

Supplementary Appendix

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

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Supplementary Appendix

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2. Recommendations for Participant Management in the Intensive Group using both HbA1c and Fasting Blood Glucose (FBG)

		Fasting Blood Glucose		
		<6.0 mmol/L/<108 mg/dl	6.0-7.0 mmol/L/108-126 mg/dl	>7.0 mmol/L/>126 mg/dl
HbA1c (%)	<6.0	GOOD CONTROL <ul style="list-style-type: none"> • Check/prevent hypos • Continue current therapy and diet and exercise recommendations 	FAIR CONTROL but possible inconsistent FBG and HbA1c <ul style="list-style-type: none"> • Check HbA1c assay reliability² • Consider adjusting treatment according to blood glucose levels • Check/prevent day time hypos 	LIKELY POOR CONTROL but inconsistent FBG and HbA1c <ul style="list-style-type: none"> • Check HbA1c assay reliability² • Obtain 24H glucose profile⁴ • Adjust levels according to blood glucose levels
	6.0-6.5	GOOD CONTROL <ul style="list-style-type: none"> • Check/prevent hypos • Continue current therapy • Optimise diet and exercise 	FAIR CONTROL <ul style="list-style-type: none"> • Consider increasing treatment • Optimise diet and exercise 	LIKELY POOR CONTROL but inconsistent FBG and HbA1c <ul style="list-style-type: none"> • Check HbA1c assay reliability² • Obtain 24H glucose profile⁴ • Adjust levels according to blood glucose levels
	6.6-7.0	LIKELY POOR CONTROL but inconsistent FBG and HbA1c <ul style="list-style-type: none"> • Check FBG reliability¹ • Check HbA1c assay reliability² • Check post prandial values • Focus on mealtime intervention³ 	INSUFFICIENT CONTROL <ul style="list-style-type: none"> • Increase in treatment required⁵ 	POOR CONTROL <ul style="list-style-type: none"> • Urgent increase in treatment required⁵
	>7.0	LIKELY POOR CONTROL but inconsistent FBG and HbA1c <ul style="list-style-type: none"> • Check FBG reliability¹ • Check HbA1c assay reliability² • Check post prandial values • Focus on mealtime intervention³ 	POOR CONTROL <ul style="list-style-type: none"> • Urgent increase in treatment required⁵ 	POOR CONTROL <ul style="list-style-type: none"> • Urgent increase in treatment required⁵

¹ FBG results can be unreliable due to inappropriate use of the meter (drop size, calibration issues etc), patient misreporting results

² HbA1c results can be unreliable due to assay issues (both over and underestimation can occur), anaemia or blood transfusion, abnormal haemoglobin

³ Optimise diet, optimise post prandial exercise, add acarbose, add short acting insulin if already treated with insulin

⁴ Obtain repeated 24h glucose profile, including post prandial and night time blood glucose values, in order to detect unexpectedly low and high values

⁵ Suggested drug treatment steps: 1. Add gliclazide MR; 2. Increase the dose of gliclazide MR (30-120 mg); 3. Add or increase the dose of metformin; 4. Add or increase the dose of thiazolidinedione; 5. Add or increase the dose of alpha-glucosidase inhibitor; 6. Add bed time insulin therapy; 7. Add a full insulin regimen or increase the dose of a full insulin regimen

3. HbA1c standardization

Laboratories participating in ADVANCE underwent a standardization process using the Wales External Quality Assurance Scheme (WEQAS) (1). Eight samples of lyophilized human whole blood covering the pathological range were analyzed by each laboratory. Target values for all samples were assigned for Diabetes Control and Complications Trial (DCCT) and the International Federation of Clinical Chemistry (IFCC) reference methods (2). Results from the central lab were considered the gold standard values and were used to calibrate the measurements from each study laboratory.

Statistical methods:

For each laboratory, the following linear regression was performed:

$$Y^L = aY^R + b + \varepsilon$$

where

- Y^L = results from 8 standard samples tested by the laboratory
- Y^R = 8 reference (gold standard) means using the same method
- a = slope parameter of linear regression to estimate
- b = intercept parameter of linear regression to estimate
- ε = residual errors.

A brief examination of the distribution of the residual errors ε served to assess the goodness-of-fit of the linear model.

Standardization of measurements: Using the regression parameters a and b estimated from the linear regression for each laboratory, all the original HbA1c measurements were corrected using the following formula:

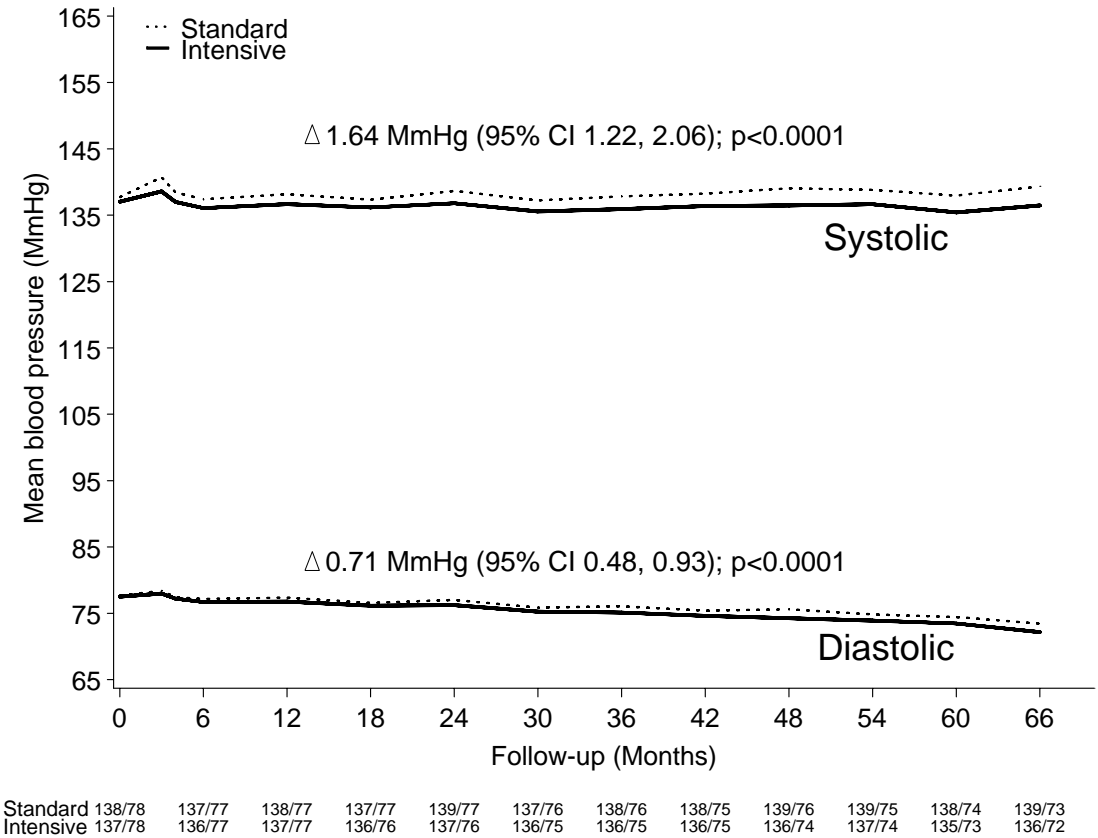
$$Y^S = (Y^O - b^{\wedge}) / \hat{a}$$

- Where
- Y^S = new standardized measurements of %HbA1c within laboratory
 - Y^O = original observed measurements of %HbA1c within laboratory
 - \hat{a} = slope parameter estimated from the previous linear regression
 - b^{\wedge} = intercept parameter estimated from the previous linear regression

References

1. Wales External Quality Assurance Scheme. (Accessed 14th March, 2008, at <http://www.weqas.com>.)
2. The American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, International Diabetes Federation. Consensus Statement on the Worldwide Standardization of the Hemoglobin A1C Measurement. *Diabetes Care*. 2007;30:2399-400.

4. Supplementary Figure 1. Mean blood pressure levels among participants randomized to intensive and standard glucose control during follow-up.



5. Supplementary Table 1. Additional data on diabetes management at baseline and end of follow-up

Characteristic	Baseline*		End of follow-up	
	Intensive glucose control (n=5571)	Standard glucose control (n=5569)	Intensive glucose control (n=4828)	Standard glucose control (n=4741)
Insulin treatment				
Treated with long-term insulin, n (%)	-	-	1953 (41)	1142 (24)
Number of insulin injections per day				
1 injection, n (%)	-	-	649 (33)	284 (25)
2 injections, n (%)	-	-	940 (48)	645 (57)
3 or more injections or insulin pump therapy, n (%)	-	-	362 (19)	210 (18)
Number of units of insulin per day, mean (sd)	-	-	37.3 (28.4)	39.8 (27.2)
Number of units of insulin per day per kg body weight, mean (sd)	-	-	0.5 (0.3)	0.5 (0.3)
Insulin type				
Long-acting insulin NPH, n (%)	-	-	638 (33)	310 (26)
Long-acting insulin analogue Glargine, n (%)	-	-	266 (14)	145 (13)
Long-acting insulin analogue Detemir, n (%)	-	-	81 (4)	32 (3)
Short-acting regular insulin, n (%)	-	-	195 (10)	129 (11)
Short-acting insulin analogue, n (%)	-	-	175 (9)	94 (8)
Premixed insulin (regular/NPH or analogue/NPH), n (%)	-	-	922 (47)	609 (53)
Combinations of glucose lowering drugs				
SU* alone, n (%)	1386 (25)	1378 (25)	482 (10)	510 (11)
MET alone, n (%)	864 (16)	903 (16)	58 (1)	561 (12)
TZD alone, n (%)	4 (0.1)	12 (0.2)	0 (0)	12 (0.3)
SU* + MET, n (%)	1999 (36)	2005 (36)	1226 (26)	1277 (28)
SU* + TZD, n (%)	28 (0.5)	44 (0.8)	84 (2)	61 (1)

SU* + MET + TZD, n (%)	116 (2)	90 (2)	350 (7)	217 (5)
Insulin alone, n (%)	9 (0.2)	14 (0.3)	112 (2)	341 (7)
Insulin + SU*, n (%)	20 (0.4)	20 (0.4)	273 (6)	70 (2)
Insulin + MET, n (%)	10 (0.2)	11 (0.2)	135 (3)	282 (6)
Insulin + TZD, n (%)	1 (<0.1)	2 (<0.1)	4 (0.1)	8 (0.2)
Insulin + SU* + MET, n (%)	22 (0.4)	17 (0.3)	809 (17)	206 (5)
Insulin + SU* + MET + TZD, n (%)	2 (<0.1)	0 (0)	126 (3)	18 (0.4)
Other parameters				
Number of mild exercise sessions lasting >15 minutes per week, mean (sd)	5.3 (6.9)	5.5 (7.1)	6.6 (7.7)	6.8 (8.2)
Number of moderate exercise sessions lasting >15 minutes per week, mean (sd)	2.9 (4.7)	3.0 (5.1)	3.2 (5.7)	3.0 (5.2)
Number of vigorous exercise sessions lasting >15 minutes per week, mean (sd)	0.5 (2.4)	0.5 (1.8)	0.5 (2.3)	0.4 (1.9)
Home blood glucose monitoring, n (%)	2140 (38)	2199 (39)	4469 (96)	2865 (63)

* includes gliclazide (modified release)

6. Supplementary Table 2. Reasons for all hospitalizations during follow-up

International Classification of Disease (version 10) term and code	Intensive glucose control (n=5645)	Standard glucose control (n=5038)
	<i>number (%)</i>	
Certain infectious and parasitic diseases (A00-B99)	72 (1.3)	59 (1.1)
Neoplasms (C00-D48)	119 (2.1)	119 (2.1)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	62 (1.1)	63 (1.1)
Endocrine, nutritional, and metabolic diseases (E00-E90) (excluding major hypoglycemia)	283 (5.0)	281 (5.6)
Major hypoglycemia (E11.64)	67 (1.2)	45 (0.9)
Mental and behavioural disorders (F00-F99)	36 (0.6)	22 (0.4)
Diseases of the nervous system (G00-G99)	127 (2.3)	96 (1.7)
Diseases of the eye and adnexa (H00-H59)	163 (2.9)	156 (2.8)
Diseases of the ear and mastoid process (H60-H95)	20 (0.4)	19 (0.3)
Diseases of the circulatory system (I00-I99)	927 (16.6)	890 (16.0)
Diseases of the respiratory system (J00-J99)	271 (4.9)	260 (4.7)
Diseases of the digestive system (K00-K93)	397 (7.1)	333 (6.0)
Diseases of the skin and subcutaneous tissue (L00-L99)	70 (1.3)	62 (1.1)
Diseases of the musculoskeletal system and connective tissue (M00-M99)	299 (5.4)	246 (4.4)
Diseases of the genitourinary system (N00-N99)	245 (4.4)	232 (4.2)
Congenital malformations, deformations, and chromosomal abnormalities (Q00-Q99)	6 (0.1)	6 (0.1)
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	363 (6.5)	316 (5.7)
Injury, poisoning, and certain other consequences of external causes (S00-T98)	209 (3.8)	171 (3.1)
External causes of morbidity and mortality (V01-Y98)	7 (0.1)	6 (0.1)
Factors influencing health and contact with health services (Z00-Z99)	51 (0.9)	51 (0.9)
Other	60 (1.1)	51 (0.9)