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HypoCOMPaSS Education Tool

This was a brief (2 to 3 hours) long education session conducted before the randomization, underpinned by a formal curriculum and workbook, referred to as the 'My Hypo COMPaSS' tool. The sessions were delivered individually or in small groups of up to four by a trained research fellow, diabetes educator, specialist nurse or dietician.

The focus of the session was rigorous avoidance of hypoglycemia while maintaining overall glycemic control, including four key elements forming the four points of the 'Hypo COMPaSS'

- Never to delay the treatment of hypoglycemia and the optimal treatments for hypoglycemia;
- To recognize the individual's unique times of increased risk;
- To recognize hypoglycemia by the presence of subtle symptoms;
- To be particularly careful about detecting and preventing nocturnal hypoglycemia.

Further areas discussed included: advice on self-adjustment of insulin doses according to carbohydrate intake, self-monitored blood glucose and planned activity and recommendation for oral carbohydrate administration for all glucose levels less than 4 mmol/l.

Follow up during 6 month study intervention

The trial was designed to prevent any potential bias from additional educational support provided to those randomised to CSII or RT-CGM and study visits and contacts were identical between groups. All participants were provided with a Medtronic Veo insulin pump (Medtronic, Northridge, CA, USA) to enable use of the bolus prandial insulin dose wizard calculator whether or not they were administering insulin by CSII. All were provided with a Contour link SMBG meter (Bayer Healthcare) enabling direct transmission to the pump dose calculator.

All participants (regardless of treatment arm) attended equivalent education sessions solely on the technical aspects of the insulin administration and glucose monitoring equipment, i.e. participants randomised to CSII / RTCGM received education restricted to technical aspects of insulin pump/ CGM management and participants randomised to MDI received education restricted to insulin device (pen) use, injection site care and conventional glucose self-monitoring. After the initiation of the new treatment, all participants were telephoned daily for the first week, to review self monitored glucose values and offer guidance in initial insulin dose adjustment.

During the 6 month study intervention period, participants were required to attend the clinic twice a month. (End of week three and week four of each study month). The visit at the end of week three was to initiate retrospective CGM (Medtronic iPro) (blinded from both patient and investigator), followed one week later by a visit at the end of each study month for downloading the CGM, collection of self monitored glucose and hypoglycemia symptom diaries and optimisation of study treatment.

Throughout the study intervention period, participants were required to maintain detailed diaries about the frequency and severity of hypoglycemia. The primary goal of insulin dose titration throughout the study, in all treatments arms, was the avoidance of all glucose levels <3mmol/L as determined by self monitored blood glucose. This was achieved by setting '4 as the floor' with all glucose levels

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<4mmol/L treated by 15g glucose with repeat self monitored blood glucose every 15 minutes until glucose was >4mmol/L, in addition to consideration of insulin dose reduction.
Where attainable without hypoglycemia, blood glucose targets were similar for all participants.

- Before breakfast and 4am targets - 5-7 mmol/L
- Before lunch and before evening meal - 4.5-7 mmol/L
- Post-prandial targets - 6-8 mmol/L.

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Supplementary Table 1. Demographic and other baseline characteristics for paired clamp and non-clamp participants in the HypoCOMPaSS trial.

	Paired-clamp cohort (N=18)	***Non-clamp cohort (N=78)***	***P***
Age (years)	49.6 ± 8.3	49.0 ± 12.9	0.78
Female Sex	12 (66.7%)	48 (61.5%)	0.45
Age at Diagnosis (years)	14.4 ± 8.3	20.8 ± 12.8	**0.01**
Diabetes Duration (years)	34.9 ± 10.8	28.1 ± 12.3	**0.03**
HbA1c at study entry (%)	8.1 ± 1.0	8.3 ± 1.2	0.42
BMI (Kg/m^2)	24.7 ± 3.6	27.0 ± 4.5	**0.03**
Gold Score at Study entry	5.4 ± 0.9	5.3 ± 0.9	0.51
CGM time <4mmol/l (%)	11.3 ± 9.0	8.9 ± 8.0	0.30
Treatment Allocation			
MDI	9	41	
CSII	9	37	
Conventional monitoring	11	37	
RT-CGM	7	41	

Data are mean ± S.D compared by independent samples t test

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Supplementary Table 2. Summary hormone results from the baseline clamp; Data shown are median (IQR).

	Time from clamp start (minutes)												
	0	**+10**	**+20**	**+30**	**+40**	**+60**	**+80**	**+100**	**+120**	**+140**	**+160**	**+180**	**+200**
Metanephrine (pmol/l)	226 (180, 282)	251 (145, 375)	206 (158, 322	183 (146, 309)	222 (161, 285)	212 (158, 279)	205 (169, 308)	219 (141, 325)	208 (164, 292)	202 (137, 305)	209 (169, 319)	235 (175, 275)	264 (219, 414)
Cortisol (nmol/l)	301 (190, 424)	245 (161, 379)	253 (150, 397)	319 (179, 446)	307 (176, 461)	261 (187, 415)	234 (186, 392)	248 (213, 346)	252 (208, 348)	245 (194, 333)	276 (212, 368)	328 (274, 512)	462 (294, 584)
Growth Hormone (ng/ml)	3.0 (0.9, 7.9)	2.5 (0.7, 6.4)	3.4 (0.7, 7.1)	4.8 (1.8, 8.1)	3.9 (2.3, 4.8)	3.2 (1.0, 11.9)	3.6 (1.5, 11.4)	6.7 (1.0, 14.5)	9.4 (1.4, 16.7)	9.2 (5.1, 16.6)	11.9 (5.6, 25.2)	13.8 (9.9, 24.7)	23.3 (12.0, 30.3)
Glucagon (pg/ml/)	158 (92, 303)	205 (114, 341)	178 (87, 297)	185 (97, 299)	180 (106, 337)	147 (100, 314)	147 (102, 320)	142 (104, 306)	181 (109, 335)	193 (98, 355)	154 (71, 372)	141 (99, 303)	123 (94, 305)

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Supplementary Table 3. Summary Hormone Results from Post-RCT Clamp; Data shown are median (IQR)

	Time from clamp start (minutes)												
	0	**+10**	**+20**	**+30**	**+40**	**+60**	**+80**	**+100**	**+120**	**+140**	**+160**	**+180**	**+200**
Metanephrine (pmol/l)	213 (153, 293)	242 (142, 300)	224 (181, 294)	223 (155, 298)	221 (131, 293)	221 (115, 293)	223 (157, 324)	256 (143, 377)	212 (147, 318)	219 (147, 373)	253 (187, 394)	298 (202, 452)	329 (257, 496)
Cortisol (nmol/l)	261 (154, 337)	223 (136, 312)	175 (135, 314)	217 (134, 310)	267 (157, 321)	247 (176, 325)	216 (183, 283)	212 (179, 290)	195 (172, 379)	250 (174, 373)	286 (221, 338)	334 (284, 487)	486 (405, 643)
Growth Hormone (ng/ml)	1.3 (0.6, 6.9)	1.2 (0.7, 7.7)	1.6 (0.7, 6.8)	2.2 (0.4, 10.2)	4.2 (0.4, 10.0)	2.8 (0.6, 9.2)	2.5 (0.5, 6.9)	4.3 (0.5, 6.1)	3.1 (1.5, 9.6)	9.9 (4.7, 14.3)	14.3 (4.3, 22.1)	17.1 (12.8, 29.7)	22.5 (16.6, 29.8)
Glucagon (pg/ml/)	143 (99, 246)	166 (106, 247)	164 (115, 205)	143 (111, 199)	137 (105, 216)	133 (102, 229)	124 (100, 212)	129 (110, 197)	118 (108, 205)	115 (96, 206)	132 (98, 210)	120 (101, 212)	124 (102, 190)

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Supplementary Table 4. Symptom and hormonal responses to clamped hypoglycemia in HypoCOMPaSS participants randomised to insulin pump therapy (CSII) and multiply daily injections (MDI).

	CSII (n=9)			***MDI (n=9)***		
	Baseline	***Post-RCT***	**P***	***Baseline***	***Post-RCT***	**P***
Glucose level subject felt low (mmol/l)	2.4 ± 0.1	3.3 ± 0.3	**0.01**	2.7 ± 0.1	3.0 ± 0.3	0.42
Symptom AUC						
Total	420 (300, 560)	920 (330, 1290)	**0.04**	660 (390, 1020)	580 (360, 1380)	0.19
Autonomic	200 (120, 330)	420 (50, 770)	0.06	260 (0, 640)	240 (90, 820)	0.32
Neuro	160 (60, 320)	340 (190, 610)	**0.04**	320 (130, 680)	360 (130, 700)	0.36
Hormone AUC (Incremental) ‡						
Metanephrine	-1186 (-5802, 6100)	7808 (1417, 22142)	**0.01**	2904 (127, 7316)	944 (-1490, 7201)	0.60
Cortisol	6320 (-6705, 12568))	7079 (2137, 15552)	0.07	-2304 (-9967, 14747)	4020 (-8356, 19500)	0.44
Glucose Thresholds (mmol/l)						
Metanephrines	2.4 (2.3, 2.5)	2.9 (2.4, 3.3)	**0.03**	2.5 (2.4, 2.6)	2.5 (2.2, 3.2)	0.37
Cortisol	2.5 (2.3, 3.0)	2.5 (2.4, 2.7)	0.59	2.6 (2.4, 3.6)	2.9 (2.3, 3.4)	0.95

Data shown are mean ± SE or median (IQR) and compared by paired samples T test or Wilcoxon Signed Ranks Test. AUC= Area Under the Curve calculated using trapezoid rule after linear interpolation of any missing data. † Incremental area under the curve for symptoms was calculated after subtracting the symptom score at the end of stage 1 from stages 2 to 5. ‡ Incremental area under the curve for hormones was calculated after subtracting the mean hormone level during euglycemia from subsequent hormone levels during hypoglycemia (stages 2 to 5)

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Supplementary Table 5. Symptom and hormonal responses to clamped hypoglycemia in HypoCOMPaSS participants randomised to real-time continuous glucose monitoring (RT-CGM) and conventional glucose monitoring alone.

	RT-CGM (N=7)			***Non RT-CGM (N=11)***		
	Baseline	***Post-RCT***	**P***	***Baseline***	***Post-RCT***	**P***
Glucose level subject felt low (mmol/l)	2.5 ± 0.1	3.5 ± 0.3	**0.01**	2.6 ± 0.1	2.9 ± 0.2	0.33
Symptom AUC						
Total	460 (400, 660)	700 (380, 1300)	**0.04**	520 (320, 760)	580 (280, 1280)	0.15
Autonomic	200 (0, 260)	300 (60, 720)	0.06	340 (160, 640)	280 (60, 860)	0.20
Neuro	320 (200, 660)	580 (300, 640)	0.07	140 (60, 320)	340 (100, 580)	0.13
Hormone AUC (Incremental) ‡						
Metanephrine	2078 (-7036, 7390)	6550 (3843, 9930)	0.09	2746 (-2512, 7242)	386 (-1376, 16262)	0.08
Cortisol	-2262 (-7632, 8058)	9816 (-188, 16126)	0.17	5944 (-12302, 14968)	3232 (-1678, 18292)	0.53
Glucose Thresholds (mmol/l)						
Metanephrines	2.4 (2.3, 2.5)	3.3 (2.5, 3.4)	**0.02**	2.5(2.3, 2.6)	2.5 (2.3, 2.9)	0.45
Cortisol	2.5 (2.4, 2.7)	2.8 (2.6, 3.6)	0.23	2.6 (2.3, 3.2)	2.5 (2.3, 2.7)	0.18

Data shown are median (IQR) and compared by Wilcoxon Signed Ranks Test. AUC= Area Under the Curve calculated using trapezoid rule after linear interpolation of any missing data. † Incremental area under the curve for symptoms was calculated after subtracting the symptom score at the end of stage 1 from stages 2 to 5. ‡ Incremental area under the curve for hormones was calculated after subtracting the mean hormone level during euglycemia from subsequent hormone levels during hypoglycemia (stages 2 to 5)

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Supplementary Table 6. Change (post RCT response minus baseline response) in subjective awareness, symptom and hormonal responses during clamped hypoglycemia according to treatment allocation, MDI vs. CSII and NO-RTCGM vs. RTCGM.

	MDI	**CSII**	**P***	**NO-RTCGM**	**RTCGM**	**P***
Glucose level subject felt low (mmol/l)	0.0 (-0.3, 0.6)	1.0 (0.2, 1.5)	0.08	0.0 (-0.3, 1.0)	0.8 (0.5, 1.5)	0.07
Symptom AUC						
Total	100 (40, 260)	380 (180, 720)	0.25	140 (-240, 740)	380 (40, 660)	0.66
Autonomic	60 (-80, 220)	340 (40, 440)	0.60	120 (-160, 440)	100 (40, 520)	0.53
Neuro	0 (-40, 200)	200 (40, 320)	0.38	40 (-40, 260)	80 (-20, 320)	0.72
Hormone AUC (Incremental) ‡						
Metanephrine	1892 (-6446, 5488)	13979 (3560, 17448)	0.09	3130 (1136, 17448)	5488 (3502, 16966)	0.47
Cortisol	3666 (1824, 6282)	4729 (785, 27524)	0.54	3666 (-3889, 15834)	6027 (3586, 28234)	0.18
Glucose Thresholds (mmol/l)						
Metanephrines	0.1 (-0.2, 0.5)	0.3 (0.1, 0.6)	0.48	0.1 (-0.2, 0.5)	0.5 (0.2, 1.0)	0.07
Cortisol	0.1 (-1.0, 0.5)	0.0 (-0.3, 0.2)	0.93	-0.2 (-1.0, 0.2)	0.3 (-0.1, 1.2)	0.07

Data shown are median (IQR) and compared by Mann-Whitney U Test. AUC= Area under the curve calculated using trapezoid rule after linear interpolation of any missing data. ‡ Incremental area under the curve for hormones were calculated after subtracting the mean hormone level during euglycemia from subsequent hormone levels during hypoglycemia (stages 2 to 5)

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Supplementary Table 7. Four Choice Reaction time (milli-seconds) during progressive hypoglycemia. Values shown are Median (IQR) .

	Time from clamp start (minutes)				
	+40	**+80**	**+120**	**+160**	**+200**
Baseline	26.7 (23.0, 44.0)	27.1 (21.6, 51.4)	30.5 (24.4, 51.5)	31.6 (23.0, 56.9)	34.5 (24.0, 61.4)
Post RCT	27.1 (23.1, 37.4)	28.4 (21.9, 40.8)	30.5 (22.8, 43.9)	26.2 (22.4, 47.5)	29.7 (23.3, 44.4)

Supplementary Table 8. Time taken to complete the black & white reading component of Stroop test (seconds) during progressive hypoglycemia. Values shown are Median (IQR).

	Time from clamp start (minutes)				
	+40	**+80**	**+120**	**+160**	**+200**
Baseline	60 (54, 62)	58 (55, 60)	59 (55, 61)	60 (60, 63)	67 (62, 71)
Post RCT	56 (52, 58)	59 (55, 63)	62 (58, 66)	64 (59, 72)	70 (64, 78)

Supplementary Table 9. Time taken to complete the color 'X' component of Stroop test (seconds) during progressive hypoglycemia. Values shown are Median (IQR).

	Time from clamp start (minutes)				
	+40	**+80**	**+120**	**+160**	**+200**
Baseline	85 (79, 94)	90 (83, 95)	89 (79, 94)	93 (84, 102)	106 (90, 128)
Post RCT	87 (75, 91)	87 (80, 91)	94 (77, 106)	97 (84, 110)	108 (100, 128)

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Supplementary Table 10. Time taken to complete the color word interference component of Stroop test (Seconds) during progressive hypoglycemia. Values shown are Median (IQR).

	Time from clamp start (minutes)				
	+40	**+80**	**+120**	**+160**	**+200**
Baseline	117 (107, 126)	115 (105, 131)	123 (105, 132)	130 (109, 157)	146 (127, 174)
Post RCT	111 (102, 120)	115 (107, 140)	119 (108, 142)	123 (115, 137)	140 (127, 188)

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Supplementary Figure 1. Panel A: Autonomic and Panel B: Neuroglycopenic symptom scores during baseline (black circles) and post-RCT (white squares) clamp studies for the whole clamp cohort (N=18). Data shown are mean ± SE