Improving outcomes for people with diabetes

Outcome trials in diabetes are few and far between, but in 2008 results have been presented from three trials that were designed primarily to determine whether improved blood glucose control could reduce the risk of cardiovascular events in people with type 2 diabetes.

Results from ACCORD, ADVANCE, VADT and UKPDS

The ACCORD (Action to Control Cardiovascular Risk in Diabetes; ACCORD Study Group, 2008), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; ADVANCE Collaborative Group, 2007) and VADT (Veterans Affairs Diabetes Trial; Abraira, 2008) studies all showed a trend toward cardiovascular risk reduction with improved blood glucose control but none achieved statistical significance. The relative risk reductions obtained for the primary cardiovascular composite endpoint in each case were 10% (P=0.16), 6% (P=0.37) and 13% (P=0.12) for differences achieved in HbA_{1c} of 7.5% versus 6.4%, 7.3% versus 6.5% and 8.4% versus 6.9%, respectively.

Although inconclusive, these trends towards reduced cardiovascular risk are in line with the results of the UKPDS (United Kingdom Prospective Diabetes Study) published in 1998, which showed a borderline non-significant 16% (P=0.052) risk reduction for myocardial infarction in the group with intensive blood glucose control, compared with those treated conventionally (UKPDS Group, 1998).

A meta-analysis of these four studies may well achieve statistical significance, but meanwhile, the 10-year UKPDS post-trial monitoring data have demonstrated a "legacy effect" of earlier improved blood glucose control, with risk reductions of 15% (P=0.01) for myocardial infarction, and 13% (P=0.007) for death from any cause (Holman et al, 2008). These emergent benefits reflect the observational data, which suggest that a 14% risk reduction can be obtained for fatal and nonfatal myocardial infarction with a 1% decrement in HbA_{1c} (Stratton et al, 2000).

Overly intensive treatment?

Alarm bells rang, however, when the glucose-lowering arm of ACCORD was discontinued prematurely because of a 22% increased relative risk of death in the intensively treated group (ACCORD Study Group, 2008). This outcome in those treated aggressively, where the aim was to reduce HbA_{1c} levels to below 6% with any or all available antidiabetic therapies, suggests that there may be unexpected hazards related to overly tight glucose control. Concerns have been expressed about chronic exposure to low blood glucose levels and hypoglycaemic episodes in the intensively treated group, or the possible role of particular therapies or specific therapy combinations, but analyses undertaken to date have not identified a plausible explanation for the increased death rate (ACCORD Study Group, 2008). Unlike the newly diagnosed people enrolled in the UKPDS, ACCORD studied people with long-standing diabetes, many of whom already had cardiovascular disease.

It seems, therefore, that we should be cautious about striving unduly for near-normal HbA_{1c} levels in such people, and instead adopt individual treatment targets that take into account their risk of microvascular disease for which the major benefits of improved glucose control have been proven (UKPDS Group, 1998) and endorsed by diabetes management guidelines worldwide (Home, 2008).

Managing cardiovascular risk

Cardiovascular risk management is a major priority for people with diabetes given that

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the majority will die from a vascular-related cause. The benefits of improved blood pressure control, cholesterol lowering, smoking cessation and, in terms of secondary prevention, aspirin therapy are well accepted, but until now the role of glucose lowering has been equivocal. Given the new trial results that have become available this year, the importance of glucose-lowering as an additional risk reduction modality seems finally to have been established. Good glycaemic control is essential in any case to minimise the risk of microvascular complications (UKPDS Group, 1998), but is of even greater relevance where measures to reduce cardiovascular risk successfully extend life expectancy.

Maintaining glycaemic control

Good glycaemic control should be the aim from the time diabetes is first diagnosed, with doses increased or therapies added sequentially whenever there is a tendency for HbA_{1c} levels to rise (Nathan et al, 2009), rather than allowing HbA_{1c} values to rise to unacceptable levels and then applying heroic "rescue therapy". Encouragingly, ACCORD, ADVANCE and VADT all showed that sustained, improved glucose control can be obtained with currently available therapies. ■

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