## More evidence to support a potential protective effect of metformin on cancer risk

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Metformin is widely accepted as the first choice oral antidiabetes agent, because, in addition to lowering blood glucose levels, it lowers vascular event risk in people with diabetes (Holman et al, 2008). It is also relatively favourable in terms of weight change, does not cause hypoglycaemia, is relatively cheap and has a good safety record over a long period of time (Bailey and Turner, 1996). If these characteristics were not sufficiently impressive, recent reports that metformin may also lower cancer risk in people with diabetes have been noted with interest. The first report of such a potential benefit came from analyses of the DARTS (Diabetes Audit and Research in Tayside Study) cohort, a study that also suggested a dose-related reduced cancer risk with metformin (Evans et al, 2005). Subsequent reports from other cohorts also demonstrated lower cancer mortality with metformin when compared with a sulphonylurea or insulin (Bowker et al, 2006), as well as better outcomes following chemotherapy for breast cancer in women with type 2 diabetes on metformin versus those not on metformin (Jiralerspong et al, 2009).

In light of these findings, the study by Landman et al (2010; summarised alongside) adds another piece of evidence to support a potentially beneficial effect of metformin on cancer. The investigators followed 1353 people over a median of 9.6 years and reported two main findings; first, in line with a wealth of data, people with type 2 diabetes have a 47% higher mortality ratio from cancer compared with the general population, and second, among people with diabetes, cancer mortality was 57% lower in metformin recipients compared with those not taking metformin. Of further interest, this study also reported a dose response association, with larger doses associated with lower cancer risk. This study has a number of strengths, including the ability to adjust for potential confounders such as gender, BMI, adiposity, smoking, diabetes duration, insulin therapy and sulphonylurea use. Furthermore, the investigators showed that the results were similar after exclusion of mortality in the first 3 years, an analysis which attempts to overcome undiagnosed cancer at study onset. In this way, Landman et al (2010) provide some of the strongest evidence to support the hypothesis, which is also supported by potential mechanisms: lowering insulin resistance and thus insulin levels via metformin could be important since hyperinsulinaemia may promote carcinogenesis (van der Burg et al, 1988); and, metformin appears to influence LKB1 (and via this, activate AMP-kinase), a well-known tumour suppressor (Ben Sahra et al, 2008).

While relevant reports appear consistent, and credible mechanistic explanations for a favourable effect of metformin on cancer risk exist, the totality of the data should be viewed as hypothesis generating rather than definitive. The possibility that residual confounding, whereby unmeasured differences between metformin recipients and those not taking or prescribed metformin, leads to erroneous results, must always be borne in mind.

Even the evidence of an apparent dose–response association of metformin with cancer risk cannot confirm a causal association, since those on higher doses may seek more doctor attention, or be more health seeking, or differ in some other way. In reality, the only way to confirm a causal association linking metformin to lower cancer risk is via a randomised controlled trial, and in this case, ideally conducted in people without diabetes (or those at high risk) to avoid confounding by other diabetes therapies. In the meantime, metformin will continue to be the first-line therapy for diabetes, and only future trials will ascertain whether we can also add "reduced cancer risk" to its impressive list of attributes.

Bailey CJ, Turner RC (1996) *N Engl J Med* **334**: 574–9

Ben Sahra I, Laurent K, Loubat A et al (2008) *Oncogene* **27**: 3576–86

Bowker SL, Majumdar SR, Veugelers P, Johnson JA (2006) *Diabetes Care* **29**: 254–8

Evans JM, Donnelly LA, Emslie-Smith AM et al (2005) *BMJ* **330**: 1304–5

Holman RR, Paul SK, Bethel MA et al (2008) *N Engl J Med* **359**: 1577–89

Jiralerspong S, Palla SL, Giordano SH et al (2009) *J Clin Oncol* **27**: 3297–302

van der Burg B, Rutteman GR, Blankenstein MA et al (1988) *J Cell Physiol* **134**: 101–8

DIABETES CARE

## Metformin protective for cancer mortality

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

1 Previous studies have pointed to an association between metformin treatment in type 2 diabetes and reduced cancer mortality. This prospective cohort study looked at the association between metformin treatment and cancer mortality.

2 A total of 1353 people with type 2 diabetes were enrolled in the ZODIAC (Zwolle Outpatient Diabetes project Integrating Available Care) study in 1998 and 1999 in the Netherlands.

3 Vital status and cancer mortality were evaluated in January 2009 using standardised mortality ratios (SMRs). A Cox proportional hazards model was used to evaluate metformin use and cancer mortality.

4 Participants were, on average, 68 years of age at baseline and mean $HbA_{1c}$ level was 7.5% (58 mmol/mol). The median follow-up time was 9.6 years.

5 Out of 570 deaths, 122 were as a result of cancer. The SMR for cancer for people with diabetes was 1.47 (95% confidence interval [CI], 1.22–1.76).

6 The metformin-treated versus non-metformin treated adjusted hazard ratio (HR) for cancer mortality was 0.43 (95% CI, 0.23–0.80) and for every 1 g increase in metformin the HR was 0.58 (95% CI, 0.36–0.93).

7 In this group of people with diabetes who were already at increased risk of cancer, metformin use was associated with a lower cancer mortality rate suggesting that the drug has a protective effect.

Landman GW, Kleefstra N, van Hateren KJ et al (2010) Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care* **33**: 322–6

DIABETIC MEDICINE

## Reliable care delivery under QOF contract

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

1 The authors of this study aimed to measure the variation of the quality of risk factor measurement across different practices by analysing data recorded through the Quality and Outcomes Framework (QOF) in the Tayside region.

2 The authors also looked at whether there were inequalities of care between different groups of people with type 2 diabetes (divided by socio-economic status, gender and age).

3 Data for 10 191 people with type 2 diabetes were analysed by multi-level regression. Included in the analysis were data for the recording of four quality measures: $HbA_{1c}$, blood pressure (BP), cholesterol and smoking status within the past 12 months. Achievement of recommended QOF indicators was also included.

4 A total of 95% of all recommended processes were delivered and 88.3% of the cohort had all four measures taken.

5 Half of the cohort achieved intermediate indicators ($HbA_{1c}$ ≤7.4% [≤57 mmol/mol]; BP <140/80 mmHg, cholesterol ≤5.0 mmol/L; not smoking). Only 16% of the cohort achieved all four targets.

6 For people under 55 years of age, process and outcome of care was found to be consistently worse, and women were less likely to achieve cholesterol targets. No associations with socio-economic status were found, with the exception of smoking.

7 Process of care is reliable under QOF, but the consistent achievement of intermediate indicators is less reliable. Although socio-economic variations in diabetes care delivery were not present, poor outcomes in young participants were found to be a significant concern.

Guthrie B, Emslie-Smith A, Morris AD (2010) Which people with type 2 diabetes achieve good control of intermediate outcomes? Population database study in a UK region. *Diabet Med* **26**: 1269–76

DIABETES CARE

## $HbA_{1c}$ ≥6.5% poorer at T2D diagnosis than other methods

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

1 Performance characteristics of diagnosis using an $HbA_{1c}$ cut-off of ≥6.5% (≥48 mmol/mol) were assessed in this retrospective analysis of the Insulin Resistance Atherosclerosis Study (IRAS).

2 Diagnosis using $HbA_{1c}$ was compared with the 1999 World Health Organization (WHO) definition and the 2003 American Diabetes Association (ADA) definition based on fasting plasma glucose (FPG) levels only.

3 Out of 855 participants, 44 were diagnosed with T2D using $HbA_{1c}$, 132 using WHO and 61 using ADA.

4 Median $HbA_{1c}$ was 5.9% (41 mmol/mol) for those diagnosed using WHO but 6.6% (49 mmol/mol) for those diagnosed using FPG.

5 Diagnosis of T2D using $HbA_{1c}$ ≥6.5% (≥48 mmol/mol) was found to identify fewer individuals than other methods. Further research should identify the impact of this on preventing long-term complications.

Lorenzo C, Haffner SM (2010) Performance characteristics of the new definition of diabetes: the insulin resistance atherosclerosis study. *Diabetes Care* **33**: 335–7

DIABETES, OBESITY AND METABOLISM

## Liraglutide reduces fat tissue

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

1 These two trials investigated liraglutide monotherapy or added to metformin in people with T2D with respect to body composition.

2 Participants were randomised to receive liragltide 1.8, 1.2 or 0.6 mg/day, or glimepiride 4 mg/day, all in combination with metformin 1.5–2 g/day in the LEAD-2 (Liraglutide Effect and Action in Diabetes-2) trial.

3 In LEAD-3, participants received liraglutide 1.8, 1.2 mg/day or glimepiride 8 mg/day.

4 In LEAD-2, liraglutide 1.2 and 1.8 mg/day plus metformin reduced body fat percentage compared with glimepiride plus metformin ($P$<0.05).

5 In LEAD-3, fat mass and fat percentage with liraglutide monotherapy were significantly different compared with increases with glimepiride ($P$<0.01).

6 Compared with glimepiride, liraglutide was found to reduce fat mass and fat percentage.

Jendle J, Nauck MA, Matthews DR et al (2009) Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. *Diabetes Obes Metab* **11**: 1163–72

DIABETES CARE

## Variation in risk for T2D by family history

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

1 Familial risks for T2D were assessed in a Swedish cohort by the type and number of affected family members, including half-siblings, adoptees and spouses.

2 For offspring with T2D whose family members had been hopitalised due to T2D over the age of 39 years, standard incidence ratios were calculated and compared with those without an affected family member.

3 People who had at least two siblings affected by T2D had the highest relative risk (>30). By contrast, the relative risk was around 5-fold from two affected parents.

4 This study highlights that the risk of T2D varies according to type and number of affected family members.

Hemminki K, Li X, Sundquist K, Sundquist J (2009) Familial risks for type 2 diabetes in Sweden. *Diabetes Care* **33**: 293–7

*"Diagnosis using $HbA_{1c}$ ≥6.5% (≥48 mmol/mol) identifies fewer individuals than other methods. Further research should identify the impact of this on preventing long-term complications."*