maintaining host's overall health and well-being has been recognized. Dietary modulation of the microbiota composition and activity has been achieved by the use of pre-, probiotics. In this review, we will summarize the available evidence on the modification of bacterial metabolism by dietary intervention with pre-, probiotics. Enhanced production of SCFA as a marker of increased saccharolytic fermentation is well documented in animal and in vitro studies. Decreased production of potentially toxic protein fermentation metabolites, such as sulfides, phenolic and indolic compounds, has been less frequently demonstrated. Besides, pre-, probiotics also affect other metabolic pathways such as the deconjugation of secondary bile acids, bacterial enzyme activities and mineral absorption. Data from human studies are less conclusive. The emergence of new analytical techniques such as metabolite profiling has revealed new pathways affected by dietary intervention. However, an important challenge for current and future research is to relate changes in bacterial metabolism to concrete health benefits. Potential targets and expected benefits have been identified: reduced risk for the metabolic syndrome and prevention of colorectal cancer.

Hansen D, Dendale P, van Loon LJ, Meeusen R.
**The impact of training modalities on the clinical benefits of exercise intervention in patients with cardiovascular disease risk or type 2 diabetes mellitus.**
Jessa Hospital/Heart Centre Hasselt, Hasselt, Belgium. rmeeusen@vub.ac.be

Exercise training intervention represents an effective means to reduce adipose tissue mass, improve glycaemic control and increase whole-body oxygen uptake capacity (VO2peak) in obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM) and heart disease patients. In this manuscript, we review the impact of different exercise training modalities on clinical benefits of prolonged exercise intervention in these patient (sub)populations. By changing training modalities, significantly greater clinical benefits can be obtained. Greater training frequency and longer programme duration is associated with greater reduction in adipose tissue mass in obesity patients. A greater training frequency (up to 2 days/week) and a longer programme duration (up to 38 weeks) seems to be associated with greater improvements in VO2peak in heart disease patients. Longer programme duration and addition of resistance-type exercise further improve glycaemic control in T2DM patients. The first line of evidence seems to indicate that high-intensity interval exercise training has a greater impact on VO2peak in heart disease patients and insulin sensitivity in subjects with metabolic syndrome, but not on adipose tissue mass in obese subjects. However, it
remains unclear whether addition of resistance-type exercise and continuous higher-intensity endurance-type exercise training are accompanied by greater improvements in VO(2peak) in heart disease patients. Furthermore, the impact of training session duration/volume on adipose tissue mass loss and glycaemic control in obesity and T2DM patients, respectively, is currently unknown. The impact of training frequency on glycaemic control remains to be investigated in T2DM patients.


Patients with schizophrenia present a two- to three-fold higher prevalence of diabetes, of metabolic syndrome and of cardiovascular morbidity. The reason for this increased prevalence may involve intrinsic vulnerability, lifestyle factors and iatrogenic effects of antipsychotic drugs. The objective of this multinational, cross-sectional, pharmacoepidemiological study was to determine the prevalence of diabetes, lipid disorders, obesity, hypertension and the metabolic syndrome in patients with schizophrenia treated with antipsychotic drugs. Particular attention was taken to acquire data on a wide a range as possible of demographic, clinical and lifestyle variables that may influence the risk of metabolic disorders, which were taken into account in the calculation of prevalence data by propensity scoring. The study included 2270 subjects from 16 European countries, predominantly from Central and Eastern Europe. The proportion of subjects presenting the pathologies of interest was relatively high, ranging from 28% for glycaemic disorders to 70% for lipid disorders.

Scheen AJ. Pharmacokinetic and pharmacodynamic evaluation of sitagliptin plus metformin. Expert Opin Drug Metab Toxicol. 2010 Oct;6(10):1265-76. Review. University of Liège, CHU Sart Tilman, Division of Diabetes, Nutrition and Metabolic Disorders and Division of Clinical Pharmacology, Department of Medicine, Liège, Belgium. andre.scheen@chu.ulg.ac.be

IMPORTANCE OF THE FIELD: Type 2 diabetes is an increasingly prevalent disease resulting from various complex combinations of defects in insulin secretion and insulin action. Adequate blood glucose control is necessary to minimize complications. DPP IV inhibitors (sitagliptin, vildagliptin, saxagliptin) offer new options for combined pharmacological therapy. AREAS COVERED IN THIS REVIEW: An extensive literature search was performed to analyze the potential pharmacokinetic (PK) and pharmacodynamic (PD) interactions between metformin (first-line drug for the management of type 2 diabetes) and sitagliptin (first commercialized DPP IV inhibitor). Metformin and sitagliptin may be administered together, either separately or in fixed-dose combination. WHAT THE READER WILL GAIN: Updated information about PK/PD data on metformin alone, sitagliptin alone and sitagliptin plus metformin. Metformin and sitagliptin are not prone to PK drug-drug interactions. Their co-administration, either separately or in a fixed-dose combination, improves blood glucose control more potently than either compound separately, without hypoglycemia and without increasing metformin-related gastrointestinal side effects. TAKE HOME MESSAGE: The combination sitagliptin plus metformin may be used as a first- or second-line therapy in the management of type 2 diabetes.


Numerous clinical, physiopathological and epidemiological studies have underlined the detrimental or beneficial role of nutritional factors in complex inflammation related disorders such as allergy, asthma, obesity, type 2 diabetes, cardiovascular disease, rheumatoid arthritis and cancer. Today, nutritional research has shifted from alleviating nutrient deficiencies to chronic disease prevention. It is known that lifestyle, environmental conditions and nutritional compounds influence gene expression. Gene expression states are set by transcriptional activators and repressors and are often locked in by cell-heritable chromatin states. Only recently, it has been observed that the environmental...
conditions and daily diet can affect transgenerational gene expression via "reversible" heritable epigenetic mechanisms. Epigenetic changes in DNA methylation patterns at CpG sites (epimutations) or corrupt chromatin states of key inflammatory genes and noncoding RNAs, recently emerged as major governing factors in cancer, chronic inflammatory and metabolic disorders. Reciprocally, inflammation, metabolic stress and diet composition can also change activities of the epigenetic machinery and indirectly or directly change chromatin marks. This has recently launched re-exploration of anti-inflammatory bioactive food components for characterization of their effects on epigenome modifying enzymatic activities (acetylation, methylation, phosphorylation, ribosylation, oxidation, ubiquitination, sumoylation). This may allow to improve healthy aging by reversing disease prone epimutations involved in chronic inflammatory and metabolic disorders.


BACKGROUND AND METHODOLOGY: Pancreatic beta cells show intercellular differences in their metabolic glucose sensitivity and associated activation of insulin production. To identify protein markers for these variations in functional glucose sensitivity, rat beta cell subpopulations were flow-sorted for their level of glucose-induced NAD(P)H and their proteomes were quantified by label-free data independent alternate scanning LC-MS. Beta cell-selective proteins were also identified through comparison with rat brain and liver tissue and with purified islet alpha cells, after geometrical normalization using 6 stably expressed reference proteins. PRINCIPAL FINDINGS: All tissues combined, 943 proteins were reliably quantified. In beta cells, 93 out of 467 quantifiable proteins were uniquely detected in this cell type; several other proteins presented a high molar abundance in beta cells. The proteome of the beta cell subpopulation with high metabolic and biosynthetic responsiveness to 7.5 mM glucose was characterized by (i) an on average 50% higher expression of protein biosynthesis regulators such as 40S and 60S ribosomal constituents, NADPH-dependent protein folding factors and translation elongation factors; (ii) 50% higher levels of enzymes involved in glycolysis and in the cytosolic arm of the malate/aspartate-NADH-shuttle. No differences were noticed in mitochondrial enzymes of the Krebs cycle, beta-oxidation or respiratory chain. CONCLUSIONS: Quantification of subtle variations in the proteome using alternate scanning LC-MS shows that beta cell metabolic glucose responsiveness is mostly associated with higher levels of glycolytic but not of mitochondrial enzymes.


Cytokines produced by islet-infiltrating immune cells induce β-cell apoptosis in type 1 diabetes. The IFN-γ-regulated transcription factors STAT1/IRF-1 have apparently divergent effects on β-cells. Thus, STAT1 promotes apoptosis and inflammation while IRF-1 down-regulates inflammatory mediators. To understand the molecular basis for these differential outcomes within a single signal transduction pathway, we presently characterized the gene networks regulated by STAT1 and IRF-1 in β-cells. This was done by using siRNA approaches coupled to microarray analysis of insulin-producing cells exposed or not to IL-1β + IFN-γ. Relevant microarray findings were further studied in INS-1E cells and primary rat β-cells. STAT1, but not IRF-1, mediates the cytokine-induced loss of differentiated β-cell phenotype, as indicated by decreased insulin, Pdx1, MafA and Glut2. Furthermore, STAT1 regulates cytokine-induced apoptosis via up-regulation of the pro-apoptotic protein DP5. STAT1 and IRF-1 have opposite effects on cytokine-induced chemokine production, with IRF-1 exerting negative feedback inhibition on STAT1 and downstream chemokine expression. The present study elucidates the transcriptional networks through which the IFN-γ/STAT1/IRF-1 axis controls β-cell function/differentiation, demise and islet inflammation.

Renal Division, Department of Internal Medicine, University Hospital Gent, Gent, Belgium. Arjan.vandertol@ugent.be

BACKGROUND: There remains debate about the screening strategies for albuminuria. This study evaluated whether a screening strategy in an apparently healthy population based on basic clinical and biochemical parameters could be more effective than a strategy where screening for albuminuria is performed unselectively.

METHODOLOGY/PRINCIPAL FINDINGS: The Unreferred Renal Insufficiency (URI) Study is a cross-sectional study on the prevalence of metabolic risk factors in Belgian workers, volunteering to be screened during a routine yearly occupational check-up. Subjects (n=295) with treated hypertension, known diabetes, treated dyslipidaemia, cardiovascular and renal disease were excluded. Among 1,191 apparently healthy subjects, 23% had unknown hypertension, 13% had impaired glucose tolerance, 15.4% had normoalbuminuria, 4.2% had microalbuminuria and 0.4% had macroalbuminuria. Subjects with resting heart rate ≥85 bpm, plasma glucose ≥5.6 mmol/L and blood pressure ≥140/90 mmHg were associated with albuminuria of any degree. A strategy where only subjects with at least one of these risk factors (n=431) were screened for albuminuria, would identify all subjects with macroalbuminuria (5/5), 64% of those with microalbuminuria (32/50), and less than half of those with normoalbuminuria (81/183). An alternative strategy whereby subjects were first screened for presence of albuminuria, and additional cardiovascular risk factors were only measured in subjects positive for albuminuria (n=238), would identify only 27% (118/431) of the subjects with additional and potentially modifiable cardiovascular risk factors. On the other hand, half of the subjects in this study with albuminuria (120/238, of which 102 had normoalbuminuria), had no additional cardiovascular risk factor at all. CONCLUSIONS: Screening an apparently healthy population directly for albuminuria will result in a high percentage of false positives, mostly measured in the normal range. Screening for microalbuminuria and macroalbuminuria based on presence of additional, potentially modifiable risk factors appears to be more beneficial.

De Greef K, Deforche B, Tudor-Locke C, De Bourdeaudhuij I.


Department of Movement and Sports Sciences, Ghent University, Watersportlaan 2, 9000 Ghent, Belgium. karlijn.degreef@ugent.be

The purpose of this study was to investigate the benefits of a pedometer and a cognitive-behavioural group intervention for promoting physical activity (PA) in type 2 diabetes patients. We recruited 41 participants and randomized them into an intervention group (IG) (n=20) and a control group (CG) (n = 21). The intervention consisted of five sessions within 12 weeks, a booster session after 22 weeks and a pedometer. Primary outcome was PA assessed by accelerometer (minutes per day) and pedometer (steps per day). Secondary outcomes were weight, body mass index, blood pressure, haemoglobin A1c and total cholesterol. After 12 weeks, the IG increased with more than 2000 steps day(-1) compared with the CG, whereas sedentary behaviour decreased more than 1 hour day(-1) in the IG and showed no change in the CG. There was no intervention effect on the accelerometer-based PA nor on health measurements. After 1 year, the increase in steps per day remained significant in the IG, but sedentary activity increased again to baseline levels. This pilot study showed that the combination of a 12-week cognitive-behavioural intervention and a pedometer has a significant short-term impact on daily steps and sedentary behaviour but that the effects on total PA and long-term effects were limited.