LANCET

# Intensive intervention only slightly reduces CV risk in T2D

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

1 Intensive treatment of cardiovascular (CV) risk factors, such as blood pressure, cholesterol and $HbA_{1c}$, can halve mortality and CV events in people with established T2D.

2 The study aim was to determine whether intensive multifactorial treatment initiated early after diagnosis would improve outcomes in people with T2D.

3 In the Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care, 343 general practices were randomly assigned to either routine care ($n$=1377) or early, intensive, multifactorial treatment ($n$=1678) for people with T2D.

4 All participants were aged 40–69 years; the primary endpoint was first CV event or end of the 5-year assessment.

5 In total, 196 people died during the study: 60 from CV events, 97 from cancer and 39 from other causes.

6 The incidence of first CV event was 7.2% (13.5 per 1000 person-years) in the intensive treatment group and 8.5% (15.9 per 1000 person-years) in the control group; for all-cause mortality this was 6.2% (11.6 per 1000 person-years) and 6.7% (12.5 per 1000 person-years), respectively.

7 The authors found that although intensive treatment slightly reduced the incidence of CV events at 5 years, this did not reach significance.

Griffin SJ, Borch-Johnsen K, Davies MJ et al (2011) Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe). *Lancet* **378**: 156–67

## The pluses and minuses of ADDITION-Europe

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At first sight, ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen Detected Diabetes in Primary Care)-Europe was a negative study since overall cardiovascular benefit from intensive treatment compared with routine care was not significantly better (Griffin et al, 2011; summarised alongside), even though some (perhaps many) may argue the results trended in the right direction. In reality, and as we have noted before (Preiss and Sattar, 2011), the emergence of evidence-based standards of routine diabetes care during the course of ADDITION-Europe, especially for lipid-lowering and antihypertensive therapies, negated potential benefits of intensive therapy in the study. Furthermore, $HbA_{1c}$ levels and reductions in smoking were similar between treatment groups, and reductions in blood pressure and LDL-cholesterol levels were only marginally more pronounced in the intensive treatment group than in the control group.

> **"... does the overall negative ADDITION-Europe result hide some potential positives?"**

Some may argue that the results may have been more promising with longer follow-up but, as with many other clinical trials in diabetes (Preiss et al, 2011), event rates were only half those expected in the initial power calculation. In this respect, it is clear that overall mortality has declined in people with diabetes (Emerging Risk Factors Collaboration, 2011) and that event rates in people without cardiovascular disease or microalbuminuria are especially low (Preiss et al, 2011), with the result that trials now need substantially more participants than in past decades. It is also clear that diabetes at or close to the point of diagnosis is by no means a cardiovascular risk equivalent (Wannamethee et al, 2011).

But does the overall negative ADDITION-Europe result hide some potential positives? Perhaps the most valuable data stem from the levels of established cardiovascular risk factors achieved at the end of the trial in participants in the routine care group. Treatment of these people according to standard guidelines led to a 12 mmHg reduction in systolic blood pressure and 1.2 mmol/L reduction in LDL-cholesterol. These observations suggest that substantial improvements in blood pressure and cholesterol can be achieved in routine care with simple attention to current guidelines, and that, as a result, vascular event rates are significantly improved, perhaps even beyond expectations.

In addition, and of potential clinical importance, neither BMI nor $HbA_{1c}$ levels (median at baseline, 6.6% [49 mmol/mol]) deteriorated during the 5.3-year follow-up, notable observations that suggest that if diabetes is picked up earlier, then people may be more able or willing to adopt healthier lifestyles to prevent weight gain and glycaemic deterioration. While this suggestion is speculative and requires further research, other key questions going forward are whether a meaningful reduction in the lead time between diabetes onset and clinical diagnosis can be achieved by implementation of simpler diagnostic criteria (i.e. $HbA_{1c}$) and, if so, to what extent this change might further reduce cardiovascular and mortality risks in people with diabetes. In short, ADDITION-Europe represents a negative study, but with positive messages.

Emerging Risk Factors Collaboration (2011) Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* **364**: 829–41

Preiss D, Sattar N (2011) The case for diabetes screening: ADDITION-Europe. *Lancet* **378**: 106–8

Preiss D, Sattar N, McMurray JJ (2011) A systematic review of event rates in clinical trials in diabetes mellitus: the importance of quantifying baseline cardiovascular disease history and proteinuria and implications for clinical trial design. *Am Heart J* **161**: 210–19

Wannamethee SG, Shaper AG, Whincup PH et al (2011) Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. *Arch Intern Med* **171**: 404–10

*"Sleeping less increases diabetes risk in those with a familial predisposition."*

## DIABETES CARE

# Short sleep affects insulin resistance

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

1 As chronic sleep insufficiency may affect glucose regulation, the authors sought to determine whether this would aggravate insulin secretion and action in people at high risk for T2D.

2 Twenty-one healthy men and 26 healthy women who had at least one parent with T2D were recruited to the study.

3 Participants were asked to complete an average of 13 days' sleep monitoring by wrist actigraphy at home and one night of laboratory polysomnography; diabetes risk was determined by oral glucose tolerance test.

4 In total, 40% of participants had curtailed sleep of <6 hours.

5 A significant link between curtailed sleep and increased insulin resistance and secretion was shown.

6 The authors concluded that sleeping less increases diabetes risk in those with a familial predisposition.

Darukhanavala A, Booth JN, Bromley L et al (2011) Changes in insulin secretion and action in adults with familial risk for type 2 diabetes who curtail their sleep. *Diabetes Care* **34**: 2259–64

## DIABETES, OBESITY AND METABOLISM

# Pioglitazone affects HDL-cholesterol to reduce CV risk

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

1 In the PROactive study, 5238 people with T2D and macrovascular disease were randomised to pioglitazone 45 mg or placebo to determine whether intensive treatment would reduce their cardiovascular (CV) risk.

2 Results showed that pioglitazone significantly reduced CV risk and improved $HbA_{1c}$ level, systolic blood pressure, triglycerides and HDL-cholesterol relative to placebo.

3 In this study, the authors determined to what extent these parameters contributed to the reduced CV risk in the PROactive participants.

4 Although pioglitazone treatment reduced participants' $HbA_{1c}$, an increase in HDL-cholesterol was the only treatment-induced change that predicted outcome ($P<0.0001$).

5 The effect of pioglitazone on HDL-cholesterol was found to be the most probable determinant of the drug's efficacy to reduce CV risk.

Ferrannini E, Betteridge DJ, Dormandy JA et al (2011) High-density lipoprotein-cholesterol and not $HbA_{1c}$ was directly related to cardiovascular outcome in PROactive. *Diabetes Obes Metab* **13**: 759–64

## EUROPEAN JOURNAL OF ENDOCRINOLOGY

# Usual risk factors predict diabetes in acromegaly

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

1 Acromegaly is a condition caused by the hyper-secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1).

2 The aim of this study was to determine the prevalence of diabetes in 519 people with acromegaly recorded in the French Acromegaly Registry.

3 In total, 22.3% of the people in the registry had diabetes.

4 Age, BMI and hypertension were significant risk factors for T2D for people with acromegaly, which is similar for the general population.

5 The authors concluded that the levels of GH and IGF-1 were not statistically different in those with and without diabetes, and were not predictive of diabetes.

Fieffe S, Morange I, Petrossians P et al (2011) Diabetes in acromegaly, prevalence, risk factors and evolution: data from the French Acromegaly Registry. *Eur J Endocrinol* **164**: 877–84

## DIABETOLOGIA

# Serum cystatin C is associated with T2D

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

1 Previous studies have shown an association between serum cystatin C levels and insulin resistance, obesity and hypertension, which are all risk factors for the development of T2D.

2 The authors sought to determine the relationship between serum cystatin C levels and the incidence of T2D over 15 years.

3 The study comprised 3472 participants in the Beaver Dam Eye Study without diabetes at baseline, followed up for 15 years.

4 Diabetes, serum cystatin C levels and risk factors for T2D were determined at baseline and at 5, 10 and 15 years.

5 Associations between serum cystatin C levels and other risk factors and the development of incident T2D were assessed using the discrete time extension of the proportional hazards model.

6 The 15-year cumulative incidence of T2D was estimated to be 9.6%; with age and sex adjustments, people with higher levels of serum cystatin C were more likely to die ($P<0.05$).

7 After further adjustments for age, sex, BMI, smoking status, $HbA_{1c}$, proteinuria, chronic kidney disease (CKD) and hypertension, serum cystatin C level at baseline was associated with the risk of T2D over 15 years (odds ratio per log of cystatin C unit, 2.19; 95% confidence interval, 1.02–4.68).

8 Serum cystatin C levels were associated with incident T2D independently of confounding risk factors.

9 The authors concluded that studies are needed to determine whether serum cystatin C level is a more specific marker than serum creatinine for early stages of CKD, a risk factor for T2D.

Sahakyan K, Lee KE, Shankar A, Klein R (2011) Serum cystatin C and the incidence of type 2 diabetes mellitus. *Diabetologia* **54**: 1335–40

DIABETIC MEDICINE

## FPG and $HbA_{1c}$ similarly predict incident diabetes

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

1 The authors sought to determine the predictive values of fasting plasma glucose (FPG) and $HbA_{1c}$ for incident T2D in three cohorts.

2 AusDiab (Australian Diabetes, Obesity and Lifestyle Study) comprised 6025 participants, the Danish Inter99 study comprised 4703 participants, and the DESIR (French Data on the Epidemiology of the Insulin Resistant Syndrome) study comprised 3784 participants.

3 All participants had FPG <7.0 mmol/L and $HbA_{1c}$ level <6.5% (<48 mmol/mol) and were not treated for diabetes at inclusion; diabetes and/or treatment for diabetes was defined as FPG ≥7.0 mmol/L or $HbA_{1c}$ ≥6.5% (≥48 mmol/mol).

4 Participants in the AusDiab and Inter99 studies were followed-up for 5 years; those in the DESIR study were followed up for 6 years.

5 The prevalence of T2D screened by FPG differed by a factor of two between cohorts; for the prevalence of T2D screened by $HbA_{1c}$ there was a six-fold difference between Inter99, with a prevalence of 6.8%, and both AusDiab and DESIR, with prevalences of 1.2%.

6 In AusDiab, incident diabetes defined by FPG was more frequent than that defined by $HbA_{1c}$, for Inter99 the reverse applied and for DESIR there was no difference.

7 FPG and $HbA_{1c}$ were concluded to be good predictors of incident diabetes, although there are variations in $HbA_{1c}$ distributions between studies.

Soulimane S, Simon D, Shaw JE et al (2011) Comparing incident diabetes as defined by fasting plasma glucose or by $HbA_{1c}$. The AusDiab, Inter99 and DESIR studies. *Diabet Med* **28**: 1311–8

DIABETIC MEDICINE

## Diabetes risk not reduced by web-based programme

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

1 The authors sought to assess the effectiveness of lifestyle intervention on diabetes risk in 49 women with a recent history of gestational diabetes.

2 Participants were randomised to a control group with no intervention or to a personalised, web-based pedometer programme for 13 weeks.

3 Outcome measures included change in fasting plasma glucose and 2-hour glucose levels on a 75-g oral glucose tolerance test between baseline and 13-week follow-up.

4 Women randomised to the pedometer programme did not have significant changes in any parameter compared with the control group.

5 It was concluded that web-based programmes should be supplemented with additional measures to reduce diabetes risk.

Kim C, Draska M, Hess ML et al (2011) A web-based pedometer programme in women with a recent history of gestational diabetes. *Diabet Med* [Epub ahead of print]

DIABETES CARE

## Metabolic syndrome underpredicts risk in African people

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

1 The metabolic syndrome (MS) is designed to identify risk for cardiovascular disease and T2D; however, its efficacy in people of African descent is uncertain.

2 Cross-sectional analyses were performed on 95 men (39 Africans vs 56 African Americans) to determine if the group with higher metabolic risk, defined by blood pressure, glycaemia and visceral adiposity, also had a higher prevalence of MS; MS was determined by the presence of three of five factors (central obesity, hypertriglyceridemia, low HDL-cholesterol, hypertension, fasting hyperglycaemia).

3 The prevalence of MS was similar in Africans and African Americans (10% vs 13%; $P$=0.74); however, Africans had a worse metabolic profile than African Americans.

4 The authors concluded that MS may underpredict metabolic risk in African people.

Ukegbu UJ, Castillo DC, Knight MG et al (2011) Metabolic syndrome does not detect metabolic risk in African men living in the US. *Diabetes Care* **34**: 2297–9

DIABETES CARE

## Baseline parameters cannot predict need for insulin in GDM

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

1 Some women with gestational diabetes (GD) require antenatal insulin treatment (AIT) to lower the risk of perinatal complications.

2 To identify those women with GD who will require AIT, data from 3009 women were studied.

3 Univariate analysis was performed on maternal historical and antenatal risk factors to determine links with AIT.

4 In total, 1535 women (51%) required AIT; ethnicity, gestation at diagnosis, $HbA_{1c}$, fasting and 60-minute oral glucose tolerance test, BMI and a family history of diabetes were predictive of the need for AIT. However, only 9% of the attributable risk for AIT was explained by these clinical factors.

5 The authors concluded that baseline parameters alone cannot usefully predict the need for AIT in GD.

Pertot T, Molyneaux L, Tan K et al (2011) Can common clinical parameters be used to identify patients who will need insulin treatment in gestational diabetes mellitus? *Diabetes Care* **34**: 2214–16

*"As the prevalence of diabetes in adults is increasing, it is important to identify those with diabetes to start treatment, and those at higher risk to initiate preventive interventions."*