Management & prevention of type 2 diabetes

Choosing antihypertensive agents: 'Keeping it clean'

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Aggressive reduction of cardiovascular risk factors in the context of diabetes has become a core part of modern diabetes care.

The recently updated Joint British Societies' guidelines on the prevention of cardiovascular disease (CVD) in clinical practice (British Cardiac Society et al, 2005;) suggest that managing overall risk, rather than individual risk factors, is the key and that the priority focus should include people with any form of established atherosclerotic disease, including adults with diabetes (types 1 and 2), and asymptomatic individuals without established CVD who have an estimated risk of developing CVD over 10 years that is above 20%.

We are told these groups all require professional lifestyle management (but what exactly is this?) and all require risk factor management to achieve defined targets. These include blood pressure (BP) below 130/80 mmHg, and the recent National Institute for Health and Clinical Excellence guidelines offer revised guidance on selection of antihypertensive agents (National Collaborating Centre for Chronic Conditions, 2006). This document recommends angiotensin-converting enzyme (ACE) inhibitors as the primary agents for younger, non-Black people, and calcium-channel blockers or thiazide diuretics for people who are aged 55 years or older or Black.

Some of the evidence basis behind the recommendations is discussed by Taylor et al (see right) in their review of antihypertensive medication and risk of incident type 2 diabetes. Although the adverse metabolic effect of thiazide diuretics and β-blockers have been hotly debated for many years, the reports were conflicting and concerns reduced by the feeling that the adverse metabolic effects were mitigated by the cardiovascular protection offered by good BP reduction. Previous studies have been bedevilled by small sample base, poor control of or adjustment for confounding, and inappropriate control groups.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggested that chlorithalidone was associated with a relative risk (RR) of diabetes of 1.4 compared with lisinopril, but whether this was a risk increase with chlorithalidone or a risk reduction with lisinopril was not certain. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) suggested less diabetes in the amlodipine than in the atenolol group, but most patients in the atenolol arm were taking concomitant thiazide diuretics and the combination may be particularly metabolically disadvantageous.

Using a prospective analysis of three large cohort studies, the paper by Taylor et al goes a long way to clarify the issue. Participants without diabetes but with a history of hypertension were followed for incident diabetes. The study population included 41 493 older women, 14 151 younger women and 19 472 men.

Thiazide use was independently associated with an RR of diabetes of 1.20–1.45. The risk was higher in younger women and lowest in older women, raising the possibility that thiazide use was accelerating progression from normal glucose tolerance to impaired glucose tolerance and diabetes in women predisposed to diabetes.

β-blockers were also associated with an increased risk of incident diabetes in older women (RR, 1.32) and men (RR, 1.20). There was no relation between either calcium-channel blockers or ACE inhibitors and type 2 diabetes.

It seems that when it comes to metabolic profile, given the multiple-risk factor approach to improving cardiovascular outcome in diabetes, we should 'keep it clean' regarding our choice of antihypertensive agents.

British Cardiac Society, British Hypertension Society, Diabetes UK et al (2005) JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* **91**(Suppl 5): v1–52

British Heart Foundation (BHF; 2006) *Factfile: Joint British Societies' Guidelines on the Prevention of Cardiovascular Disease in Clinical Practice: Risk Assessment.* BHF, London

National Collaborating Centre for Chronic Conditions (2006) *Hypertension: management of hypertension in adults in primary care.* Royal College of Physicians, London

DIABETES CARE

Thiazide diuretics and β-blockers linked to increased risk of incident type 2 diabetes

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

1 Previous studies on the relationship between incident diabetes and the use of antihypertensives have yielded conflicting results; this study aimed to clarify the confusion.

2 The Nurses' Health Study I and II cohorts as well as the Health Professional Follow-up Study cohort were analysed prospectively.

3 Applying the exclusion criterion of having diabetes at baseline left 14 151 younger women (aged 38–55 in 2002), 41 193 older women (aged 56–81 years in 1976) and 19 472 men (aged 56–91 in 2002), all of whom had hypertension.

4 The ongoing biennial questionnaire mailing of the three parent studies was used to follow up the older women for 8 years, the younger women for 10 years and the men for 16 years.

5 The number of incident cases of diabetes documented was 3589.

6 The multivariate relative risk (RR) of incident diabetes in people on a thiazide diuretic was 1.20 (95% confidence interval [CI], 1.08–1.33) in older women, 1.45 (95% CI, 1.17–1.79) in younger women and 1.36 (95% CI, 1.17–1.58) in men.

7 The multivariate RR of incident diabetes in people on a β-blocker was 1.32 (95% CI, 1.20–1.46) in older women and 1.20 (95% CI, 1.05–1.38) in men.

Taylor EN, Hu FB, Curhan GC (2006) Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care* **29**(5): 1065–70

'It is proposed by the authors that interventional trials in people with type 2 diabetes should have attention directed towards acute glucose swings.'

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Interventional trials should target acute glucose swings

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

1 It is known that glycaemic disorders are associated with the activation of oxidative stress; this trial sought to establish their relative contributions.

2 This case–control study compared 21 people who had type 2 diabetes with 21 age- and sex-matched controls in Montpellier, France.

3 Estimates of oxidative stress were obtained using 24-hour urinary excretion rates of free 8-iso prostaglandin $F_{2\alpha}$.

4 Postprandial glycaemic instability and general glucose fluctuations were both found to significantly contribute to oxidative stress; this was not the case, though, for long-term glucose exposure, as assessed by HbA_{1c} fasting plasma glucose and mean 24-hour glucose levels.

5 It is therefore proposed by the authors that, as well as targeting HbA_{1c} levels and mean glucose concentrations, interventional trials in people with type 2 diabetes should have attention directed towards acute glucose swings.

Monnier L, Mas E, Ginet C et al (2006) Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *Journal of the American Medical Association* **295**(14): 1681–7

MEDICAL JOURNAL OF AUSTRALIA

Diabetes not being managed proactively in Australian setting

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

1 Based on an optimal HbA_{1c} level of <7.0%, the authors aimed to discover – in an urban setting in Australia – whether diabetes treatment was being prescribed to keep people within the optimal range of glycaemic control. They found that it was not.

2 The cohort being investigated comprised 531 participants with type 2 diabetes from the Fremantle Diabetes Study; data came from baseline assessment and annual reviews between 1993 and 2001.

3 The mean HbA_{1c} level at the reviews before oral hypoglycaemic agents were commenced was 7.7% (inter-quartile range [IQR], 6.9–8.8%).

4 The mean HbA_{1c} level at the reviews before insulin was started was 9.4% (inter-quartile range [IQR], 8.0–10.7%).

Davis TM, Davis WA, Bruce DG (2006) Glycaemic levels triggering intensification of therapy in type 2 diabetes in the community: the Fremantle Diabetes Study. *Medical Journal of Australia* **184**(7): 325–8

DIABETES

Brain MRI correlates found for cognitive impairment in type 2 diabetes

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

1 There is a lack of clarity surrounding structural correlates of cognitive impairment in people with type 2 address.

2 This study compared both magentic resonance imaging (MRI) results and cognition in 113 people with diabetes and 51 control participants, and it also assessed the relationship between MRI findings and cognitive function within the group with diabetes.

3 Type 2 diabetes was found to correlate with impaired cognitive function ($P<0.05$), deep white matter lesions (WMLs; $P=0.02$), and both cortical and subcortical atrophy ($P<0.001$ and $P<0.05$, respectively).

4 Within the type 2 diabetes group: information processing speed was inversely related to the presence of periventricular and deep WMLs, cortical and subcortical atrophy and infarcts; attention and executive function was inversely related to periventricular WMLs and subcortical atrophy; and abstract reasoning and visuoconstruction were both inversely related to subcortical atrophy.

Manschot SM, Brands AM, van der Grond J et al (2006) Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. *Diabetes* **55**(4): 1106–13

'Dietary fat was positively related to diabetes incidence and inversely related to long-term weight loss, while the opposite effect was found for dietary fibre.'

DIABETOLOGIA

Fat and fibre in diet predict weight loss and type 2 diabetes

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

1 The authors investigated the associations that dietary components have with weight parameters and diabetes incidence in 522 middle-aged people with impaired glucose tolerance from the Finnish Diabetes Prevention Study.

2 Dietary fat was positively related to diabetes incidence and inversely related to long-term weight loss, while the opposite effect was found for dietary fibre.

Lindstrom J, Peltonen M, Eriksson JG et al (2006) High-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk: the Finnish Diabetes Prevention Study. *Diabetologia* **49**(5): 912–20

'Pioglitazone but not glipizide significantly reduced systemic vascular resistance and increased total body water, the latter accounting for around 75% of the total weight gain.'

'More research is needed to test whether the prevention and treatment of depression can lead to a reduced incidence of type 2 diabetes.'

DIABETOLOGIA

Depression in adults increases risk of type 2 diabetes

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

1 There is strong evidence for a link between depression and type 2 diabetes, but the relative strength of cause and effect has not yet been established.

2 This meta-analysis examined the effect of depression as a risk factor for type 2 diabetes.

3 Literature was sourced from MEDLINE and PsycINFO; nine studies were included, with the most recent being published in 2004.

4 Fixed and random effects models were applied to obtain pooled relative risks – the latter type of model yields wider confidence intervals and thus gives more conservative estimates, in light of potential heterogeneity between studies.

5 The pooled relative risks for type 2 diabetes given depression were 1.26 (95% confidence interval [CI], 1.13–1.39) for the fixed effects model and 1.37 (95% CI, 1.14–1.63) for the random effects model.

6 The underlying pathogenesis of the relationship merits further study, the authors felt.

7 However, the authors do tentatively offer possible hypotheses: chronically high cortisol levels, which are common in people with depression, could contribute to the onset of diabetes; alternatively, either dysregulation of the immune system or low omega-3 fatty acid intake could lead to both depression and type 2 diabetes.

8 Further research could also test whether the prevention and treatment of depression can lead to a reduced incidence of type 2 diabetes.

Knol MJ, Twisk JW, Beekman AT et al (2006) Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia* **49**(5): 837–45

DIABETES CARE

Increased body water accounts for majority of weight gain with pioglitazone

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

1 Nineteen people with diabetes were randomised to pioglitzone 45 mg once daily or uptitrated glipizide with a median daily dose of 10 mg to examine changes in body water, body composition and haemodynamic parameters.

2 Pioglitazone but not glipizide significantly reduced systemic vascular resistance and increased total body water, the latter accounting for around 75% of the total weight gain.

Basu A, Jensen MD, McCann F et al (2006) Effects of pioglitazone versus glipizide on body fat distribution, body water content, and hemodynamics in type 2 diabetes. *Diabetes Care* **29**(3): 510–4

DIABETES, OBESITY & METABOLISM

Adding pioglitazone to insulin may address poor control

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

1 This double-blind trial (n=690) randomised people whose diabetes was poorly controlled on a stable insulin dose to pioglitazone 30 or 45 mg once daily for 24 weeks.

2 Significant, dose-dependent improvements were seen in HbA_{1c}, fasting plasma glucose and components of the lipid profile; in addition, the authors reported a generally good tolerability profile.

Davidson JA, Perez A, Zhang J; The Pioglitazone 343 Study Group (2006) Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes. *Diabetes, Obesity & Metabolism* **8**(2): 164–74

DIABETES CARE

No effect found with chromium in people with insulin-treated type 2 diabetes

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

1 There are reports of chromium treatment improving insulin sensitivity and glycaemic control in certain groups of people with type 2 diabetes.

2 This study tested for an effect on glycaemic control in insulin-dependent Westerners with type 2 diabetes and with a body mass index >25 kg/m^2.

3 The protocol involved a 6-month, double-blind randomisation to placebo, chromium 500 µg per day or chromium 1000 µg per day (chromium picolinate was used); 17, 14 and 15 people from the respective groups were included in the analysis.

4 The primary study endpoint was change in HbA_{1c}, while secondary endpoints were changes in blood pressure, lipids, body mass index and insulin requirements.

5 At study end, no significant differences were found between the groups.

6 In a post hoc analysis of correlations after 6 months between differences in chromium concentrations and differences in the parameters investigated, increased chromium levels were found to be significantly related to decreased total cholesterol, LDL-cholesterol and the ratio of total to HDL-cholesterol.

7 Given that this was found in a post hoc analysis, the authors concluded nothing more than that it is of interest.

Kleefstra N, Houweling ST, Jansman FG et al (2006) Chromium treatment has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese Western population. *Diabetes Care* **29**(3): 521–5