Cardiovascular journals

Could vitamin D supplementation have beneficial effects on cardiovascular health?

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In addition to its well-recognised effect on bone and calcium metabolism, there is a growing awareness that vitamin D may be an important factor from the perspective of cardiovascular (CV) health. Indeed, recent evidence supports an association of vitamin D deficiency with hypertension, peripheral vascular disease, diabetes, metabolic syndrome, coronary artery disease, and heart failure. Furthermore, the prevalence of vitamin D deficiency may be as high as 30–50% in the general population (Vacek et al, 2011). Despite such considerations, little is known as to the effect of vitamin D supplementation on patient outcomes.

The observational, retrospective study by Vacek et al (2011; summarised alongside) examined associations between vitamin D deficiency, vitamin D supplementation and patient outcomes in a large cohort of people attending a specialist CV centre. Of 10 899 patients, the mean age was 58±15 years, 71% were women (*n*=7758), with an average BMI of 30±8 kg/m^2. Mean serum vitamin D level was 24.1±13.6 ng/mL; 3294 (29.7%) people were in the normal vitamin D range and 7665 (70.3%) were deficient.

Vitamin D deficiency was associated with several CV-related diseases, including hypertension, coronary artery disease, cardiomyopathy, and diabetes (all $P<0.05$). Vitamin D deficiency was a strong independent predictor of all-cause death (odds ratio [OR], 2.64; 95% confidence interval [CI], 1.901–3.662; $P<0.0001$) after adjusting for multiple clinical variables. Vitamin D supplementation conferred substantial survival benefit (OR for death, 0.39; 95% CI, 0.277–0.534; $P<0.0001$).

The findings of this study support previous observations of an association between vitamin D deficiency and multiple adverse patient outcomes. This study also further extends these observations by demonstrating an outcome benefit following vitamin D supplementation. The benefits of vitamin D supplementation on survival were highly significant for those patients with a documented deficiency, with the benefit being independent of the concomitant use of other cardioprotective drugs such as aspirin or statins.

These findings could have clinical implications for the usual recommended daily allowance for vitamin D. The regular intake of the recommended 400 IU/day might be adequate to avoid deficiency in many people, and supplementation with >1000 IU/day might be required to achieve optimal levels. However, prospective studies evaluating the effects of vitamin D supplementation are few and have failed to consistently demonstrate benefit, which may relate to suboptimal dosing of vitamin D in the range of 400–800 IU/day. The results of this study imply that much higher vitamin D doses (>1000 IU/day) may be required to achieve outcome benefit.

When evaluating the clinical relevance of this study it must be remembered that this was a retrospective, observational study with a selected population, introducing possible selection bias. The study population was derived from patients who had their vitamin D levels measured at a hospital laboratory and who were patients in a CV practice. Extrapolation to other populations might therefore not be appropriate. In addition, isolated vitamin D measurements, as used in this study, might not reflect long-term levels.

Multiple other possible confounding issues also need to be considered: the dose and duration of vitamin D supplementation were not analysed, and patient compliance was not assessed, while inclusion of vitamin D in multivitamin supplements was not considered. Nevertheless, this study supports the growing body of evidence linking vitamin D deficiency to adverse outcome and provides further rational for a well-designed prospective outcome study to evaluate the optimal dose and potential benefits of vitamin D supplementation.

AMERICAN JOURNAL OF CARDIOLOGY

Supplementation with vitamin D improves survival

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Although vitamin D deficiency has been associated with diabetes, hypertension, metabolic syndrome, peripheral vascular disease, coronary artery disease and heart failure, the effect of vitamin D supplementation has not been well studied.

2 This observational, retrospective study examined the associations between vitamin D deficiency, vitamin D supplementation, and patient outcomes in 10 899 people (mean age, 58.3±14.9 years; 71% women [*n*=7758]; mean BMI, 29.9±7.7 kg/m^2).

3 Vitamin D levels were defined as normal (>30 ng/mL) or deficient (<30 ng/mL).

4 Mean serum vitamin D level was 24.1±13.6 ng/mL; 3294 (29.7%) people were in the normal range and 7665 (70.3%) were deficient.

5 Vitamin D deficiency was associated with several cardiovascular diseases (CVDs), including hypertension, cardiomyopathy, coronary artery disease and diabetes (all $P<0.05$), and, after adjusting for multiple clinical variables, was a strong independent predictor of all-cause death (odds ratio [OR], 2.64; 95% confidence interval [CI], 1.901–3.662; $P<0.0001$).

6 Supplementation of vitamin D was found to confer substantial survival benefit (OR for death, 0.39; 95% CI, 0.277–0.534; $P<0.0001$).

7 Vitamin D deficiency was associated with a significant risk of CVD and reduced survival. It was concluded that vitamin D supplementation was significantly associated with improved survival, especially in those with documented vitamin D deficiency.

Vacek JL, Vanga SR, Good M et al (2011) Vitamin d deficiency and supplementation and relation to cardiovascular health. *Am J Cardiol* **109**: 359–63

AMERICAN HEART JOURNAL

Intensive glycaemic control has no impact on heart failure

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Poor glycemic control is known to be associated with an increased risk of heart failure (HF) in people with T2D, but it is not known whether improved glycemic control reduces this risk.

2 The authors of this study conducted a meta-analysis of randomised controlled trials (RCTs) that compared a more intensive blood glucose-lowering regimen to a standard regimen, with HF events the outcome of interest.

3 A range of web-based databases were searched from January 1970 to October 2010, which identified eight RCTs totalling 37 229 patients with a follow-up of 2.3–10.1 years.

4 There were 1469 HF-related events (55% in the intensive treatment arm), and the mean difference in HbA_{1c} level between intensive versus standard care was 9.8 mmol/mol (0.9%).

5 Difference in the risk of HF-related events between intensive versus standard treatment was not significant (odds ratio [OR], 1.20; 95% confidence interval [CI], 0.96–1.48), but the effect estimate was highly heterogeneous (I^2=69%).

6 When analysed at subgroup level, intensive therapy using thiazolidinediones significantly increased HF risk (OR, 1.33; 95% CI, 1.02–1.72).

7 The authors concluded that the occurrence of HF events was not reduced by intensive glycemic control in people with T2D. Furthermore, intensive control with thiazolidinediones increased the risk of HF.

Castagno D, Baird-Gunning J, Jhund PS et al (2011) Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: Evidence from a 37,229 patient meta-analysis. *Am Heart J* **162**: 938–48.e2

AMERICAN HEART JOURNAL

CV events in people with T2D, CKD and anaemia treated with darbepoetin-alfa

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The authors of this study undertook an analysis of TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) participants to determine predictors of cardiovascular (CV) mortality and morbidity in people with T2D, chronic kidney disease (CKD) and anaemia treated with darbepoetin-alfa .

2 Predictors were identified for the composite of CV death, myocardial infarction, stroke, hospitalisation for myocardial ischaemia, or heart failure (HF) in 3847 people (961 experienced this composite outcome).

3 Values for CV risk prediction were: previous HF (hazard ratio [HR], 1.74; 95% confidence interval [CI], 1.51–2.01), age (HR, 1.03; 95% CI, 1.02–1.04 per year), protein–creatinine ratio (HR, 1.19; 95% CI, 1.13–1.26), C-reactive protein ≥6.6 mg/L (HR, 1.44; 95% CI, 1.23–1.69 compared with C-reactive protein ≤3.0 mg/L), and abnormal electrocardiogram (HR, 1.42; 95% CI, 1.21–1.66); all P<0.0001).

4 Risk estimation was improved with the use of cardiac-derived biomarkers (first 1000 people), particularly N-terminal pro B-type natriuretic peptide (P<0.001) and troponin T.

5 It was concluded that these results suggest ways to improve CV risk stratification in people with T2D, CKD and anaemia.

McMurray JJ, Uno H, Jarolim P et al (2011) Predictors of fatal and nonfatal cardiovascular events in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia: an analysis of the Trial to Reduce cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy (TREAT). *Am Heart J* **162**: 748–55

CIRCULATION

Stroke in people with T2D, CKD and anaemia treated with darbepoetin alfa

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) found that correction of anaemia in people with T2D and non-dialysis chronic kidney disease (CKD) using the erythropoiesis-stimulating agent darbepoetin alfa (dabe-a) had no overall effect on death or non-fatal cardiovascular (CV) events. Moreover, a significant increase in the rate of stroke in those assigned to darbe-a was observed.

2 This study aimed to identify baseline characteristics (n=4038) and post-randomisation factors (blood pressure [BP], haemoglobin level, platelet count or treatment dose) that might explain the increased rate of stoke in TREAT participants treated with darbe-a.

3 One hundred and one people had a stroke in the darbe-a group (n=2012) versus 53 in the placebo arm (n=2026) (hazard ratio, 1.9; 95% confidence interval [CI], 1.4–2.7).

4 Independent predictors of stroke included assignment to darbe-a (odds ratio [OR], 2.1; 95% CI, 1.5–2.9), previous stoke (OR, 2.0; 95% CI, 1.4–2.9), more proteinuria and CV disease.

5 In those assigned to darbe-a, post-randomisation systolic and diastolic BP, haemoglobin level, platelet count and darbe-a dose did not differ between people with and without stroke.

6 The authors concluded that the two-fold increase in stroke observed with darbe-a treatment in TREAT could not be attributed to baseline characteristics or post-randomisation BP, haemoglobin level, platelet count or treatment dose, and that these factors could not be used to reduce the risk of stroke in people treated with darbe-a.

Skali H, Parving HH, Parfrey PS et al (2011) Stroke in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia treated with Darbepoetin Alfa: the trial to reduce cardiovascular events with Aranesp therapy (TREAT) experience. *Circulation* **124**: 2903–8

> *"The two-fold increase in stroke observed with darbepoetin alfa treatment in TREAT could not be attributed to baseline characteristics or post-randomisation blood pressure, haemoglobin level, platelet count or treatment dose."*

"Type 2 diabetes, HbA_{1c} level and poor glycaemic control are independently associated with atrial fibrillation risk."

HEART

Poor T2D control associated with increased risk of AF

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 This prospective cohort study aimed to determine the association between T2D and atrial fibrillation (AF) in 13 025 people categorsied as having no diabetes, pre-diabetes or diabetes at baseline (1990–92).

2 Diagnoses of incident AF were obtained throughout 2007.

3 A significant association was found between T2D and AF risk; no association was found between pre-diabetes/undiagnosed T2D and AF risk.

4 A positive linear association was found between HbA_{1c} and AF risk in people with and without T2D. No association was found between fasting plasma glucose (FBG) or insulin in those without T2D, but a significant association was found with FBG in those with T2D (P=0.0002).

5 It was concluded that T2D, HbA_{1c} level and poor glycaemic control are independently associated with AF risk.

Huxley RR, Alonso A, Lopez FL et al (2011) Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: the Atherosclerosis Risk in Communities study. *Heart* **98**: 133–8

CIRCULATION

Hypoglycaemia reduces myocardial blood flow in T1D and non-T1D

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 To examine the association of hypoglycaemia with increased cardiovascular mortality, this study tested the hypothesis that myocardial blood flow reserve (MBFR) is decreased during hypoglycaemia in people with T1D (n=28) and healthy controls (n=19).

2 MBFR was assessed during sequential 60-minute periods of induced euglycaemia and hypoglycaemia.

3 Compared with baseline, MBFR increased in the control group during euglycaemia (by 0.57 U; P<0.0001) and decreased during hypoglycaemia (by 0.36 U; P<0.0001); similar changes were observed in the T1D group. The presence of microvascular complications in the T1D was associated with a reduction in MBFR (P<0.0001).

4 The authors concluded that hypoglycaemia decreases MBFR in both people with T1D and healthy people.

Rana O, Byrne CD, Kerr D et al (2011) Acute hypoglycemia decreases myocardial blood flow reserve in patients with type 1 diabetes mellitus and in healthy humans. *Circulation* **124**: 1548–56

CIRCULATION

Atherosclerosis and inflammation reduced by DPP-4 inhibition

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The authors sought to test the hypothesis that dipeptidyl peptidase-4 (DPP-4) inhibition would have beneficial effects on atherosclerosis.

2 Male mice, fed either a high-fat or normal diet for 4 weeks, were randomised to the DPP-4 inhibitor alogliptin or vehicle for 12 weeks. Assays of DPP-4 inhibition (DPP-4i) on monocyte activation/migration were undertaken in both human and murine cells.

3 DPP-4i improved markers of insulin resistance, and reduced blood pressure and visceral adipose tissue macrophage content. Aortic plaque decreased with DPP-4i, with a striking reduction in plaque macrophages.

4 It was concluded that DPP-4i reduced atherosclerosis and inflammation via inhibition of monocyte activation/chemotaxis.

Shah Z, Kampfrath T, Deiuliis JA et al (2011) Long-term dipeptidyl-peptidase 4 inhibition reduces atherosclerosis and inflammation via effects on monocyte recruitment and chemotaxis. *Circulation* **124**: 2338–49

AMERICAN JOURNAL OF CARDIOLOGY

Miglitol improves vascular endothelial dysfunction in people with T2D and CAD

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Miglitol exerts an increased suppression on the elevation of blood glucose levels shortly after a meal compared with other alpha-glucosidase inhibitors. However, the effect of 3-month repeated administration of miglitol on endothelial dysfunction is unknown.

2 The authors of this study enrolled 50 people with T2D and coronary artery disease (CAD), who were then randomised to miglitol or voglibose therapy for 3 months.

3 Measurements were taken at baseline and at 3 months for lipid and blood glucose profiles, HbA_{1c} level, 1,5-anhydroglucitol, serum insulin levels, C-reactive protein and flow-mediated dilatation. Baseline characteristics were similar in both groups.

4 By 3 months, HbA_{1c} levels had decreased in both groups; however, improvements in 1,5-anhydroglucitol in the miglitol group were significantly higher than in the voglibose group.

5 Improvements in insulin resistance index, C-reactive protein, and percentage flow-mediated dilatation were observed in the miglitol group but not in the voglibose group.

6 The authors concluded that 3-month repeated administration of miglitol was associated with improved vascular endothelial dysfunction as a result of strong suppression of postprandial hyperglycaemia, and that miglitol may, therefore, have antiatherogenic effects in people with T2D and CAD.

Emoto T, Sawada T, Hashimoto M et al (2011) Effect of 3-month repeated administration of miglitol on vascular endothelial function in patients with diabetes mellitus and coronary artery disease. *Am J Cardiol* **109**: 42–6