Diabetes journals

Vit D or not vit D, that is the question

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"To be, or not to be, that is the question:
Whether 'tis nobler in the mind to suffer
The slings and arrows of outrageous fortune,
Or to take arms against a sea of troubles,"

Hamlet, Act 3, Scene 1 by William Shakespeare

The overall aim of CARDIPP (Cardiovascular Risk in Type 2 Diabetes – A Prospective Study in Primary Care) was to identify predictors of cardiovascular disease (CVD) in middle-aged people with type 2 diabetes. In their article (summarised alongside), Samefors and colleagues report on the association between vitamin D levels and CV morbidity and mortality in this community-based cohort study.

In Sweden, 761 people with type 2 diabetes, who were not receiving vitamin D supplementation, were recruited from 222 primary care centres. The cohort had serum 25-hydroxyvitamin D_3 levels and all the main known CVD risk factors measured at baseline. Vitamin D_3 levels were divided into quartiles.

Over a mean follow-up of 7.3 years, compared with the highest quartile, the lowest quartile of vitamin D_3 was associated with a hazard ratio (HR) for CV morbidity and mortality of 3.46, while the second-lowest had an HR of 2.26. The HR for quartile 3 was not significant, at 1.62. Statistical significance was maintained after adjustment for the other main CVD risk factors, including physical activity, statin use, smoking, BMI, age, gender and season.

The authors calculated that, after adjustment for age, gender and season, each 20-nmol/L increase in vitamin D_3 level was associated with a 37% reduction in the risk of CV morbidity and mortality. One could, therefore, argue that increasing vitamin D_3 levels by 20 nmol/L would produce a similar benefit to that of statins. Intriguingly, in a recent, albeit small and uncontrolled, study of 146 statin-intolerant people, 88% of the participants had no muscle side effects when given vitamin D supplementation (Khayznikov et al, 2015).

I think Hamlet had it easy, as he was only contemplating his own actions in his existentialist angst. As healthcare professionals, we still have no clear answer to the question of whether to prescribe vitamin D supplements. This research certainly shows that low vitamin D levels are associated with CV morbidity and mortality. However, there is no compelling body of evidence to suggest that supplementation would reduce CV risk. The dilemma remains. Personally, I am of the opinion that *'tis* ***not*** *nobler in the* ***heart*** *to suffer*, and I choose *to take arms* ***[with vitamin D_3]*** *against a sea of troubles.* And do get out into the sunlight – often but safely. ■

Khayznikov M, Hemachrandra K, Pandit R et al (2015) Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation. *N Am J Med Sci* **7**: 86–93

Diabet Med

Vitamin D levels and CVD risk in people with T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this prospective, observational, community-based study, 698 people with T2D (mean age, 61 years) were followed for a mean of 7.3 years to determine the association between serum 25-hydroxyvitamin D_3 levels and risk of cardiovascular disease (CVD).

2 Vitamin D levels at baseline ranged from 7.5 to 164.9 nmol/L, and were divided into quartiles (Q1: <35.5 nmol/L; Q2: 35.5–47.5 nmol/L; Q3: 47.5–61.8 nmol/L; Q4: ≥61.8 nmol/L).

3 Over the study period, the primary outcome – a composite of the first hospitalisation for acute myocardial infarction or stroke, or cardiovascular mortality – occurred in 66 people (9%).

4 After adjustment for age, gender and season in which blood samples were taken, compared with people in the highest vitamin D quartile (Q4), the hazard ratio (HR) for the primary endpoint was 3.46 in Q1, 2.26 in Q2 and 1.62 (*P*=non-significant) in Q3.

5 After adjustment for further CVD risk factors, including physical activity, smoking and BMI, the risk remained significantly higher for people in Q1 (HR, 2.77) but not Q2 or Q3.

6 A 20-nmol/L increase in vitamin D levels was associated with a 37% reduction in CVD risk (95% confidence interval, 17–52%), after adjustment for age, gender and season.

7 The authors point out that a causal relationship cannot be inferred from this study; however, ongoing clinical trials of vitamin D supplementation may address this in the future.

Samefors M, Scragg R, Länne T et al (2017) Association between serum 25(OH)D_3 and cardiovascular morbidity and mortality in people with type 2 diabetes: a community-based cohort study. *Diabet Med* **34**: 372–9

Diabet Med

Stroke risk at different BP ranges in people with T2D

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 Using Swedish national records, these authors conducted a large, observational, case–control study to assess the risk of stroke at varying blood pressure (BP) ranges in people with T2D compared with the general population.

2 A total of 408 076 people with and 1 913 507 without T2D were analysed over a median follow-up of 4 years.

3 Overall, 19 548 people with T2D (4.8%) had a stroke, compared with 61 690 controls (3.2%). Incidence rates per 1000 person-years were higher in the T2D group for overall stroke (10.6 vs 6.8), ischaemic stroke (9.6 vs 5.9) and haemorrhagic stroke (1.0 vs 0.9).

4 After adjustment for age, gender, diabetes duration and comorbidities, the hazard ratio (HR) for any stroke in people with T2D as a whole was 1.43 (95% confidence interval, 1.41–1.46).

5 The excess risk was derived from the three highest BP categories: 130–139/80–89 mmHg (HR, 1.20), 140–159/90–99 mmHg (HR, 1.47) and ≥160/100 mmHg (HR, 1.97).

6 People with T2D and BP <130/80 mmHg had a similar risk of stroke to the general population. This was partly due to a reduced risk of haemorrhagic stroke, which offset the small increases in risk of ischaemic stroke (HRs ranging from 1.06 to 1.18) present even in people with lower BP.

7 These findings further emphasise the importance of good BP control in people with T2D.

Hedén Ståhl C, Lind M, Svensson AM et al (2016) Long-term excess risk of stroke in people with type 2 diabetes in Sweden according to blood pressure level: a population-based case-control study. *Diabet Med* **34**: 522–30

Diabetes Care

Cardiac effects of sulfonylurea-related hypoglycaemia

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 In this single-centre, observational study, the authors examined the short-term cardiovascular effects of hypoglycaemia in people with well-controlled T2D taking second-generation sulfonylureas (SUs).

2 Thirty participants underwent 48 hours of blinded continuous glucose monitoring and simultaneous Holter monitoring. A hypoglycaemic episode was defined as blood glucose levels <3.5 mmol/L for >20 minutes.

3 Over the study period, nine of 30 participants had a total of 15 distinct hypoglycaemic episodes. Episodes were mostly nocturnal (67%) and asymptomatic (73%).

4 QTc prolongation was observed in five of nine people with hypoglycaemia. Furthermore, higher QT dynamicity, a marker of poor prognosis in people with established heart disease, was observed in those with hypoglycaemia compared to those without (0.193 vs 0.159 in the nocturnal period; P=0.01).

5 Rates of ventricular and supraventricular ectopy were also higher during hypoglycaemia; however, these findings failed to reach significance.

6 Similar, although non-significant, findings were observed in a separate insulin-treated cohort, suggesting that the results were linked to hypoglycaemia in general rather than SU-related hypoglycaemia.

7 These results suggest that SU-related hypoglycaemia can have detrimental cardiac effects, and the authors call for larger, longer studies to elucidate this hypothesis.

Middleton TL, Wong J, Molyneaux L et al (2017) Cardiac effects of sulfonylurea-related hypoglycemia. *Diabetes Care* **40**: 663–70

Diabetes Res Clin Pract

CV risk of insulin vs DPP-4 inhibitors as second-line therapy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 The aim of this observational study using full-population data from Swedish registries was to compare cardiovascular (CV) risk between insulin and dipeptidyl peptidase-4 (DPP-4) inhibitors as second-line therapy.

2 A total of 27 767 people with T2D who started insulin or a DPP-4 inhibitor as an adjunct to or replacement for metformin were identified. After matching for propensity scores, 9278 insulin recipients were compared with the same number of gliptin recipients.

3 Over a median follow-up of around 4 years, in the insulin group, the incidence (per 1000 person-years) of death, fatal/non-fatal CV disease (CVD) and severe hypoglycaemia was 20.7, 25.2 and 2.7, respectively. Corresponding rates in the DPP-4 inhibitor group were 12.3, 18.1 and 0.6, respectively.

4 The hazard ratios for insulin versus DPP-4 inhibitors were all significant at 1.69, 1.39 and 4.35 for death, CVD and severe hypoglycaemia, respectively.

5 The survival curves separated within 6 months of treatment initiation and widened further thereafter.

6 The results were similar when using multivariate analysis in the whole (unmatched) cohort, and when analysis was restricted to people without pre-existing CVD.

7 The authors postulate that the higher rates of severe hypoglycaemia may have contributed to the increased mortality rates. This study was funded by AstraZeneca.

Nyström T, Bodegard J, Nathanson D et al (2017) Second line initiation of insulin compared with DPP-4 inhibitors after metformin monotherapy is associated with increased risk of all-cause mortality, cardiovascular events, and severe hypoglycemia. *Diabetes Res Clin Pract* **123**: 199–208

"People with type 2 diabetes and blood pressure <130/80 mmHg had a similar risk of stroke to the general population."