Diabetes journals

DIABETES RESEARCH AND CLINICAL PRACTICE

Insulin lowers risk of future cardiovascular events

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

1 Risk of cardiovascular disease (CVD) events is increased in people with diabetes. This study aimed to identify the association between incidence of CVD events and treatment with insulin in individuals with type 2 diabetes.

2 Data from a total of 342 692 individuals participating in a managed-care plan in the USA were included in this retrospective study. Analysis included details of each person's treatment plan, and the date of the first CVD event for each individual, if one occurred.

3 Of a total of 14 167 people receiving treatment with insulin, 19 per 1000 patient-years studied experienced a CVD event. However, in the non-insulin group of 328 077 individuals, CVD events were experienced by 22 per 1000 patient-years studied.

4 The authors adjusted these figures for several risk factors and comorbidities, such as age, adjunctive therapies and gender, and found that the odds ratio for a CVD event was 0.66 in patients receiving treatment with insulin, compared with those not receiving insulin. The odds ratio was 25% lower in people >65 years of age, and 42% lower in individuals aged between 31 and 45 years.

5 The authors conclude that, compared with other treatments, people with type 2 diabetes receiving insulin therapy have a reduced risk of CVD events.

Engel-Nitz NM, Martin S, Sun P et al (2008) Cardiovascular events and insulin therapy: a retrospective cohort analysis. *Diabetes Research and Clinical Practice* **81**: 97–104

Is insulin therapy of benefit with respect to cardiovascular disease outcomes in people with type 2 diabetes?

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Type 2 diabetes is a complex and progressive condition, with an increased risk of vascular complications. Cardiovascular disease (CVD) accounts for over 65% of diabetes-related mortality. Good blood glucose control is associated with reduced microvascular complications, but its impact on large-vessel disease remains unclear following the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study (ACCORD Study Group, 2008). Furthermore, the extent to which specific therapy regimens for blood glucose control influence cardiovascular risk is not clear.

Insulin replacement therapy is usually introduced when oral hypoglycaemic therapies have failed to maintain adequate glucose control. The cardiovascular effects of both oral therapy and insulin replacement are unclear, and individual therapy regimens may have different effects on the risk of macrovascular events.

Various studies have shown a decrease in cardiovascular risk associated with insulin use, while other studies have suggested that insulin use was not superior with respect to outcome compared with other therapies. The association of insulin use and CVD events in clinical practice is, therefore, not fully understood.

The study by Engel-Nitz et al (summarised alongside) was a retrospective cohort-based observational study, with a primary objective being to assess the impact of insulin therapy, in addition to other risk factors, on the risk of CVD events in people with type 2 diabetes. Data from 342692 individuals from a US managed-care plan database were analysed, with a date of first CVD event being defined as the index date. CVD event rates were calculated, with the odds of a CVD event being compared between individuals with and without insulin use; analysed events including stroke, myocardial infarction, and other cardio- or cerebrovascular events.

Among the insulin-treated group, 19 people per 1000 patient-years experienced a CVD event, compared with 22 individuals per 1000 patient years in the group not using insulin. Adjusting for risk factors and comorbidities, the odds ratio of CVD events for the insulin-treated group compared with the group not treated with insulin was 0.66, ranging from 25% lower in those aged 65 years or over, to 42% lower for those aged from 31–65 years.

This real-world study, therefore, suggests that, in spite of confounding factors (in particular a longer duration of diabetes) in the insulin-treated group, insulin therapy was associated with improved outcomes.

These data provide no mechanistic insight into the potential effects of insulin on CVD risk, and one possible explanation may be that, in this study, those receiving insulin were more advanced in the natural history of the condition, and therefore less responsive to the therapeutic benefits of oral agents.

There are limitations associated with this type of analysis, in particular the retrospective and non-randomised nature of the study, along with the potential to introduce selection bias. The issue of selection bias was controlled for as much as possible by including indicators of comorbid illnesses within the analysis. In addition, penetration of cardioprotective medications was similar in both the insulin and non-insulin treated groups.

In summary, this large population-based study provides a suggestion that insulin therapy is of benefit with respect to CVD outcomes, but clearly this concept needs further evaluation in large randomised controlled trials.

ACCORD Study Group (2008) Effects of intensive glucose lowering in type 2 diabetes. *NEJM* **358**: 2545–59

"Additional treatment with colesevelam improves blood glucose control and lowers LDL-cholesterol levels in people with type 2 diabetes."

DIABETES CARE

Colesevelam for blood glucose control in people on sulphonylurea-based treatment

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

1 Hyperglycaemia can increase the risk of microvascular complications in patients with type 2 diabetes; this study aimed to investigate the effect of treatment with colesevelam, an LDL-cholesterol lowering agent, on blood glucose control.

2 This randomised, double-blind, controlled trial included people with type 2 diabetes who had poor blood glucose control and were receiving treatment with a sulphonylurea, either alone or in combination with another agent. A total of 461 participants were randomly allocated to receive additional therapy with colesevelam or placebo.

3 The authors measured the effect of additional therapy on glycaemia after 26 weeks; a –0.32% least squares mean change in HbA_{1c} levels was observed in the colesevelam group, compared with a +0.23% change in the placebo group (treatment difference –0.54%, $P<0.001$).

4 A further –16.1% change in LDL-cholesterol was observed in the colesevelam group, compared with +0.6% in placebo (treatment difference –16.7%, $P<0.001$).

5 The authors also observed significant reductions in levels of fasting plasma glucose, fructosamine and total cholesterol in individuals treated with colesevelam, compared with placebo.

6 In conclusion, additional treatment with colesevelam improves blood glucose control and lowers LDL-cholesterol levels in people with type 2 diabetes.

Fonseca VA, Rosenstock J, Wang AC et al (2008) Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care* **31**: 1479–84

DIABETES CARE

High percentage of people with metabolic syndrome at high risk of CHD

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

1 This study investigated the range of risk for coronary heart disease (CHD) in a large patient population with metabolic syndrome.

2 A total of 4293 adults with metabolic syndrome were included in this analysis; risk status was defined as low, moderate, moderately high and high-risk, based on the Framingham risk score algorithm of probability of CHD in 10 years.

3 Overall, a total of 38.5% of participants were found to be at a low risk of CHD, 8.5% were at moderate risk, 15.8% were at moderately high, and 37.3% were at high risk of CHD. These results indicate a need for assessment of CHD factors in people with the metabolic syndrome in order to provide appropriate cardioprotective treatment.

Hoang KC, Ghandehari H, Lopez VA et al (2008) Global coronary heart disease risk assessment of individuals with the metabolic syndrome in the U.S. *Diabetes Care* **31**: 1405–9

DIABETOLOGIA

High but modifiable risk of CHD in people with type 2 diabetes

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

1 The ADDITION (Anglo–Danish–Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care) aimed to investigate the efficacy of intensive, multifactorial treatment on cardiovascular disease-related morbidity and mortality in people with type 2 diabetes.

2 This analysis included 3057 individuals with diabetes from the Netherlands, UK and Denmark; all were screened for diabetes and assessed for risk of coronary heart disease (CHD).

3 The risk of developing CHD within 10 years was 11% in women, and 21% in men. Differences in risk factors varied between countries, resulting from the different diagnostic and preventative treatment strategies utilised.

4 High blood pressure and cholesterol levels were observed in 73% and 70% of participants, respectively; 91% of those with cholesterol levels >5.0mmol/L were not receiving lipid-lowering treatment.

Sandbaek A, Griffin SJ, Rutten G et al (2008) Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. *Diabetologia* **51**: 1127–34

DIABETES CARE

Effect of lowering hypertension and cholesterol offset by diabetes in CKD

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

1 This study aimed to identify the effect of increasing prevalence of independent risk factors, such as smoking, obesity, hypertension, cholesterol and diabetes, on the increasing incidence of chronic kidney disease (CKD) in a US national population.

2 Data analysis showed that, although prevalence ratios for hypertension and high cholesterol decreased during the study period ($P=0.005$ and $P=0.028$, respectively), prevalence ratios for the incidence of diabetes and undiagnosed diabetes remained the same.

3 The authors conclude that the positive effect on risk of CKD from improvements in cardiovascular risk factors are offset by the incidence of diabetes, whether diagnosed or not.

Fox CS, Muntner P (2008) Trends in diabetes, high cholesterol, and hypertension in chronic kidney disease among U.S. adults: 1988-1994 to 1999-2004. *Diabetes Care* **31**: 1337–42

DIABETES RESEARCH AND CLINICAL PRACTICE

Age guideline for preventative statin therapy for Asian–Indian people with diabetes

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

1 Asian–Indian people with diabetes are at a high risk of coronary heart disease (CHD); this study aimed to determine specific age thresholds for increased risk of CHD, in order to develop guidelines for preventative CHD treatment with statins.

2 A total of 1087 patients with diabetes participated in this study, which was a cross-sectional analysis of individuals participating in the Chennai Urban Rural Epidemiological Studies trial.

3 Risk of CHD was assessed in all individuals, and association of CHD risk and age, and the age threshold for increased risk of CHD were determined using the line of best fit.

4 The researchers found that age was a strong indicator of CHD risk; the threshold from low- to moderate-risk of CHD was found to be 37 years of age in men, and age 50 years in women.

5 Further analysis showed that the sensitivity of these age thresholds for CHD risk was 98.7% in men and 87.1% in women.

6 These results support the prescription of preventative treatment with statins in women with diabetes over the age of 50, and men with diabetes over the age of 37.

Idris I, Deepa R, Fernando DJ, Mohan V (2008) Relation between age and coronary heart disease (CHD) risk in Asian Indian patients with diabetes: A cross-sectional and prospective cohort study. *Diabetes Research and Clinical Practice* **81**: 243–9

DIABETES CARE

Increased risk of CVD in women with gestational diabetes

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

1 This study investigated the effect of gestational diabetes on increased risk of subsequent cardiovascular disease (CVD). Data from women with gestational diabetes who had a live birth were matched with those of controls, and the incidence of CVD and future diagnosis of type 2 diabetes was compared between groups.

2 A total of 8191 women with gestational diabetes were included in this study, and median follow-up was 11.5 years.

3 Overall, the hazard ratio for incidence of CVD events was found to be 1.71 (95% CI: 1.08–2.69); however, the hazard ratio decreased to 1.31 upon adjustment for diagnosis with type 2 diabetes.

4 The authors suggest that much of the increased CVD risk in women with gestational diabetes was due to the subsequent development of type 2 diabetes.

Shah BR et al (2008) Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. *Diabetes Care* **31**: 1668–9

DIABETES CARE

Combination therapy increases overall risk of CVD-related mortality and hospitalisation

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

1 The effect of combination therapy with metformin and sulphonylurea on the incidence of cardiovascular disease (CVD) in people with type 2 diabetes is not known.

2 This meta-analysis compared data from observational studies of metformin–sulphonylurea combination treatment versus diet, metformin or sulphonylurea alone for type 2 diabetes, and calculated the adjusted relative risk of CVD or mortality or both.

3 For mortality due to any cause, the pooled relative risk ratios for people with type 2 diabetes receiving treatment with combination therapy was 1.19; for CVD-related hospitalisation or mortality, the relative risk ratios for these individuals were 1.29 and 1.43, respectively.

4 Combination therapy increased CVD risk, but with no effect on CVD-related mortality or overall mortality.

Rao AD, Kuhadiya N, Reynolds K, Fonseca VA (2008) Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. *Diabetes Care* **31**: 1672–8

DIABETES CARE

ACE inhibitors for left ventricular hypertrophy in diabetes

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

1 Risk of cardiovascular events is increased in people with type 2 diabetes who have left ventricular hypertrophy (LVH). This study compared the efficacy of treatment with ACE inhibitors compared with other drugs in the prevention of LVH.

2 A total of 816 individuals with hypertension and type 2 diabetes were included in this study, and were randomly assigned to receive either an ACE inhibitor or no-ACE-inhibitor therapy for 3 years.

3 After median follow-up of 36 months, only 13 patients in the ACE inhibitor group (n=423) developed LVH, compared with 31 patients in the no ACE-inhibitor group (n=376, *P*=0.0012).

Ruggenenti P, Iliev I, Costa GM et al (2008) Preventing left ventricular hypertrophy by ACE inhibition in hypertensive patients with type 2 diabetes: a prespecified analysis of the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT). *Diabetes Care* **31**: 1629–34

> *"The researchers found that age was a strong indicator of coronary heart disease (CHD) risk; the threshold from low- to moderate-risk of CHD was found to be 37 years of age in men, and age 50 years in women."*