

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007;357:1716-30. DOI: 10.1056/NEJMoa075392.

**4-T One-year results online Appendix: Table 1**

<b>4-T Insulin Titration Algorithm</b>
<p>Prior to each visit and telephone contact patients are asked to perform three self-measured capillary glucose profiles, before breakfast and the evening meal for those in the biphasic and basal groups, and before and 2 hours after each meal and at bedtime in the prandial group. All patients are also asked to perform an 8-point profile (including 3 a.m.) at baseline and at weeks 12, 24, 38 and 52. All profiles available and any reported grade 2 or 3 hypoglycemic episodes within two weeks prior to a visit are used by the Trial Management System to suggest possible insulin dose changes aiming to achieve plasma glucose in the range:</p> <ul style="list-style-type: none"> <li>▪ <b>72 - 99 mg/dl (4.0 - 5.5 mmol/l)</b> for fasting and pre-meal values</li> <li>▪ <b>90 - 126 mg/dl (5.0 - 7.0 mmol/l)</b> for two-hour post-prandial values</li> </ul>
<b>Twice-daily Biphasic Insulin Dose Titration</b>
<p><b>Maintain</b> insulin doses</p> <ul style="list-style-type: none"> <li>▪ If more than 2/3 of pre-breakfast or pre-evening meal glucose readings are within range</li> </ul> <p><b>Increase</b> breakfast insulin dose (when no hypoglycemia)</p> <ul style="list-style-type: none"> <li>▪ If more than 1/3 of pre-evening meal glucose readings remain high</li> </ul> <p><b>Increase</b> pre-evening meal insulin dose (when no hypoglycemia)</p> <ul style="list-style-type: none"> <li>▪ If more than 1/3 of pre-breakfast meal glucose readings remain high</li> </ul> <p><b>Decrease</b> insulin doses in the presence of</p> <ul style="list-style-type: none"> <li>▪ Any Grade 2 or 3 hypoglycemic episodes at relevant time points</li> <li>▪ Mean glucose readings &lt;70 mg/dl (&lt;3.9 mmol/l) at relevant time points</li> </ul>
<b>Thrice-daily Prandial Insulin Dose Titration</b>
<p><b>Maintain</b> insulin doses</p> <ul style="list-style-type: none"> <li>▪ If more than 2/3 of 2-hour post-meal and next pre-meal or pre-bed glucose readings are within range</li> </ul> <p><b>Increase</b> breakfast insulin dose (when no hypoglycemia)</p> <ul style="list-style-type: none"> <li>▪ If more than 1/3 of 2-hour post-breakfast or pre-lunch meal glucose readings remain high</li> </ul> <p><b>Increase</b> lunch insulin dose (when no hypoglycemia)</p> <ul style="list-style-type: none"> <li>▪ If more than 1/3 of 2-hour post-lunch or pre-evening meal glucose readings remain high</li> </ul> <p><b>Increase</b> evening meal insulin dose (when no hypoglycemia)</p> <ul style="list-style-type: none"> <li>▪ If more than 1/3 of 2-hour post-evening, pre-bed and pre-breakfast glucose readings remain high</li> </ul> <p><b>Decrease</b> insulin doses in the presence of</p> <ul style="list-style-type: none"> <li>▪ Any Grade 2 or 3 hypoglycemic episodes at relevant time points</li> <li>▪ Mean glucose readings &lt;70 mg/dl (&lt;3.9 mmol/l) at relevant time points</li> </ul>
<b>Once-daily Basal Insulin Dose Titration</b>
<p><b>Maintain</b> pre-bedtime insulin doses</p> <ul style="list-style-type: none"> <li>▪ If more than 2/3 of pre-breakfast and pre-evening meal glucose readings are within range</li> </ul> <p><b>Increase</b> pre-bedtime insulin dose (when no hypoglycemia)</p> <ul style="list-style-type: none"> <li>▪ If more than 1/3 of pre-breakfast meal glucose readings remain high</li> </ul> <p><b>Add</b> a pre-breakfast insulin injection</p> <ul style="list-style-type: none"> <li>▪ If glucose readings are at target before breakfast but not before the evening meal and nocturnal hypoglycemia limits further pre-bedtime insulin dose increases</li> </ul> <p><b>Decrease</b> insulin doses in the presence of</p> <ul style="list-style-type: none"> <li>▪ Any Grade 2 or 3 hypoglycemic episodes at relevant time points</li> <li>▪ Mean glucose readings &lt;70 mg/dl (&lt;3.9 mmol/l) at relevant time points</li> </ul>
<b>Insulin Dose Reductions</b>
<ul style="list-style-type: none"> <li>• By 10% or 4 units (whichever is the greater) in the presence of grade 3 hypoglycemia or mean glucose readings &lt;56 mg/dl (&lt;3.1 mmol/l)</li> <li>• Otherwise by 5% or 2 units (whichever is the greater)</li> </ul>
<b>Insulin Dose Increases</b>
<ul style="list-style-type: none"> <li>• By 10% or 4 units (whichever is the greater) if the mean glucose reading for a given time point is &gt;72 mg/dl (&gt;4.0 mmol/l) above upper end of the range</li> <li>• Otherwise by 5% or 2 units (whichever is the greater)</li> </ul>