Diabetes journals

Preventing death, CVD and renal complications in type 1 patients: The triple shield

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Anecdotally, I know that many of my colleagues in diabetes care worry about the attention we give to our patients with type 1 diabetes. Type 2 diabetes is at least 90% of the workload in relation to diabetes – there is enough clinical work to occupy us fully with prevention, aggressive risk-factor control and polypharmacy. The latter is particularly exciting, with new agents galore with high "standards of promotion" and an emerging evidence base.

There is good news for patients with type 1 diabetes. An Australian study (Huo et al, 2016) shows that life expectancy has improved by 1.5 years in women and 1.9 years in men, over a relatively short period (2003 to 2010). Hidden away somewhat in the paper is the fact that patients with type 1 diabetes still lose 12.2 years of life in comparison to the general population, however.

So, what can we do? Three of the papers summarised in this issue can give us a clear strategy to narrow this gap in life expectancy. From the DCCT/EDIC study (alongside) we learn that early good glycaemic control creates a metabolic legacy that reduces the risk of cardiovascular disease (CVD) over a 20-year period. The mechanism discussed is interesting and may be related to vascular stiffening, which is accelerated by poor glycaemic control by glycation of the vascular wall of arteries.

Severe hypoglycaemia must be avoided (see summary of Lu et al on page 93). Even a single episode of severe hypoglycaemia in the preceding year was associated with an odds ratio of 2.74 of all-cause mortality and 2.02 of CVD. The figures are similar if there have been episodes of hypoglycaemia in the preceding 1 to 3 years and 3 to 5 years. Severe hypoglycaemia simply has to be avoided. The newer longer-acting insulins may help in this respect.

Older evidence from a meta-analysis shows that there is the potential to reduce progress to clinically significant diabetic nephropathy by early use of ACE inhibitors (ACE Inhibitors in Diabetic Nephropathy Trialist Group, 2001).

Easiest to implement in most of our patients with type 1 diabetes is lipid-lowering. In a Swedish study of 24 230 patients with type 1 diabetes (also alongside), lipid-lowering (97% statins) was associated with a reduction in CVD by 40%, stroke by 44% and acute myocardial infarction by 22%. There was also a reduction in all-cause mortality of 44%. The follow-up period was only 6 years of treatment. It is very important to state that only 5387 out of the 24 230 were on lipid-lowering therapy. The potential for reducing CVD complications and death is, therefore, substantial, as only 22.2% appear to be on this basic lipid-lowering treatment. The number needed to treat to save one death per year was 297 treatment-years. This seems high, but equates to only around £4500 to save a life, as statins only cost approximately £15 a year.

NICE guidelines for type 1 diabetes have given us the remit to implement a widespread lipid-lowering strategy (NICE, 2015). All patients over the age of 40 years should be considered for statin treatment (atorvastatin 20 mg od) or, if they have had type 1 diabetes for 10 years or more, at any age. Clearly, effective contraception is essential in women of child-bearing potential.

I would like to end by keeping the key clinical messages simple. There is a compelling evidence base to suggest that the life-years lost to type 1 diabetes can be reduced. We need to renew our focus on the triple shield of good glycaemic control (good early control and avoiding severe hypoglycaemia), blood-pressure-lowering and lipid-lowering treatment with a statin. ■

ACE Inhibitors in Diabetic Nephropathy Trialist Group (2001) Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Inter Med* **134**: 370–9

Huo L, Harding JL, Peeters A et al (2016). Life expectancy of type 1 diabetic patients during 1997–2010: a national Australian registry-based cohort study. *Diabetologia* **59**: 1177–85

NICE (2015) *Type 1 diabetes in adults: diagnosis and management* (NG17). NICE, London. Available at: www.nice.org.uk/guidance/ng17 (accessed 05.12.16)

Diabetes Care

Longitudinal CV risk factors in T1D

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

1 The DCCT (Diabetes Control and Complications Trial) randomised participants with T1D to receive intensive or conventional therapy. After of 6.5 years' follow-up, 96% of the surviving cohort were enrolled in the EDIC (Epidemiology of Diabetes Interventions and Complications) study for a further 20 years.

2 The prior studies demonstrated the beneficial effect of intensive therapy on atherosclerosis and major cardiovascular disease (CVD) events. This study evaluated the association of glycaemic exposure with CVD risk factors and described differences in CVD risk factors between the original groups.

3 HbA_{1c} values in the two treatment groups converged at the beginning of the EDIC follow-up period, but the DCCT/EDIC study time-weighted mean HbA_{1c} values remained significantly higher in the conventional treatment group over the 20 years of follow-up.

4 Higher HbA_{1c} correlated significantly with longitudinal changes for all the main CVD risk factors over 30-years' follow-up. The strongest associations were with increases in triglyceride and LDL-cholesterol levels.

5 Increasing pulse pressure resulted from rising systolic blood pressure (SBP) with relatively level diastolic blood pressure (DBP) to year 17, and decreasing DBP with stable SBP thereafter. The persistent widening was not fully explained by use of antihypertensive drugs, and could be related to diastolic dysfunction and accelerated arterial ageing due to diabetes.

6 A better understanding of diabetes-related and traditional CVD risk factors may help with the development of targeted treatment regimens.

DCCT/EDIC Research Group (2016) Coprogression of cardiovascular risk factors in type 1 diabetes during 30 years of follow-up in the DCCT/EDIC Study. *Diabetes Care* **39**: 1621–30

Diabetes Care

Lipid-lowering therapy, CVD and death

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

1 This nationwide longitudinal study used propensity scores to estimate the effect of lipid-lowering therapy (LLT) in primary prevention on cardiovascular disease (CVD) and death in a Swedish cohort of 24 230 adults with T1D without a history of CVD.

2 In the cohort, 18 843 individuals were untreated, while 5387 received LLT (>97% statins). The mean follow-up time was 6.0 years. A matched cohort of 4025 untreated and 4025 treated individuals was also included.

3 Propensity scores were calculated from 32 baseline clinical and socioeconomic variables.

4 Hazard ratios for treated versus not treated in the overall cohort were significant for all outcomes: cardiovascular death, 0.60 (95% confidence interval, 0.50–0.72); all-cause death, 0.56 (0.48–0.64); fatal/non-fatal stroke, 0.56 (0.46–0.70); fatal/non-fatal acute myocardial infarction, 0.78 (0.66–0.92); and fatal/non-fatal coronary heart disease, 0.85 (0.74–0.97).

5 Hazard ratios in the matched cohort were significant only for all-cause death (0.74 [95% CI, 0.62–0.88]).

6 The results from the overall cohort indicate that treating such a population with LLT could substantially reduce cardiovascular morbidity and mortality.

7 Although these analyses did not examine the benefits of LLT in those <40 years of age, observations suggest that more studies in this age range are warranted.

Hero C, Rawshani A, Svensson AM et al (2016) Association between use of lipid-lowering therapy and cardiovascular diseases and death in individuals with type 1 diabetes. *Diabetes Care* **39**: 996–1003

Diabetologia

Ideal CV health with incident T2D: a multi-ethnic study

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

1 The American Heart Association defined ideal cardiovascular health (ICH), identifying seven factors associated with healthy ageing: total cholesterol, blood pressure, fasting plasma glucose, dietary intake, tobacco use, physical activity and BMI.

2 This study explored whether participants with higher levels of cardiovascular health (based on ICH components) were less likely to develop diabetes in four racial/ethnic groups: non-Hispanic whites (NHW), African-Americans (AA), Chinese-Americans (CA) and Hispanic-Americans (HA).

3 Participants (n=5341) were without diabetes and cardiovascular disease at baseline. They were scored based on the number of ICH components met: (0–1, poor; 2–3, intermediate; and ≥4, ideal).

4 Over a median follow-up of 11.1 years, there were 587 cases of incident diabetes. After adjustment, participants with 2–3 and ≥4 ICH components vs 0–1 components had a 34% lower and a 75% lower diabetes incidence, respectively.

5 Incident diabetes rates decreased for every additional ICH component achieved in the overall cohort and for each group. There were significant differences by race/ethnicity, with highest incidence rates amongst the HA and AA groups.

6 With fewer than one in six participants from a racial/ethnic minority attaining ≥4 components, research on attainment of ICH is essential to lower cardiovascular risk and diabetes.

Joseph JJ, Echouffo-Tcheugui, Carnethon MR et al (2016) The association of ideal cardiovascular health with incident type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis. *Diabetologia* **59**: 1893–903

Diabetes Res Clin Pract

Second-line risks: SU vs DPP-4 inhibitors with Met

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

1 This observational, full-population study investigated the risk of cardiovascular disease (CVD), all-cause mortality and severe hypoglycaemia in individuals with T2D starting second-line treatment with either metformin + sulfonylurea (SU) or metformin + dipeptidyl peptidase-4 inhibitor (DPP-4i).

2 All people with T2D in Sweden who were initiated on either treatment (n=40 736 and 12 024, respectively) from 2006–2013 were identified and followed from initiation until death or end of the study.

3 Before adjustment, incidence of severe hypoglycaemia, CVD and all-cause mortality in the SU cohort were 2.0, 19.6 and 24.6 per 1000 patient-years and in the DPP-4i cohort were 0.8, 7.6 and 14.9 per 1000 patient-years, respectively.

4 After adjustment for known risk factors, the hazard ratios (95% confidence intervals) for severe hypoglycaemia, fatal and non-fatal CVD and all-cause mortality when comparing SU with DPP-4i were 2.07 (1.11–3.86), 1.17 (1.01–1.37) and 1.25 (1.02–1.54), respectively.

5 Propensity-adjusted and matched analyses confirmed these results. Of the SU drugs, glibenclamide had the highest risks.

6 Although causal relationships need to be elucidated through randomised trials, the authors conclude that the results from this and other observational studies should be considered in the choice of treatments for people with T2D.

Eriksson JW, Bodegard J, Nathanson D et al (2016) Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality. *Diabetes Res Clin Pract* **117**: 39–47

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