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Vitamin D deficiency: a marker or a prognostic factor?

Tomson J, Emberson J, Hill M, Gordon A, Armitage J, Shipley M, et al. Vitamin D and risk of death from vascular and non-vascular causes in the Whitehall study and meta-analyses of 12000 deaths. **Eur Heart J 2013;34:1365-74. http://doi.org/npr**

Different observational studies have reported that low circulating concentrations of 25-hydroxyvitamin D [25(OH) D] are associated with higher risk of mortality. The independent prognostic value of low vitamin D concentrations is controversial as people with lower concentrations are sicker and less exposed to sunlight. Lack of significant outcome improvement reported by randomized trials of vitamin D contributes to cast doubt on the real meaning of the association.

The epidemiological study by Whitehall recruited 19019 male civil servants from London between 1967 and 1970. A resurvey was conducted in 1997 of all surviving 8448 participants in this cohort. A substudy exploring the prognostic value of 25(OH) D levels and its association with specific causes of death is presented. Measurement of Vitamin D levels was obtained in 5409 participants who were divided by quintiles according to increasing concentrations of 25(OH) D. The participants included in quintiles I and V were further divided by half to better characterize the relationship between extreme concentrations and the prognosis. Mean age was 77 years. Lower levels of 25(OH) D were associated with greater prevalence of cardiovascular disease, diabetes and cancer, lower cholesterol and albumin levels and higher concentrations of C-reactive protein and fibrinogen. After a mean follow-up of 13 years, annual mortality was 6.4% (2.7% due to vascular causes and 3.7% due to non-vascular causes). As in previous studies, lower 25(OH) D concentrations were associated with higher total mortality, but an association between grater vascular and non-vascular mortality was specifically demonstrated for the first time. After adjustment for age, twice the concentration of 25(OH) D was associated with 34% lower risk of vascular mortality and 36% lower risk of non-vascular mortality. After additional adjustment for prior disease, vascular risk factors, markers of inflammation and renal function, twice the concentration of 25(OH) D was associated with a significant risk reduction of 20% and 23%, respectively. A meta-analysis of all observational studies published until 2012 including their own data confirmed the association of lower 25(OH) D levels with greater total and vascular mortality.

It seems that the evidence relating low 25(OH) D levels with adverse outcomes is sufficient. Yet, some doubts still persist. Is there a causal relationship or does the multivariate analysis fail putting into evidence that the low values represent the sickest subjects? Are confounders really responsible for the association? If the relationship exists, which is the mechanism involved? The association with different causes of mortality generates uncertainty. The meta-analyses of studies on vitamin D administration showed either a modest reduction in mortality or no change at all. Were the doses insufficient or doesn't the supplement produce any effect? New studies are being conducted. Meanwhile, the information presented is challenging but is not sufficient to make any recommendation.

U-shaped relationship between glycosylated hemoglobin levels and outcome in type 2 diabetes

Nichols G, Joshua-Gotlib S, Parasuraman S. Glycemic control and risk of cardiovascular disease hospitalization and all-cause mortality. **J Am Coll Cardiol 2013;62:121-7. http://doi.org/nps**

Historically, target glycosylated hemoglobin (HbA1c) level < 7% has been accepted for the treatment of type 2 diabetes. The VADT, ACCORD and ADVANCE studies failed to demonstrate that strict glycemic control with a target HbA1c ≤ 6.5% was associated with better outcome and, in fact, the ACCORD trial was associated with higher mortality. Observational studies performed in elderly patients with diabetes or heart failure show presence of a U-shaped curve with greater risk at both higher and lower HbA1c levels. The results of the register here presented expand these findings to a larger population of diabetics which is more representative of the "real world".

This retrospective cohort study was conducted by the Kaiser Permanente health care system and included 26973 patients who had been diagnosed with type 2 diabetes between 1997 and 2007, were enrolled in a medical plan between 2002 and 2011 and did not receive insulin during the first year of treatment. Patients with known cardiovascular disease were excluded. The mean of all HbA1c measurements from each patient over the follow-up period was considered. HbA1c categories considered were ≤ 6.0%, 6.0% to 6.4%, 6.5% to 6.9%, and so on, with 0.5% steps by category until reaching ≥ 9% values. The end points were cardiovascular disease hospitalization, all-cause mortality and a composite of both end points.

During mean follow-up of 6 years, the rate of cardiovascular disease hospitalization was 8.2% and all-

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cause mortality was 12.6% The results were adjusted for age, sex, coronary risk factors, duration of diabetes and presence of macrovascular and microvascular complications, hypoglycemic medication, antihypertensive treatment and number of HbA1c determinations.

Cardiovascular disease hospitalization, compared with patients in the 7.0-7.4% HbA1c category considered as the reference group (HR1), showed that those patients with HbA1c ≤ 6% had a HR of 1.68, and those with HbA1c between 6-6.4% or with HbA1c in the range of 6.5-6.9% a HR of 1.18. Patients with HbA1c between 8.5-9% had a HR of 1.58, and those with HbA1c ≥ 9%, a HR of 1.98. In all cases the higher risk was statistically significant.

Risk of all-cause mortality compared with the reference 7.0-7.4% HbA1c category group, showed that patients with HbA1c ≤ 6% had HR of 1.87, those with HbA1c ranging from 6-6.4% a HR of 1.45, and with HbA1c between 6.5-6.9%, a HR of 1.15. Patients with HbA1c ≥ 9% had a HR of 1.63. In all the cases the higher risk was statistically significant.

Although previous observational studies had reported a U-shaped relationship between HbA1c and the incidence of events in selected groups of diabetics (elderly patients or with heart failure), this study extends this finding to a broader population. As in any observational study where the population or the intervention are not randomly assigned, there may be underlying mechanisms which have not been considered that could account for the findings. In any case, although HbA1c levels ≤ 7% seem to be associated with a worse outcome, it is also possible that this value may not be harmful for some patients. A preferable option might be a treatment with individual targets considering data about diabetes, response to the agents used or renal function, among others.

Pericarditis with or without myocardial involvement: clinical characteristics and outcome

Imazio M, Brucato A, Barbieri A, Ferroni F, Maestroni S, Ligabue G, et al. Good prognosis for pericarditis with and without myocardial involvement. Results from a multicenter, prospective cohort study. **Circulation 2013;128:42-9. http://doi.org/npt**

Patients presenting with clinical signs suggestive of acute pericarditis frequently have manifestations of myocardial involvement. This condition is referred to as myopericarditis or perimyocarditis, and its appropriate management is still unknown. An Italian study contributes to clarify some concepts.

Between 2007 and 2011, 486 patients were evaluated in three referral centers for pericardial diseases. The diagnosis of acute pericarditis (n = 346, 71.2%) was based on the presence of two of the following signs or symptoms: pericarditis chest pain, pericardial rub, widespread ST-segment elevation or PR depression, and new or progressive pericardial effusion. The diagnosis of myopericarditis (n = 114, 23.5%) was made in the presence of pericarditis plus elevation of cardiac biomarkers suggestive of myocardial involvement (troponin T or I or CK-MB) but without evidence or global segmental ventricular dysfunction. Perimyocarditis was considered in the presence of acute pericarditis, elevated cardiac biomarkers and depressed LV systolic function (n = 26, 5.3%). Echocardiogram was performed in all cases; gadolinium-enhanced cardiac magnetic resonance (CMR) imaging was done within 2 weeks in patients suspected of having myocardial involvement on the basis of localized ECG changes, atypical ST-T changes for myocarditis, Q-waves, arrhythmias, elevated cardiac biomarkers, or new or progressive ventricular dysfunction.

Compared to patients with acute pericarditis, those with myocardial involvement were younger (median age < 30 years vs. 41 years), male gender was more frequent (71% vs. 54%) and they had greater prevalence of ECG changes (85% vs. 55%). Although presenting low global incidence, prevalence of arrhythmia was higher in patients with ventricular involvement (5% vs. 0.3%) as well as of clinical heart failure (11.5% in perimyocarditis, 3.5% in myopericarditis, 0% in pericarditis). In patients with pericarditis, 97% presented chest pain, 55% had ECG changes and only el 24% had pericardial rub. The clinical picture mimicked an AMI in 76.4% of patients with myocardial involvement vs. 2.3% of those with pericarditis; a coronary angiography was performed to all of them to make differential diagnosis. All the patients with myocardial involvement (n = 140) underwent CMR imaging; late gadolinium enhancement was observed in all of them. In the 115 patients with pericarditis in whom myocardial involvement was suspected, late gadolinium enhancement was seen in 90% of cases. Over a median follow-up of 3 years, there were no cases of heart failure or death. Recurrences occurred in 32% of patients with pericarditis and 11% of patients with myocardial involvement. During follow-up, left ventricular dysfunction (left ventricular ejection fraction < 55%) was observed in 1% of cases with pericarditis, 8% of patients with myopericarditis and 15% of cases of perimyocarditis.

The information provided by this register is valuable, as it describes the different characteristics of these presentations with pericardial involvement, helps to suspect associated myocardial injury and remarks the intrinsic favorable outcome in all cases.

Riociguat: a new option for the treatment of pulmonary hypertension

Ghofrani HA, Galiè N, Grimminger F, Grünig E, Humbert M, Jing ZC, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. **N Engl J Med 2013;369:319-29. http://doi.org/npv**

Ghofrani HA, Galiè N, Grimminger F, Grünig E,

Humbert M, Jing ZC, et al. Riociguat for the treatment of pulmonary arterial hypertension. **N Engl J Med 2013;369:330-40. http://doi.org/npw**

Impairment of nitric oxide synthesis and cGMP formation through the nitric oxide soluble guanylate cyclase is involved in the complex pathogenesis of pulmonary hypertension (PH), reducing vasodilator capacity. Riociguat, a member of a new class of therapeutic agents, has a dual mode of action directly stimulating soluble guanylate cyclase and increasing its sensitivity to nitric oxide. Riociguat increases the level of GMPc resulting in vasorelaxation and antifibrotic and antiproliferative effects. Recently, the effects of this drug have been reported for the treatment of two groups of the Dana Point classification of PH: group 4 (chronic thromboembolic PH) and group 1 (pulmonary arterial hypertension).

The CHEST-1 study included group 4 patients who were considered by the treating physicians to be ineligible for pulmonary endarterectomy (the treatment of choice for these cases) or in whom pulmonary endarterectomy had failed. Additional inclusion criteria were: pulmonary vascular resistance of more than 300 dyn•sec•cm^{-5} and a 6-minute walk distance of 150 to 450 m. Patients were excluded if they had received an endothelin-receptor antagonist, phosphodiesterase type 5 inhibitor or prostacyclin analogue within 3 months before study entry. Patients were randomly assigned in a 1:2 ratio to receive placebo or riociguat for 16 weeks. The primary end point was the change in the distance walked in 6 minutes. Secondary efficacy end points included changes in clinical and hemodynamic parameters and in NT-proBNP level. A total of 261 patients were included (173 in the riociguat group and 88 in the placebo group). Mean age was 59 years, 66% were women, 31% were in FC II and 64% in FC III. At week 16, the 6-minute walk distance had increased by 39 m in the riociguat group, compared with a decrease of 6 m in the placebo group ($p < 0.0001$). Pulmonary vascular resistance decreased by 226 dyn•sec•cm^{-5} in the riociguat group, compared with an increase of 23 dyn•sec•cm^{-5} in the placebo group ($p < 0.0001$). Levels of NT-proBNP were significantly reduced in patients treated with riociguat. There was no significant difference in the incidence of clinical-adverse events determining study abandonment (2%) between the riociguat and placebo groups .

The PATENT-1 study included 443 patients from PH group 1 (idiopathic pulmonary artery hypertension, familial, or associated with connective tissue diseases) with characteristics that were similar to those of patients included in the CHEST-1 study. The patients were randomly assigned to placebo (n = 126) or riociguat up to 2.5 mg (n = 254) or 1.5 mg (n = 63) 3 times daily. Patients who were receiving treatment with endothelin-receptor antagonists or oral prostanoids were eligible; patients who were receiving phosphodiesterase type 5 inhibitors were not eligible. At week 12, the 6-minute walk distance had increased by 30 m and pulmonary vascular resistance had decreased by 223 dyn•sec•cm^{-5} with a dose of 2.5 mg 3 times daily and had decreased by 6 m and 9 dyn•sec•cm^{-5} in the placebo group ($p < 0.0001$ in both cases). The incidence of adverse events was significantly lower with riociguat (1% vs. 6% with placebo).

A new class of drugs arises for the treatment of PH. It is still unclear whether these agents are superior to phosphodiesterase type 5 inhibitors and what will happen with the natural history of the disease beyond improving the functional test and the hemodynamic parameters. Further studies are necessary to provide an answer.

Prosthetic heart valve thrombosis: surgery or thrombolysis? Results of a meta-analysis

Karthikeyan G, Senguttuvan NB, Joseph J, Devasenapathy N, Bahl VK, Airan B. Urgent surgery compared with fibrinolytic therapy for the treatment of left-sided prosthetic heart valve thrombosis: a systematic review and meta-analysis of observational studies. **Eur Heart J 2013;34:1557-66. http://doi.org/npx**

Left-sided prosthetic valve thrombosis (PVT) is a potentially devastating complication that occurs in patients with mechanical heart valves who are poorly anticoagulated, and which has very severe short-term consequences: cerebral or systemic embolism, heart failure and death. Different guidelines suggest diverse recommendations before PVT develops, from fibrinolysis as a general rule to surgery as the almost exclusive treatment. Lack of results from randomized trials makes the choice more difficult.

A recent meta-analysis tries to provide help in the decision-making process. The meta-analysis considered studies published until 2012 comparing urgent surgery and thrombolysis in patients with PVT and reporting data on successful restoration of valve function and presence or absence of complications with each of the interventions. The authors included only those studies which enrolled at least 5 patients in each study arm. Data of 690 episodes in 598 patients from seven studies were selected. The mean age of patients ranged from 52 to 63 years. There was a preponderance of females (range 60–82%). The mitral valve was involved in 65% to 95% of cases. All the studies were retrospective and the decision to perform a treatment was at the discretion of the treating physicians. Overall, 446 episodes of PVT were treated with surgery (in 64 after failed thrombolysis and hence considered by the authors of the individual studies as belonging to the surgical arm) and 244 with fibrinolytic agents. A strong trend was seen towards a better success rate with surgery (86.5% vs. 69.7%, OR 2.53, 95% CI 0.94-6.78; $p = 0.066$). More deaths occurred in the surgical arm (13.5% vs. 9%), but this difference was not significant (OR 1.95, 95% CI 0.63-5.98; $p = 0.24$). The

incidence of adverse events was significantly lower in the surgical arm: 1.4% vs. 5% for major bleeding, 1.6% vs.16% for cerebral or systemic embolism and 7.1% vs. 25.4% for PVT recurrence. There was no record about which patients had undergone some kind of surgery due to more severe baseline characteristics or clinical condition at hospitalization.

This meta-analysis has several limitations, primarily arising out of the observational design and retrospective data collection of the included studies, with not always pre-specified endpoints and heterogeneity in the results. Probably, some unknown confounders could have influenced on the better outcome of surgery, although the wide difference in the rate of embolic events seems to be a definite finding. This systematic review suggests that in experienced centers, surgery is safer and perhaps more efficacious when compared with thrombolysis for the treatment of left-sided PVT. However, these results need to be confirmed in adequately powered randomized controlled trials (if they are ever performed...).

Is an intensive weight loss program useful in type 2 diabetes?

The Look-AHEAD Research Group. Cardiovascular effect of intensive lyfestile intervention in type 2 diabetes. **N Engl J Med 2013;369:145-54. http://doi.org/np3**

Weight loss is recommended for overweight or obese patients with type 2 diabetes to improve glycemic control and risk factors for cardiovascular disease and reduce the risk of other obesity-related coexisting illnesses. However, the information about the benefit of this intervention on cardiovascular prognosis is inconclusive. The Look AHEAD study was a multicenter, randomized, open-label (but with blind event adjudication) trial designed to answer this question.

The study included patients with type 2 diabetes with a body mass index (BMI) ≥ 25 and specifically ≥ 27 in patients taking insulin, with blood pressure levels ≤ 160-100 mm Hg, HbA1c ≤ 11% and triglycerides ≤ 600 mg/dl. The patients were randomly assigned to participate in an intensive weight loss program (IWLP) or to the control group. Intensive weight loss included: a) weekly group and individual counseling sessions during the first 6 months, with decreasing frequency over the course of the trial, b) a calorie goal of 1200 to 1800 calories per day, with <30% of calories from fat, and, c) at least 175 minutes of moderate-intensity physical activity per week. The intervention was aimed at achieving and maintaining a weight loss ≤ 7% body weight. The control group featured three group sessions per year focused on diet, exercise, and social support during years 1 through 4 and then one annually. The primary end point was the first occurrence of a composite outcome of cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke, and the anticipated maximal follow-up period was 11.5 years. During the first 2 years of the trial, the primary-event rate was lower than expected. Therefore, hospitalization for angina was added to the primary outcome, and planned follow-up was extended to 13.5 years.

Between 2001 and 2004, 5145 patients were enrolled (2570 in the IWLP group and 2575 in the control group). Mean age was 58.7 years, about 60% were women, mean BMI was 36; mean HbA1c was 7.3% and 16% were taking insulin. In September 2012 the study was discontinued after a median follow-up of 9.6 years on the basis of a futility analysis of the intervention. During the first year there were significant differences in the metabolic parameters, obesity and physical capacity between both groups (weight loss of 8.6% in the IWLP group and of only 0.7% in the control group); yet, these differences were markedly reduced during follow-up, particularly due to loss of what had been initially achieved in the IWLP arm. Thus, the average effect of the intervention compared with control consisted in a reduction of 0.22 in the HbA1c level, 3.2 cm in waist circumference, and 4% weight loss (and only 2.5 % by the end of the study), while exercise capacity slightly increased by 0.6 MET. There were no differences in the primary outcome (1.9% per year in control vs. 1.8% in the IWLP arm) or in any of the individual cardiovascular events making up the composite outcome.

Which is the cause of lack of a significant difference in the outcome between groups? Several theories can be outlined: probably medical treatment in the control group was so effective that made the relative benefit of IWLP more difficult to demonstrate, or the target proposed in this arm was in fact not sufficiently ambitious. Follow-up data suggest that failure was due to lack of sustaining what was initially achieved. The results should not be interpreted as evidence of the lack of usefulness in lifestyle changes in this population but as the failure of preserving the motivation in the attempt.

Predicting mortality in heart failure: the MAGGIC score

Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39372 patients from 30 studies. **Eur Heart J 2013;34:1404-13. http://doi.org/npz**

The possibility of predicting the outcome of patients with a chronic disease is useful to decide which diagnostic tests should be performed and to implement diverse treatments. Several clinical prediction rules for patients with heart failure have been developed. Undoubtedly, the MAGGIC score here presented is the most ambitious score in terms of development and scope.

This score was developed from a meta-analysis of 6 randomized trials and 24 observational studies comprising 39372 patients with a mean follow-up of 2.5 years during which 40.2% of patients died. The score is based on 13 highly significant and easily available

variables obtained from a large number of observations (with the largest number of patients and deaths ever investigated in heart failure).

The following variables with their corresponding points are included in the score: 1) LVEF ≥ 40% = 0 points and up to 7 if EF < 20%; 2) age < 55 years = 0 points, with increasing value up to 80 years; 3) systolic blood pressure ≥ 150 mmHg = 0 points, with increasing value as blood pressure decreases to < 110 mm Hg; 4) body mass index ≤ 30 = 0 points, with increasing value up to 6 if BMI < 15; 5) creatinine ≤ 1.02 mg/dl = 0 points, with increasing value up to 8 if creatinine is ≥ 2.84 mg/dl; 6) functional class I = 0 points with increasing value up to 8 for FC IV; 7) male gender, current smoking and not on angiotensin-converter enzyme inhibitors or angiotensin II receptor blockers = 1 point each; 8) chronic obstructive pulmonary disease and first diagnosis of heart failure in the past 18 months = 2 points each; and 9) diabetes and not on beta blockers = 3 points each.

The merit of this score is that it considers the interaction phenomenon, meaning that the impact of some predictive variables may be stronger than the impact of other variables. For example, age is associated with worse outcome, particularly in patients with higher LVEF: 80 years plus LVEF < 30% corresponds to a score of 10 points, and of 15 points if LVEF is ≥ 40%.

The score ranges between 0 and 52 points. A score of 10 means a predicted mortality of 10% at 3 years and a score of 40 a predicted mortality of 84%.

Of interest, this score does not consider the traditional prognostic markers as heart rate or sodium plasma levels, probably because neurohormonal antagonists associated to these markers (beta blockers to heart rate and renin-angiotensin system antagonists to sodium plasma levels) are included. The value of concomitant diseases and nutritional condition should be remarked. The authors did not consider that external validation of this score was necessary because it was developed from a meta-analysis of sufficiently different cohorts with different settings and different characteristics, and included patients with diverse ejection fraction values. However, despite the excellent study design, the medical community still has to find this score "user-friendly". The score can be calculated from the website www.heartfailurerisk.org using patient's data.

Perioperative oral anticoagulation before pacemaker surgery is better than changing to heparin: the BRUISE CONTROL study

Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. **N Engl J Med 2013;368:2084-93. http://doi.org/np2**

Many patients requiring pacemaker (PM) or implantable cardioverter–defibrillator (ICD) surgery are taking oral anticoagulants, and the standard of care is to interrupt oral anticoagulant therapy and to use bridging therapy with heparin around the time of surgery. This approach consumes considerable health care resources in visits to the hematologist and controls, involves a short period of normal coagulability and risk of device-pocket hematoma which can have serious consequences, such as an increased risk of infection, the need for prolonged hospitalization, cessation of oral anticoagulation therapy and the need for further surgery. The BRUISE CONTROL is a multicenter, single-blinded, randomized trial, designed to compare current standard of practice with a strategy of continued oral anticoagulant treatment.

The study enrolled patients who were taking warfarin, had an annual predicted risk of thromboembolism of 5% and required nonemergency device (PM or ICD) surgery. The patients were randomly assigned to two groups: a) continued-warfarin group with a target INR on the day of surgery of 3.0 or lower (3.5 for patients with prosthetic heart valves), or b) heparin-bridging group: patients discontinued warfarin 5 days before the procedure and started receiving intravenous heparin 3 days before the procedure (until 4 hours before surgery) or low-molecular-weight heparin (until the morning of the day before the procedure). The primary outcome was clinically significant device-pocket hematoma. To prevent allocation bias, and because blinding was not possible, each center was required to identify two patient-care teams, one responsible of perioperative and surgical management and one in charge of postoperative care.

Low-molecular weight heparin was used in 90% of cases. The median INR on the day of surgery was 1.2 in the heparin group and 2.3 in the continued-warfarin group. The study was terminated when 681 patients were included, after the second interim analysis showed that the primary end point occurred in 3.5% of patients in the warfarin group and in 16% of patients in the heparin group (RR 0.19, 95% CI 0.10-0.36, p < 0.001). There were no significant differences in the incidence of embolic events or death.

The results of this study are in some sense unexpected because they challenge our "common sense" and our common medical practice. The authors mentioned that continuing with oral anticoagulants can facilitate the detection of bleeding during surgery and allow appropriate management, while during a normal coagulation status such bleeding may be apparent only when anticoagulation therapy is resumed postoperatively. Beyond this explanation, the evidence is consistent enough to justify a change in guideline recommendations and in daily practice.