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Ambulatory glycaemic control – recent developments

Three recent studies – ACCORD, ADVANCE and VADT – have given cause to re-examine the intensity of outpatient glycaemic control for diabetes.

The ACCORD study randomized 10,251 participants with significant cardiovascular risk/history, aiming to achieve HbA_{1c} < 6% in the study group. This study was halted early due to excess deaths (driven by cardiovascular death) in the intense treatment group. The composite primary outcome, however, was reduced in the intensive treatment group (but not achieving statistical significance) due to a reduction in non-fatal myocardial infarctions ($p = 0.16$). There was no clear explanation for the excess mortality in the study arm. The subgroup of intensively managed patients with no previous cardiovascular event and those with a baseline HbA_{1c} < 8% had a significant reduction in the primary outcome.

ADVANCE randomized 11,140 participants with known vascular disease/ risk factors, aiming for a target HbA_{1c} < 6.5%, using gliclazide to achieve this target in the study group. Median HbA_{1c} levels were 6.3% and 7.0% in the study and control groups, but this took several years to achieve. The primary outcome (reduction in microvascular complications and macrovascular events) was achieved ($p = 0.01$), but this was largely attributable to a reduction in microvascular outcomes. There was no difference in mortality.

VADT randomized 1,791 participants with uncontrolled diabetes (median HbA_{1c} 9.4%) to intensive (target HbA_{1c} < 6.0%) or standard glycaemic control. Composite cardiovascular events were 12% lower (non-significant) in the study group after 5.6 years ($p = 0.12$). Those with duration of diabetes < 12 years achieved significant benefit from intensive glycaemic control, while those with a longer duration of disease saw neutral or even adverse impact.

Interpretation of ACCORD is difficult due to a number of “downstream” affects associated with the intensive arm (e.g. greater hypoglycaemia, insulin use, thiazolidinediones, and weight gain, all of which may counterbalance any benefits). It has also been suggested hyperinsulinaemia may be a confounding factor. It is likely the increased mortality was related to the overall treatment strategies for intensifying glycaemic control, rather than the HbA_{1c} in itself. Subset analysis of the three trials suggests benefit was seen for participants with shorter duration of diabetes, lower HbA_{1c} at entry, and/or absence of known cardiovascular disease.

In a recent position paper on these three studies, the American Diabetes Association still maintains a HbA_{1c} goal of < 7.0%, and advocates control of non-glycaemic risk factors (blood pressure, lipids, aspirin use, lifestyle) as the primary strategies for reducing cardiovascular burden in diabetes. However, this organization now suggests that less stringent HbA_{1c} goals may be appropriate for those with a history of severe hypoglycaemia, advanced vascular disease, or those with long-standing diabetes – for these patients the HbA_{1c} goal of < 7.0% is difficult to obtain.

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FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
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