

■ Items 22–25

A 55-year-old man presents for a routine physical examination. He is very concerned with his on-going weight gain for the past several years and seeks your advice about various options to prevent diabetes and cardiovascular disease. He recalls an uncle who had diabetes and one of his 3 siblings were told of “borderline diabetes” a few years ago. His only medication is simvastatin 20 mg/day prescribed by his primary care physician for “high cholesterol”.

Fasting Plasma Glucose	102 mg/dL
A1C	6.1%
Blood Pressure	126/78 mm Hg
BMI	31.0 kg/m ²

22. Which *one* of the following statements is CORRECT regarding the relationship between obesity and his metabolic risk?
- A. BMI is one of the components of Metabolic Syndrome as defined by the National Cholesterol Education Program, ATP III Panel.
 - B. As many as 30% of obese adults in the U.S. are metabolically healthy.
 - C. Obesity almost always precedes insulin resistance.
 - D. Morbid obesity is defined by BMI greater than 35 kg/m².
23. Which *one* of the following statements is INCORRECT regarding the pathogenesis of insulin resistance and diabetes associated with obesity?
- A. Markers of low grade inflammation are known to be associated with insulin resistance and precede the development of diabetes.
 - B. There is a positive correlation between insulin resistance and circulating levels of pro-inflammatory cytokine TNF-alpha (TNF- α) and a negative correlation with adiponectin.
 - C. Adiponectin is an anti-inflammatory marker, produced by adipose tissue and liver.
 - D. In patients with impaired glucose tolerance, thiazolidinediones may prevent progression to diabetes by 55–75%.
 - E. Liver fat is a better discriminator than visceral fat in defining insulin resistance.

You advise him to see a nutritionist for dietary counseling and engage in an exercise program in an effort to reduce his risk for developing diabetes.

The patient attempts to follow your advice and presents 3 years later. Despite a modest 5 lb. weight loss, he was diagnosed with diabetes a year ago and advised to start metformin 500 mg b.i.d. He has been monitoring his glucose levels at home. His lab results were as follows:

Total Cholesterol	190 mg/dL
HDL-C	38 mg/dL
LDL-C	104 mg/dL
Triglycerides	240 mg/dL
Fasting Glucose	140 mg/dL
Postprandial Glucose	150–190 mg/dL
A1C	7.6%

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Item 29

Answer B

The DCCT-EDIC trial in patients with type 1 diabetes was completed in 1993 after a mean follow-up of 6.5 year. At the end of DCCT, there was a highly significant A1C difference between the intensive and conventional treatment (7.4 vs 9.1%, respectively; $P < 0.01$). However, there were no significant differences in CVD endpoints at that time. These differences were minimal between the two groups during the subsequent 11 year observational follow-up during the EDIC, such that the mean A1C levels during the entire 11 years were 8.0 and 8.2% respectively, and 7.9 and 7.8% at the end of the 11 years. Yet, during the 11 year follow-up, there were 46 total CVD events in 31 patients in the original intensive treatment arm and 98 CVD events in 52 patients in the conventional treatment arm. Overall, there was a significant 42% reduction in any CVD endpoints ($P = 0.02$), and a 57% reduction in major CVD endpoints including, non-fatal MI, stroke, and fatal CVD ($P = 0.02$).

Significant differences between those who had CVD endpoints, compared to those who did not, included total cholesterol and LDL-C, history of smoking, history of parental myocardial infarction, and urinary albumin excretion. However, the effect of intensive therapy and reduction in A1C during the DCCT, remained significant after adjustment for all of these variables.

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Item 30

Answer E

The randomized phase of the UKPDS trial in patients with type 2 diabetes was completed in 1997. At the end of the trial, there were highly significant differences in the microvascular endpoints in the intensive treatment arm (sulfonylurea-insulin), but a marginal, non-significant effect on myocardial infarction and no significant effect on mortality. The majority of these patients were asked to continue follow-up during the post-trial monitoring for 10 years. The between-group differences in A1C levels were lost after the first year. Yet, by the end of the 10-year follow-up, the risk reduction for myocardial infarction (15%, $P = 0.01$) and death from any cause (13%, $P = 0.007$) became significantly different. The significant differences in the microvascular events remained significant. In the smaller metformin-treated cohort, the rates of myocardial infarction and death from any cause were significantly different at the end of the trial, and these differences persisted during the post-trial follow-up (Figure 6).

A subgroup of patients in the UKPDS trial was randomized to a blood pressure intervention strategy of tight versus less tight control. By the end of the trial in 1997, there were significant risk reductions in diabetes-related death (RR 32%, $P = 0.002$), stroke (RR 44%, $P = 0.01$), as well as microvascular endpoints (RR 37%; $P = 0.009$). Most of these patients were followed during post-trial monitoring up to 10 years. The blood pressure differences between the two groups disappeared within 2 years. Of note, none of the risk reductions noted above were maintained, with RR declining to 16%, 23%, and 16% respectively ($P = 0.12$ or higher for each).

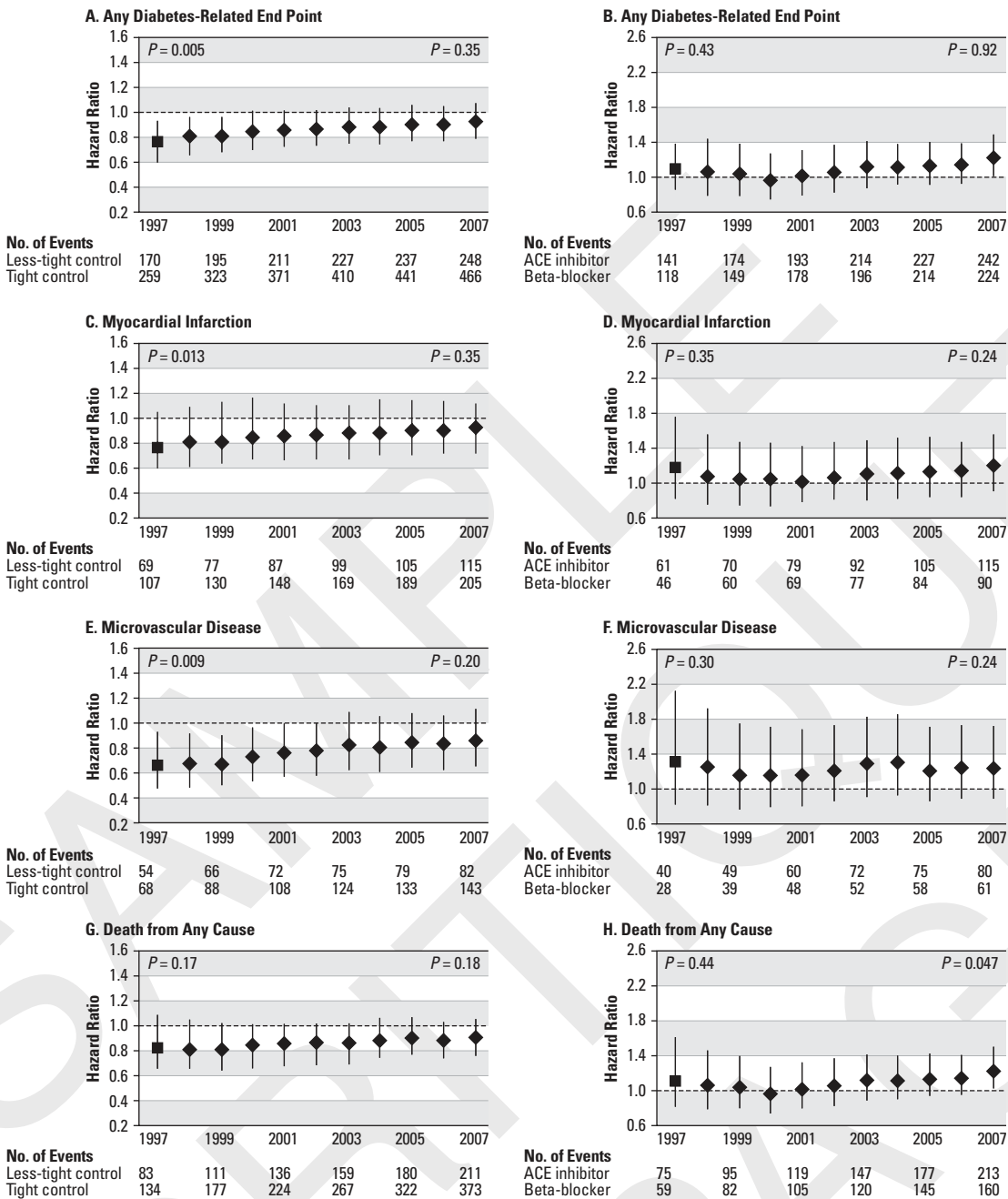


Figure 6. UKPDS Follow-up: Prespecified End Points. 884 of Original 1148 Patients.

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