Selected Abstracts From Other Journals

Edited by: Gehani A.A. and Hammoudeh M.
Hamad Medical Corporation, Doha, Qatar

Published in Arch Intern Med. 2007; 167(16): 1730-1737.

Vitamin D Supplementation and Total Mortality: A Meta-analysis of Randomized Controlled Trials

Philippe Autier, MD; Sara Gandini, PhD

Background: Ecological and observational studies suggest that low Vitamin D status could be associated with higher mortality from life-threatening conditions including cancer, cardiovascular disease, and diabetes mellitus that account for 60% to 70% of total mortality in high-income countries. We examined the risk of dying from any cause in subjects who participated in randomized trials testing the impact of Vitamin D supplementation (ergocalciferol (Vitamin D2) or cholecalciferol (Vitamin D3) on any health condition.

Methods: The literature up to November 2006 was searched without language restriction using the following databases: PubMed, ISI Web of Science (Science Citation Index Expanded), EMBASE, and the Cochrane Library.

Results: We identified 18 independent randomized controlled trials, including 57,311 participants. A total of 4777 deaths from any cause occurred during a trial size-adjusted mean of 5.7 years. Daily doses of Vitamin D supplements varied from 300 to 2000 IU. The trial size-adjusted mean daily Vitamin D dose was 528 IU. In 9 trials, there was a 1.4- to 5.2-fold difference in serum 25-hydroxy Vitamin D between the intervention and control groups. The summary relative risk for mortality from any cause was 0.93 (95% confidence interval, 0.87-0.99). There was neither indication for heterogeneity nor indication for publication biases. The summary relative risk did not change according to the addition of calcium supplements in the intervention.

Conclusions: Intake of ordinary doses of Vitamin D supplements seems to be associated with decreases in total mortality rates. The relationship between baseline Vitamin D status, dose of Vitamin D supplements, and total mortality rates remains to be investigated. Population-based, placebo-controlled randomized trials with total mortality as the main end point should be organized for confirming these findings.

Address for correspondence:
Please send your abstracts on diskette or by e-mail: qmj@hmc.org.qa

Published in The Lancet, Volume 372, Issue 9651, Pages 1756-1764, 15 November 2008

Cardiovascular Events Associated with Rofecoxib: Final analysis of the APPROVe trial

Prof John A Baron, MD

Background: Selective inhibition of cyclo-oxygenase-2 has been associated with an increased risk of cardiovascular events in several clinical trials. The Adenomatous Polyp Prevention on Vioxx (APPROVe) study assessed the effect of 3-year treatment with a cyclo-oxygenase-2 inhibitor, rofecoxib (25 mg), on recurrence of neoplastic polyps of the large bowel. We report the cardiovascular outcomes of a long-term follow-up of participants in the trial.

Methods: The APPROVe study is a multicentre, randomised, placebo-controlled, double-blind trial. 2587 patients with a history of colorectal adenomas were recruited at 108 centres worldwide during 2000 and 2001. Participants were followed for adverse events while on treatment and during the following 14 days. However, after early termination of treatment because of cardiovascular toxicity, we attempted to follow up all randomised patients for at least 1 year after stopping study treatment. External committees blindly assessed potential serious cardiovascular events. The focus of the analysis was the combined incidence of non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular, haemorrhagic, and unknown causes (Antiplatelet Trialists' Collaboration (APTC) combined endpoint). We used Cox proportional hazards regression to calculate endpoint hazard ratios. The study is registered with ClinicalTrials.gov, number NCT0282386.

Findings: We obtained extended post-treatment cardiovascular follow-up data from 84% of participants, and extended mortality follow-up from 95%. In total, 59 individuals had an APTC endpoint in the rofecoxib group and 34 in the placebo group (hazard ratio 1.17, 95% CI 1.17-2.73; p=0.006). In the first year after cessation of treatment, there was a non-significant increase in the risks of APTC endpoints. The APTC hazard ratio did not substantially change over time.

Interpretation: Use of rofecoxib is associated with increased rates of APTC events. Study data are compatible with an early increase in risk that persists for one year after stopping treatment.

We obtained extended post-treatment cardiovascular follow-up data from 84% of participants, and extended mortality follow-up from 95%. In total, 59 individuals had an APTC endpoint in the rofecoxib group and 34 in the placebo group (hazard ratio 1.17, 95% CI 1.17-2.73; p=0.006). In the first year after cessation of treatment, there was a non-significant increase in the risks of APTC endpoints. The APTC hazard ratio did not substantially change over time.
Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M. Ridker, MD
Jupiter Study Group

Background: Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment.

Methods: We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

Results: The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio, 0.56; 95% CI, 0.46 to 0.69; P=0.00001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; P=0.00002), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; P<0.00001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes.

Conclusions: In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.

Nasal Insulin to Prevent Type 1 Diabetes in Children with HLA Genotypes and Autoantibodies Conferring Increased Risk of Disease: A double-blind, randomised controlled trial

Dr Kirsti Näntö-Salonen, MD

Background: In mouse models of diabetes, prophylactic administration of insulin reduced incidence of the disease. We investigated whether administration of nasal insulin decreased the incidence of type 1 diabetes, in children with HLA genotypes and autoantibodies increasing the risk of the disease.

Methods: At three university hospitals in Turku, Oulu, and Tampere (Finland), we analysed cord blood samples of 116,720 consecutively born infants, and 3,430 of their siblings, for the HLA-DQB1 susceptibility alleles for type 1 diabetes. 17,397 infants and 1,613 siblings had increased genetic risk, of whom 11,225 and 1,574, respectively, consented to screening of diabetes-associated autoantibodies at every 3-12 months. In a double-blind trial, we randomly assigned 224 infants and 40 siblings positive for two or more autoantibodies, in consecutive samples, to receive short-acting human insulin (1 unit/kg; n=115 and n=22) or placebo (n=109 and n=18) once a day intranasally. We used a restricted randomisation, stratified by site, with permuted blocks of size two. Primary endpoint was diagnosis of diabetes. Analysis was by intention to treat. The study was terminated early because insulin had no beneficial effect. This study is registered with ClinicalTrials.gov, number NCT00223613.

Findings: Median duration of the intervention was 1.8 years (range 0-9.7). Diabetes was diagnosed in 49 index children randomised to receive insulin, and in 47 randomised to placebo (hazard ratio [HR] 1.14; 95% CI 0.73-1.77), 42 and 39 of these children, respectively, continued treatment until diagnosis, with yearly rates of diabetes onset of 16.8% (95% CI 11.7-21.9) and 15.3% (10.5-20.2). Seven siblings were diagnosed with diabetes in the insulin group, versus six in the placebo group (HR 1.93; 0.56-6.77). In all randomised children, diabetes was diagnosed in 56 in the insulin group, and 53 in the placebo group (HR 0.98; 0.67-1.43, p=0.91).

Interpretation: In children with HLA-conferred susceptibility to diabetes, administration of nasal insulin, started soon after detection of autoantibodies, could not be shown to prevent or delay Type 1 diabetes.

Bone Marrow Cells are a Rich Source of Growth Factors and Cytokines: Implications for cell therapy trials after myocardial infarction

Mortimer Korf-Klingebiel, Tibor Kempf, Thomas Sauer, Eva Brinkmann, Philipp Fischerl, Gerd P. Meyer, Arnold Ganser, Helmut Drexlzner and Kai C. Wollert

Aims: Results from clinical trials suggest that cardiac function after acute myocardial infarction (AMI) can be enhanced by an intracoronary infusion of autologous unselected nucleated bone marrow cells (BMCs). Release of paracrine factors has been proposed as a mechanism for these therapeutic effects; however, this hypothesis has not been tested in humans.

Methods and Results: BMCs and peripheral blood leucocytes (PBLs) were obtained from 15 patients with AMI and cultured in serum-free medium to obtain conditioned supernatants (SN). BMC-SN stimulated release of paracrine factors has been proposed as a mechanism for these therapeutic effects; however, this hypothesis has not been tested in humans.

Key Words: Acute myocardial infarction, Cell therapy, Paracrine hypothesis

An in Vitro Beating Heart Model for Long-term Assessment of Experimental Therapeutics

Walter Hahler, Séverine Pouillot, Alexandra Plancheron, Michel Ducat, Marc Peschanski and Christelle Monville

Aims: Within the framework of studies aiming at regenerative medicine for cardiovascular disease, we have developed an in vitro model to analyse human embryonic stem (ES) cell engraftment into the myocardium.

Methods and Results: This model is based on organotypic rat ventricular slices maintained in culture at the air-medium interface on semi-porous membranes. Survival and differentiation of human cardiomyocytes derived from ES cells were then assessed for several months. In addition, we observed that ventricular tissue slices not only exhibited normal histology, but also rhythmic contractions till the end of the experiments (up to 3 months). Similar results were obtained using ventricular slices obtained from two human foetuses at 8 and 9.5 weeks of age. Calcium transients were associated with the beating frequency, and the pattern was modulated in a dose-dependent manner by epinephrine.

Conclusion: Our data suggest that the organotypic heart slice culture on semi-porous membranes is a relevant in vitro heart model for long-term histological and physiological studies.

Keywords: Heart slice cultures; Cell therapy; Human embryonic stem cells


Risk of Breast Cancer Associated with Papilloma

Objective: The purpose of this study was to investigate the risk of carcinoma in patients with a diagnosis of papilloma of the breast made on ultrasound large core biopsy or stereotactic vacuum-assisted biopsies.

Material and Methods: This retrospective database review (2000-2007) included 130 patients with a papilloma diagnosed on preoperative biopsies or excisional surgery specimen. The mean patient age was 52 years (range, 20-80 years). The examinations included mammography and ultrasonography in all 130 patients. The final surgical histology was obtained from two human foetuses at 8 and 9.5 weeks of age. Calcium transients were associated with the beating frequency, and the pattern was modulated in a dose-dependent manner by epinephrine.

Conclusion: Our data suggest that the organotypic heart slice culture on semi-porous membranes is a relevant in vitro heart model for long-term histological and physiological studies.


Different Effects of Cardiac Resynchronization Therapy on Left Atrial Function in Patients with Either Idiopathic or Ischaemic Dilated Cardiomyopathy: A two-dimensional speckle strain study.


Aims: In dilated cardiomyopathy (DCM), attenuation of left atrial (LA) booster pump function has been observed, and attributed both to altered LA loading conditions owing to left ventricular (LV) diastolic dysfunction and to LA involvement in the myopathic process. The aim of the present study was to detect LA systolic dysfunction in DCM using speckle-tracking two-dimensional strain echocardiography (2DSE), and to assess the effects of cardiac resynchronization therapy (CRT) on LA myocardial strain during 6 month follow-up.

Methods and Results: A total of 90 patients (aged, 52.4 +/- 10.2 years)
Abstracts from other Journals

with either idiopathic (n = 47) or ischaemic (n = 43) DCM underwent standard Doppler echo and 2DSE analysis of atrial longitudinal strain in the basal segments of LA septum and LA lateral wall, and in LA roof. The two groups were comparable for clinical variables (NYHA class: III in 72.2%; IV in 27.8%). LV volumes, ejection fraction, stroke volume, and mitral valve effective regurgitant orifice were similar between the two groups. No significant differences were evidenced in Doppler transmural inflow measurements. LA diameter and maximal volume were also similar between the two groups. Conversely, LA active emptying volume and fraction were both lower in patients with idiopathic DCM. Peak systolic myocardial atrial strain was significantly compromised in patients with idiopathic DCM compared with ischaemic DCM in all the analysed atrial segments (P < 0.001). At follow-up, 64 patients (71.1%) (37 idiopathic and 27 ischaemic) were responders, and 26 (28.9%) (10 idiopathic; 16 ischaemic) were non-responders to CRT (responder: decrease of LV end-systolic volume >15%). A significant improvement in LA systolic function was obtained only in patients with ischaemic DCM responders to CRT (P < 0.001). By multivariable analysis, in the overall population, it was found that ischaemic aetiology of DCM (beta-coefficient = 0.62; P < 0.0001) and positive response to CRT (beta-coefficient = 0.42; P < 0.01) were the only independent determinants of LA lateral wall systolic strain.

Conclusions: Two-dimensional strain represents a promising non-invasive technique to assess LA atrial myocardial function in patients with DCM. LA pump and reservoir function at baseline and after CRT are more depressed in idiopathic compared with ischaemic DCM patients. Future longitudinal studies are warranted to understand further the natural history of LA myocardial function, the extent of reversibility of LA dysfunction with CRT, and the possible prognostic impact of such indexes in patients with congestive heart failure.