Why the Look AHEAD study results should not be a surprise

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All healthcare professionals agree that lifestyle changes can prevent the development of type 2 diabetes in those at risk. Indeed, several high quality trials strongly confirm this notion (Gillies et al, 2007), and so clinical practice has put in to place interventions for those at high risk. However, whether lifestyle changes can lessen cardiovascular events is sparsely studied, in part, because such trials require much greater investment of time and money than diabetes prevention trials.

The Look AHEAD (Attention for Health in Diabetes) investigators designed such a study (summarised alongside) to fill this gap. Their ambitious, randomised study involved over 2500 individuals with diabetes being assigned to an intensive lifestyle modification (termed the intervention group; including the use of meal replacements and optional pharmacotherapy, plus a hike in activity levels) versus over 2500 individuals following usual care.

The study investigators asked the question, "Will intentional weight loss reduce the incidence of fatal and non-fatal cardiovascular and cerebrovascular events?" After year 1, the intervention group had a weight loss of more than 8.6% versus 0.7% in the usual care group, but by year 4, the differential weight loss between the two groups had attenuated to around 4%. Nevertheless, this difference remained highly significant and the weight change pattern largely predicted the glycaemic pattern, whereby there was a near 0.55 mmol/mol (0.6%) difference in HbA_{1c} seen by year 1, narrowing considerably by year 4 to an average over the first 4 years of 0.02 mmol/mol (0.27%) in favour of the intervention group (Look AHEAD Research Group, 2010). In view of low primary cardiovascular disease (CVD) end-point event rates, the investigators subsequently added softer end-points to the primary outcome. Yet, few were expecting an announcement in October 2012 that reported the study had been terminated prematurely due to futility.

So what went wrong? Is lifestyle really so futile in terms of cardiovascular protection in individuals with type 2 diabetes that we should not stress its importance to our patients? Or are there any explanatory factors for the Look AHEAD results? Perhaps the most striking aspects of the study were the very low levels of conventional risk factors in the recruited participants: most were women, the percentage of smokers was remarkably low at around 4.5% of the cohort, LDL cholesterol levels were excellent at about 2.90 mmol/L and average blood pressures were near ideal at 129/70 mmHg. Average HbA_{1c} levels were also excellent at around 55 mmol/mol (7.2%).

Thus, by any criteria, average CVD risk for the population, despite being of high BMI and with type 2 diabetes, was modest at best. Therefore, one can conclude that, whereas weight reduction can rapidly alter HbA_{1c}, its effects on CVD risk do not emerge quickly, especially when other key CVD risk factors are low from onset and do not change (i.e. LDL cholesterol) or only change modestly with intervention (i.e. systolic blood pressure), as happened in the Look AHEAD study. Similarly, the results reinforce the notion that small changes in HbA_{1c} also offer minimal CVD risk protection. In this way, the Look AHEAD results confirm an emerging paradigm (Sattar, 2013), whereby targeting glycaemic control to prevent CVD is an initially weaker approach when set against achieving cholesterol and blood pressure goals. This does not mean lowering glucose levels is not important; microvascular benefits are more closely linked to glycaemic changes, whereas CVD benefits may take much longer to accrue.

So what do Look AHEAD results mean for clinical practice? Here, one must remember that patients like to lose weight and be more active – such changes improve quality of life and may often allow for fewer drugs to be prescribed to control glucose and blood pressure levels. Yet, our patients find it hard to make lifestyle changes, especially those that are sustainable. Thus, helping individuals identify potential sustainable changes in the context of their lives remains important, even if challenging. However, making sure cholesterol and blood pressure goals are achieved, and trying to help individuals to stop smoking, continue to be the best options to lessen their CVD risks.

Gillies CL, Abrams KR, Lambert PC et al (2007) Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ* **334**: 299

Look AHEAD Research Group (2010) Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* **170**: 1566–75

Sattar N (2013) Revisiting the links between glycaemia, diabetes and cardiovascular disease. *Diabetologia* **56**: 686–95

Look AHEAD study: Intensive lifestyle intervention

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

1 The Look AHEAD (Attention for Health in Diabetes) study aimed to determine whether intensive lifestyle interventions decreased cardiovascular morbidity and mortality in obese/overweight individuals with T2D.

2 In total, 5145 participants were randomly assigned to either the intensive lifestyle intervention group (decreased caloric intake and increased physical activity) or the usual care group (received diabetes support and education).

3 The aim was for participants in the intervention group to achieve and maintain at least a 7% weight loss. The primary clinical outcome was the first occurrence of a composite cardiovascular outcome (i.e. death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke).

4 At the 1-year follow-up, a weight loss of 8.6% (intervention group) versus 0.7% (usual care group) was achieved, as well as decreased waist circumference, and improved fitness and HbA_{1c} levels in the intervention group; gradual weight regain followed.

5 After 9.6 years, the study was terminated on the basis of a futility analysis as there was no significant between-group difference in the primary clinical outcome, and the probability of observing a significant positive result at the planned study-end of 13.5 years was estimated at 1%.

6 The authors concluded that intensive lifestyle interventions did not reduce cardiovascular morbidity or mortality, but individuals in the intervention group reported lifestyle improvements in various areas of life.

Look AHEAD Research Group (2013) Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* **396**: 145–54

BMJ

Hypoglycaemia and CVD: meta-analysis

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

1 Six studies were eligible for inclusion in this systematic review and meta-analysis investigating the association between severe hypoglycaemia and risk of cardiovascular disease (CVD). In total, 903 510 participants were identified with a mean age range of 60–67 years. Mean follow-up time was between 1 and 5.6 years.

2 The meta-analysis identified a strong association between severe hypoglycaemia and risk of CVD (relative risk 2.05, 95% CI; $P<0.001$).

3 The bias analysis indicated that confounding from a severe comorbid illness alone may not explain the association between hypoglycaemia and CVD.

Goto A, Arah OA, Goto M et al (2013) Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ* **347**: f4533

BMJ

Fruit consumption and risk of T2D

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

1 Data from three prospective longitudinal cohort studies were analysed to determine whether whole fruit consumption was associated with a risk of T2D.

2 In total, 187 382 participants who were free from major chronic diseases at baseline were involved, and during 3 464 641 person years of follow-up, 12 198 developed T2D.

3 Participants received follow-up questionnaires every 2 years and incidences of T2D were confirmed by supplementary questionnaires.

4 There was a weak association between whole fruit consumption and a lower risk of T2D; the hazard ratio (HR) of T2D for every three servings/week of whole fruit consumption was 0.98 (95% CI, 0.96–0.99).

5 Consumption of blueberries, grapes and apples was significantly associated with a reduced risk of T2D, and a greater consumption of strawberries (HR 1.03; 95% CI), cantaloupe (HR 1.10; 95% CI) and fruit juice (HR 1.08; 95% CI, 1.05–1.11) were associated with a higher risk.

Muraki I, Imamura F, Manson JE et al (2013) Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *BMJ* **347**: f5001

DIABETIC MEDICINE

Systematic review: Use of technology to promote exercise

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

1 A search of the Cochrane library, EMBASE, MEDLINE, PsycINFO and PubMed found 15 articles that were eligible for inclusion in this systematic review determining the effectiveness of technology to promote physical activity in people with T2D. Nine of the 15 articles showed a significant increase in physical activity.

2 The interventions lasted between 6 weeks and 1 year, and the sample sizes ranged from 26 to 958 participants.

3 Various technology modes were investigated (web-based, mobile phone, CD-ROM and computer-based).

4 A personal coach, logbooks and reinforcing strategies, such as phone calls and email counselling, were found to be effective techniques for behavioural change.

Connelly J, Kirk A, Masthoff J, Macrury S (2013) The use of technology to promote physical activity in Type 2 diabetes management: a systematic review. *Diabet Med* 22 Jul [Epub ahead of print]

DIABETES CARE

Rationale and design of the GRADE study

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

1 The GRADE (Glycaemic Reduction Approaches in Diabetes: a comparative Effectiveness) study will compare the long-term effects of T2D medications. The trial will follow an intention-to-treat design, and is fully funded by the NIH.

2 In total, 5000 adults with relatively recently diagnosed T2D (<5 years) are currently being recruited from 37 US centres. The participants will already receive metformin, and then one of the four following medication classes will be randomly assigned as a secondary agent: sulphonylurea, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist and insulin.

3 The primary outcome will be the time to primary metabolic failure as defined as an HbA_{1c} of ≥53 mmol/mol (7%) when the participant is on the maximum tolerated dose of the assigned agent.

4 The secondary metabolic outcome will be an HbA_{1c} of >58 mmol/mol (7.5%) when the participant is on the maximum tolerated dose of the assigned agent. When this is reached, medication will be intensified to included basal insulin, along with metformin and the assigned agent (except for the insulin group).

5 The tertiary metabolic outcome will be an HbA_{1c} of >58 mmol/mol (7.5%) when the participant is receiving metformin, the assigned agent and insulin. At this point, rapid-acting insulin will be added to the basal insulin and metformin, and the assigned agent will be stopped.

6 The four classes will be compared for their success, failure and other factors over a planned follow-up of 4 to 7 years.

Nathan DM, Buse JB, Kahn SE et al (2013) Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). *Diabetes Care* **36**: 2254–61

> "The meta-analysis identified a strong association between severe hypoglycaemia and the risk of cardiovascular disease."