Long-term Health Benefits to Newly Diagnosed Type-2 Diabetes from Short-term Continuous-subcutaneous Insulin Injection Therapy

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Research

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Abstract

Background

Continuous-subcutaneous insulin injection (CSII) therapy to type 2 diabetes mellitus (T2DM) patients generated short-term health benefits. Our aims were to investigate long-term health benefits of CSII monotherapy, in combination with metformin and pioglitazone, or with sitagliptin.

Methods

In this randomized clinical trial, patients were treated for around 90 days and were monitored for one year. Demographic and laboratory data were analysed using the UKPDS_OM2 program to estimate 20-year health benefits. Multiple linear regression model was used to identify factors associated with changes of each health benefit.

Results

For the 134 treated patients, most health benefit indicators were improved significantly, except for renal failure. For example, life expectancies increased by 0.41±0.48 year and quality-adjusted life expectancy (QALE) by 0.45±0.46 year ($p<0.001$). Reductions in 20-year risk were: amputation by 70.6%, ulcer 66.7%, blindness 57.1%, stroke 45.5%, myocardial infarction 43.5%, all-causes of death 20.5%, ischaemic heart disease 6.7%, with heart failure < 0.1%. However, no difference in benefits was found among the three therapeutic protocols. Health benefits were lower for older patients, for females in amputation and ulcer risk, and for smokers in blindness risk.

Conclusions

Short-term CSII therapy produced significant and multiple long-term health benefits (based on simulated risk analyses) to T2DM patients and benefits were modified by age, sex and smoking factors. The three therapeutic protocols produced the same benefits.

Trial registration

The clinical trial was registered in ClinicalTrials.gov on November 15, 2011, with the registration number: NCT01471808.

Background

Type 2 Diabetes Mellitus (T2DM) is a common non-communicable disease around the world and is characterized by two major features: insulin resistance and insufficient insulin secretion from pancreatic beta-cells [1]. Furthermore, progressive deteriorations of beta-cell often lead to fasting and postprandial hyperglycaemia [1], which accelerates beta-cell dysfunction [2] and mortality. Therefore, insulin supplement therapy is often applied to these patients.

Short-term intensive insulin therapy by continuous subcutaneous insulin infusion (CSII) or by multiple daily injections can enhance beta-cell function, and induce long-term glycaemia remission in T2DM patients [3, 4]. Additionally, one year after termination of the insulin therapy, nearly 50% of the patients maintained glycaemic remission [3–6], and 40% showed drug-free remission even after 2 years [4, 7].

In addition to CSII therapy alone, combined therapies with other anti-hyperglycaemic medicines have shown additional short-term benefits. For example, the combined therapy patients often required less total daily insulin doses [8–12], achieved their glycaemic goals sooner [10], experienced less hypoglycaemia [10, 12] and nocturnal hypoglycaemia [13], and showed reduced glycaemic variability [8, 14] – a risk factor to vascular complications of diabetes [15] – than those with the CSII monotherapy. However, long-term health benefits from these therapeutic protocols need to be determined systematically.

The objectives for this study were to evaluate and to compare long-term health benefits among and within three clinical CSII therapies. Factors which contribute to the benefits, e.g., impacts of demographic characteristics and baseline indicators on long-term benefits, were considered. Subgroups of people with greater long-term benefits from these treatments were also identified.

Methods

Clinical trial design and participants

This study was based on a multi-site, randomized, prospective, controlled trial (NCT01471808, ClinicalTrials.gov) design and was conducted in five hospitals – the First Affiliated Hospital of Sun Yat-sen University, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Nanfang Hospital of Southern Medical University, Peking University Shenzhen Hospital, and Foshan First People's Hospital – in China from November 2011 to December 2018. Patients who were newly diagnosed with T2DM without anti-hyperglycaemic treatments were recruited. The inclusion criteria were: between 25 and 65 years old, with body-mass index (BMI) of 21–35 kg/m^2 and with fasting plasma glucose of 7.0 to 16.7mmol/L. The exclusion criteria were: with positive tests for autoimmune antibodies to islet, with severe acute or chronic complications due to diabetes, with alcohol abuse or a psychiatric disorder, being pregnant or planning pregnancy.

All patients were randomly assigned to one of the three in-hospital treatment groups: short-term continuous subcutaneous insulin infusion (CSII) monotherapy using rapid-acting insulin analogues (Humalog or NovoRapid), CSII plus metformin (Gehuazhi® 0.5 tid) and pioglitazone (actos® 30mg qd) (CSII-MP), and CSII plus sitagliptin (JANUVIA® 100mg qd) group (CSII-S). The CSII treatments for the three groups were the same, with an initial insulin dosage 0.5-0.7IU/kg/d. In 2 to 3 day after initiation of CSII treatments for the three groups of patients, when the glycaemic targets (fasting plasma glucose ≤ 6.0 mmol/l and postprandial blood glucose ≤ 8.0 mmol/l) were achieved and then maintained for two weeks, CSII treatments would be withdrawn. After the two-week CSII treatments, all patients were monitored at the 3rd and 12th months as outpatients. For two groups of patients, the three drugs were administered at the same time with CSII, but continued for 3 months from CSII initiation.

Data collection

Before initiation of treatment, data were collected from all patients: demographics, behavioural characteristics (age, sex, duration of diabetes, smoking status), anthropometric indices (height), and some additional conditions (peripheral vascular disease, atrial fibrillation, albuminuria). In addition, during pre- and post-therapy (end of in-hospital treatment, 3rd and 12th months), laboratory data were conducted: blood indicators (haemoglobin, white blood cell count, glycated haemoglobin [HbA1c], lipid profiles – high-density lipoprotein cholesterol [HDL-c], low-density lipoprotein cholesterol [LDL-c] and estimated glomerular filtration rate [eGFR]), and other anthropometric indices (weight, serum creatinine, hart rate, systolic blood pressure [SBP]).

Assessment of long-term health benefit

Using the demographic and laboratory data at pre-treatment and at three time points post-treatment, eleven health indicators were simulated using the United Kingdom Prospective Diabetes Study Outcomes Model II (UKPDS_OM2). Algorithms for the model were developed based on 30 years of follow-up data from the United Kingdom Perspective Diabetes Study [16]. The eleven health indicators were: an aggregation of life expectancy, quality-adjusted life expectancy (QALE), cumulative risk of all-causes of death and of eight essential diabetes-related complications, ischaemic heart disease [IHD], myocardial infarction [MI], heart failure [HF], stroke, amputation, renal failure [RF], blindness and ulcer.

Values of health indicators at pre-treatment were simulated by using values of parameters – demographic and laboratory data – collected at baseline (Table 1). Values of health indicators at post-treatments were simulated by synthetically using values of parameters at three time-points: end of in-hospital treatment, 3-month follow-up and 12-month follow-up. In parameter setting of the simulation model, it was necessary to assume changes for each parameter over time. Parameters in continuous types were raised by 1.5% annually, while binary ones were not changed [17].

Table 1
Baseline parameters and test results from three therapy protocols

Parameters	Total(N = 134)	CSII (N = 42)	CSII-MP (N = 48)	CSII-S (N = 44)	*P*-value
					0.811
Age (year)	46.34 ± 8.63	46.69 ± 8.48	45.00 ± 8.27	47.45 ± 9.15	0.378
Male n (%)	99(73.9)	30 (71.4)	37 (77.1)	32 (72.7)	0.812
BMI (kg/m^2)	25.74 ± 2.95	25.44 ± 2.52	26.34 ± 3.32	25.38 ± 2.86	0.216
Duration of diabetes (year)	0.89 ± 1.03	0.94 ± 1.20	0.91 ± 1.04	0.83 ± 0.84	0.887
Current Smoker n (%)	58 (43.3)	19 (45.2)	20 (41.7)	19 (43.2)	0.943
PVD n (%)	72 (53.7)	19 (45.2)	26 (54.2)	27 (61.4)	0.324
WBC ($\times 10^9/l$)	6.41 ± 1.59	6.42 ± 1.82	6.56 ± 1.63	6.24 ± 1.30	0.639
Hemoglobin (g/dl)	14.73 ± 1.31	14.65 ± 1.30	15.00 ± 1.16	14.51 ± 1.45	0.187
HbA1c (%)	10.38 ± 2.20	10.40 ± 2.16	10.39 ± 2.22	10.34 ± 2.26	0.991
HDL-c (mmol/l)	1.09 ± 0.25	1.14 ± 0.27	1.04 ± 0.25	1.11 ± 0.23	0.130
LDL-c (mmol/l)	3.73 ± 0.84	3.70 ± 0.80	3.78 ± 0.87	3.70 ± 0.85	0.871
SBP (mmHg)	126.04 ± 14.17	121.88 ± 13.71	129.58 ± 13.82	126.14 ± 14.20	**0.035**
DBP (mmHg)	80.81 ± 10.43	77.98 ± 11.38	83.29 ± 8.39	80.82 ± 11.01	0.053
Heart rate (bpm)	78.45 ± 10.40	76.02 ± 9.47	77.54 ± 9.67	81.75 ± 11.35	**0.028**
eGFR ($ml/min/1.73m^2$)	118.78 ± 24.13	115.88 ± 23.06	117.86 ± 26.35	122.55 ± 22.61	0.420
Baseline life expectancy (year)	13.10 ± 1.53	13.20 ± 1.59	13.18 ± 1.44	12.91 ± 1.57	0.610
Baseline Total QALE (year)	10.33 ± 1.29	10.43 ± 1.35	10.38 ± 1.21	10.16 ± 1.32	0.593

CSII, continuous subcutaneous insulin infusion monotherapy group; CSII-MP, continuous subcutaneous insulin infusion plus metformin and pioglitazone group; CSII-S, continuous subcutaneous insulin infusion plus sitagliptin group.

Values are expressed as mean ± sd.

BMI, body mass index; PVD, peripheral vascular disease; WBC, white blood cell; HbA1c, glycated haemoglobin A1c, HDL-c, high-density lipoprotein; LDL-c, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimating glomerular filtration rate; Total QALE: total quality-adjusted life expectancy.

Only patients who had completed all laboratory parameters for the 12 months were included into the simulation model and in this report. Certain missing values at 3-month were inputted with five-fold Multiple Imputation by Chained Equations via the “mice” package of R based on all candidate predictors and outcomes [18]. Variables which had high correlations (Coefficient of determination R square > 0.8) with others were inputted through the Bayesian linear regression method, whereas the rests were inputted via the Random Forest Imputations method. Patterns of missing data were investigated by the R function – “densityplot” – for inspecting the imputations and graphical representations [18].

Statistical Analyses

In description of data distribution, continuous variables which conformed approximately to normal distributions were presented as mean ± standard deviations, while others were presented as medians and internal-quartiles. Categorical variables were presented in terms of quantities and percentages.

Differences for all parameters at baseline among the three therapy groups were compared. The Chi-square test or Fisher exact test was used in categorical variables, and the paired t test or Wilcoxon’s test was used for continuous variables.

The multiple linear regression model was used to identify effects of key factors on change extent for each health indicator. In model fitting for each health indicator, each dependent variable was the difference as calculated by subtracting the pre-treatment from the post-treatment simulation values. The independent variables included therapy strategies, sex, age, peripheral vascular disease (PVD), baseline life expectancy, baseline total QALE, baseline SBP and baseline HR. Baseline life expectancy and baseline total QALE were for adjustment, and other variables were also used to identify their effects. All analyses were performed using R 4.0.3. A two-sided P value of 0.05 or less was considered to be significant.

Results

Among the 262 recruited patients in our clinical trial, 134 completed the one-year follow-up laboratory tests. Therefore, the latter were the study subjects for this report. Distribution of these subjects in the three treatment groups were: 42, 48 and 44 in CSII, CSII-MP and CSII-S, respectively. Their characteristics at baseline are summarized in Table 1. There was no significant difference in these characteristics among the three groups, except the pre-treatment SBP (P = 0.035) and HR (P = 0.028).

For all patients, simulation analyses of the collected data indicate that the treatments significantly increased life expectancy by 0.41 ± 0.48 year and QALE by 0.45 ± 0.46 year (all p < 0.001). Based on univariate analyses, there were no significant changes in the two indicators among the three treatment groups (Table 2).

Table 2
Simulated life expectancies and total QALE between pre- and post-treatments from three therapy protocols

Group	Life expectancy (years)					Total QALE (years)				
	Pre-treatment	Post-treatment	D	t	P-value	Pre-treatment	Post-treatment	D	t	P-value
Total	13.10 ± 1.53	13.51 ± 1.20	0.41 ± 0.48	9.818	**< 0.001**	10.33 ± 1.29	10.77 ± 1.00	0.45 ± 0.46	11.365	**< 0.001**
CSII	13.20 ± 1.59	13.55 ± 1.21	0.36 ± 0.50	4.592	**< 0.001**	10.43 ± 1.35	10.82 ± 1.00	0.39 ± 0.47	5.377	**< 0.001**
CSII-MP	13.18 ± 1.44	13.60 ± 1.17	0.42 ± 0.44	6.623	**< 0.001**	10.38 ± 1.21	10.85 ± 0.97	0.46 ± 0.41	7.754	**< 0.001**
CSII-S	12.91 ± 1.57	13.36 ± 1.24	0.45 ± 0.52	5.792	**< 0.001**	10.16 ± 1.32	10.65 ± 1.03	0.49 ± 0.49	6.573	**< 0.001**
CSII, continuous subcutaneous insulin infusion monotherapy group; CSII-MP, continuous subcutaneous insulin infusion plus metformin and pioglitazone group; CSII-S, continuous subcutaneous insulin infusion plus sitagliptin group.										
Total QALE: total quality-adjusted life expectancy.										

From simulated risk analyses on the collected data, the nine health indicators at baseline (pre-treatment) for all patients were classified into four levels: the highest risk level, from 37% and 48%, included all causes of death and MI; the second level, from 10–18%, included amputation, IHD and stroke; the third level, from 4–7%, included blindness, ulcer and HF; and the lowest level included only RF with risk less than 3%.

After treatment, changes in simulation values of 20 years cumulative risks for all-causes of death, MI, amputation, IHD, stroke, blindness, ulcer and HF were all statistically significant (p < 0.001), except RF (Table 3). The most reductions were observed for MI, amputation and all-causes of death 20%, 12% and 8%, respectively. Reductions for stroke, ulcer and blindness were around 4% each.

Table 3
Simulation of 20 years of cumulative health risks in nine health benefit indicators

Variables	Pre-treatment	Post-treatment	Δ	Percentage	*P*-value	Variables	Pre-treatment	Post-treatment	Δ	Percentage	*P*-value
All-causes of death						**Blindness**					
Total	0.39 ± 0.22	0.31 ± 0.19	-0.08 ± 0.07	-20.5	**< 0.001**	Total	0.07 ± 0.04	0.03 ± 0.01	-0.04 ± 0.03	-57.1	**< 0.001**
CSII	0.37 ± 0.22	0.31 ± 0.19	-0.07 ± 0.06	-18.9	**< 0.001**	CSII	0.07 ± 0.04	0.03 ± 0.01	-0.04 ± 0.03	-57.1	**< 0.001**
CSII-MP	0.39 ± 0.21	0.30 ± 0.18	-0.09 ± 0.07	-23.1	**< 0.001**	CSII-MP	0.07 ± 0.03	0.03 ± 0.01	-0.04 ± 0.03	-57.1	**< 0.001**
CSII-S	0.42 ± 0.22	0.34 ± 0.20	-0.08 ± 0.07	-19	**< 0.001**	CSII-S	0.07 ± 0.04	0.03 ± 0.01	-0.04 ± 0.03	-57.1	**< 0.001**
MI						**Ulcer**					
Total	0.46 ± 0.22	0.26 ± 0.13	-0.20 ± 0.14	-43.5	**< 0.001**	Total	0.06 ± 0.04	0.03 ± 0.02	-0.04 ± 0.03	-66.7	**< 0.001**
CSII	0.42 ± 0.19	0.25 ± 0.11	-0.17 ± 0.13	-40.5	**< 0.001**	CSII	0.06 ± 0.05	0.03 ± 0.02	-0.03 ± 0.03	-50	**< 0.001**
CSII-MP	0.48 ± 0.25	0.27 ± 0.14	-0.22 ± 0.16	-45.8	**< 0.001**	CSII-MP	0.06 ± 0.04	0.03 ± 0.01	-0.04 ± 0.03	-66.7	**< 0.001**
CSII-S	0.47 ± 0.23	0.26 ± 0.13	-0.20 ± 0.14	-42.6	**< 0.001**	CSII-S	0.07 ± 0.05	0.03 ± 0.02	-0.04 ± 0.03	-57.1	**< 0.001**
Amputation						**HF**					
Total	0.17 ± 0.14	0.05 ± 0.04	-0.12 ± 0.12	-70.6	**< 0.001**	Total	0.04 ± 0.02	0.04 ± 0.02	0.00 ± 0.01	0	**0.009**
CSII	0.14 ± 0.12	0.05 ± 0.04	-0.10 ± 0.10	-71.4	**< 0.001**	CSII	0.04 ± 0.03	0.04 ± 0.03	0.00 ± 0.01	0	0.091
CSII-MP	0.18 ± 0.16	0.05 ± 0.04	-0.13 ± 0.12	-72.2	**< 0.001**	CSII-MP	0.04 ± 0.02	0.04 ± 0.02	0.00 ± 0.01	0	0.079
CSII-S	0.18 ± 0.15	0.05 ± 0.03	-0.13 ± 0.14	-72.2	**< 0.001**	CSII-S	0.04 ± 0.02	0.04 ± 0.02	0.00 ± 0.01	0	0.332
IHD						**RF**					
Total	0.15 ± 0.05	0.14 ± 0.05	-0.01 ± 0.03	-6.7	**0.019**	Total	0.0024 ± 0.0036	0.0029 ± 0.0034	0.0005 ± 0.0034	20.8	0.092
CSII	0.14 ± 0.04	0.14 ± 0.05	0.00 ± 0.03	0	0.758	CSII	0.0029 ± 0.0047	0.0030 ± 0.0035	0.0002 ± 0.0043	6.9	0.790
CSII-MP	0.16 ± 0.06	0.15 ± 0.05	-0.01 ± 0.04	-6.3	**0.015**	CSII-MP	0.0026 ± 0.0030	0.0032 ± 0.0039	0.0006 ± 0.0033	23.1	0.194
CSII-S	0.15 ± 0.05	0.14 ± 0.05	-0.01 ± 0.03	-6.7	0.095	CSII-S	0.0016 ± 0.0028	0.0023 ± 0.0027	0.0007 ± 0.0026	43.8	0.097
Stroke											
Total	0.10 ± 0.06	0.06 ± 0.04	-0.04 ± 0.04	-40	**< 0.001**						

Variables	Pre-treatment	Post-treatment	Δ	Percentage	*P*-value	Variables	Pre-treatment	Post-treatment	Δ	Percentage	*P*-value
CSII	0.10 ± 0.06	0.06 ± 0.03	-0.04 ± 0.04	-40	**< 0.001**						
CSII-MP	0.11 ± 0.06	0.06 ± 0.04	-0.04 ± 0.03	-45.5	**< 0.001**						
CSII-S	0.11 ± 0.06	0.07 ± 0.04	-0.04 ± 0.04	-36.4	**< 0.001**						

CSII, continuous subcutaneous insulin infusion monotherapy group; CSII-MP, continuous subcutaneous insulin infusion plus metformin and pioglitazone group; CSII-S, continuous subcutaneous insulin infusion plus sitagliptin group.

Δ, changes from pre-treatment to post-treatment.

Values are expressed as mean ± sd.

Percentage, Δ divide pre-treatment value, %.

MI, myocardial infarction; IHD, ischaemic heart disease; HF, heart failure; RF, renal failure.

The extents of changes were calculated by the differences between post-treatment and baseline values over baseline. Among the eight health indicators, significant variations in improvements were observed for amputation 70.6%, ulcer 66.7%, blindness 57.1%, stroke 45.5%, MI 43.5%, all-causes of death 20.5%, IHD 6.7% and HF with less than 0.1%.

Comparing results from the three treatment protocols, patients in CSII-MP group showed larger reductions for the 20 years cumulative risks in MI, amputation and all-causes of death (22%, 13% and 9%, respectively) than the other two groups (Table 3). On the other hand, the CSII group had fewer reductions for the same three health indicators: 17%, 10% and 7% respectively. However, there were no significant differences among results from the three protocols, except the 20 years cumulative risks for IHD by 1% in the CSII-MP group (Table 3).

Results from the multiple linear regression analyses show that prolongation of either life expectancy or total QALE among the three groups were not statistically significant, after the demographic characteristics and baseline indicators were adjusted. This model also shows that extensions of life expectancy were age-dependent. The second (aged 41 to 46 years), third (aged 47 to 53 years), and fourth (aged 54 to 65 years) quartile age groups had less extension by 0.15, 0.28 and 0.61 years less, respectively, than the first quartile (aged 29 to 40 years) age group. The changes of total QALE from pre-treatment to post-treatment were similar, with 0.18, 0.29 and 0.63 years shorter in the second, third and fourth quartile age groups, respectively. In addition, patients who were smoker gained less extension of total QALE (by 0.13 year) compared to those who were non-smokers or ex-smokers (Table 4).

Table 4
Multivariate analyses of factors associated with changes in extent of life expectancy and QALE

	Life expectancy		Total QALE	
	Partial regression coefficient(95%CI)	P-value	Partial regression coefficient(95%CI)	P-value
CSII	0	-	0	-
CSII-MP	0.0005(-0.12, 0.12)	0.994	-0.0019(-0.11,0.11)	0.983
CSII-S	-0.02(-0.14, 0.10)	0.786	-0.01(-0.12, 0.10)	0.856
Sex, female	-0.05(-0.19,0.09)	0.455	-0.05(-0.18, 0.08)	0.462
Age,29–40 years	0	-	0	-
Age,41–46 years	-0.15(-0.29, -0.01)	**0.033**	-0.18(-0.31, -0.05)	**0.006**
Age,47–53 years	-0.28(-0.44, -0.12)	**0.001**	-0.29(-0.44, -0.15)	**< 0.001**
Age,54–65 years	-0.61(-0.85, -0.37)	**< 0.001**	-0.63(-0.85, -0.41)	**< 0.001**
Smoker	-0.11(-0.24, 0.01)	0.072	-0.13(-0.25, -0.02)	**0.024**
PVD	0.07(-0.04, 0.18)	0.199	0.06(-0.05, 0.16)	0.301
Baseline life expectancy	-0.34(-0.41, -0.28)	< 0.001	-	-
Baseline Total QALE	-	-	-0.39(-0.46, -0.32)	< 0.001
Baseline SBP	0.001(-0.002,0.005)	0.490	0.001(-0.002, 0.005)	0.430
Baseline HR	0.01(0.0004, 0.010)	0.034	0.005(0.0004, 0.01)	0.033
CI, confidence interval.				
CSII, continuous subcutaneous insulin infusion monotherapy group; CSII-MP, continuous subcutaneous insulin infusion plus metformin and pioglitazone group; CSII-S, continuous subcutaneous insulin infusion plus sitagliptin group.				
PVD, peripheral vascular disease; Total QALE: total quality-adjusted life expectancy; SBP, systolic blood pressure; HR, heart rate.				

After the demographic characters and main baseline indicators were adjusted, the multiple linear regression analyses indicate that reductions of the 20 years cumulative risks in all-causes of death and the eight diabetic complications were not statistically significant among the three therapy groups (Table 5). Compared to patients aged 29 to 40 years, the 41 to 46 years patients achieved smaller decline of cumulative risks in amputation, MI and ulcer, with 7%, 6% and 1% less, respectively; the 47 to 53 years patients achieved 10% and 2% less reduction of cumulative risks in MI and IHD, respectively; the 54 to 65 years patients gained achieved 23%, 9%, 8% and 4% less decline in cumulative risks for MI, amputation, all-causes of death and stroke, respectively. Female patients achieved 8% and 2% less reduction of cumulative risks for amputation and ulcer, respectively. Those who had pre-treatment PVD, in comparison to those without, achieved 2% less reduction in stroke risk, but 10%, 4% and 2% more reduction in risks for amputation, all-causes of death and ulcer, respectively. Current smokers achieved 1% less reduction in blindness risk than non-smokers and ex-smokers. An increase of 1 bpm in baseline HR was correlated with 0.1% of more reduction in all-causes of death risk. An increase of 1 bpm of mmHg in baseline SBP was correlated with 0.1% more reduction in stroke risk.

Table 5
Multivariate analyses of factors associated with changes in extent of 20 years of cumulative risks in nine health benefit indictors

Variables	Partial regression coefficient(95%CI)	P-value	Variables	Partial regression coefficient(95%CI)	P-value
All-causes of death			**Stroke**		
CSII	0	-	CSII	0	-
CSII-MP	-0.004(-0.03, 0.02)	0.709	CSII-MP	0.001(-0.01, 0.01)	0.915
CSII-S	0.004(-0.02, 0.03)	0.723	CSII-S	0.002(-0.01, 0.01)	0.701
Sex, female	0.01(-0.01, 0.04)	0.307	Sex, female	0.003(-0.01, 0.01)	0.625
Age,29–40 years	0	-	Age,29–40 years	0	-
Age,41–46 years	0.02(-0.01, 0.05)	0.157	Age,41–46 years	0.01(-0.004, 0.02)	0.170
Age,47–53 years	0.02(-0.01, 0.05)	0.221	Age,47–53 years	0.01(-0.003, 0.02)	0.125
Age,54–65 years	0.08(0.03, 0.13)	**0.001**	Age,54–65 years	0.04(0.01, 0.06)	**0.001**
Smoker	0.01(-0.01, 0.03)	0.399	Smoker	0.01(-0.0004, 0.02)	0.058
PVD	-0.04(-0.06, -0.02)	**0.001**	PVD	0.02(0.01, 0.03)	**0.001**
Baseline life expectancy	0.03(0.02, 0.04)	< 0.001	Baseline life expectancy	0.02(0.02, 0.03)	< 0.001
Baseline SBP	-0.0003(-0.001,0.0004)	0.461	Baseline SBP	-0.001(-0.0013, -0.0007)	< 0.001
Baseline HR	-0.001(-0.002,-0.0004)	0.007	Baseline HR	0.00003(-0.00039,0.00044)	0.901
HF			**Ulcer**		
CSII	0	-	CSII	0	-
CSII-MP	0.0001(-0.003, 0.004)	0.943	CSII-MP	0.005(-0.01, 0.01)	0.373
CSII-S	0.002(-0.002, 0.005)	0.411	CSII-S	0.004(-0.01, 0.01)	0.489
Sex, female	-0.005(-0.009, -0.0005)	**0.029**	Sex, female	0.02(0.01, 0.03)	**< 0.001**
Age,29–40 years	0	-	Age,29–40 years	0	-
Age,41–46 years	-0.00001(-0.004, 0.004)	0.997	Age,41–46 years	0.01(0.002, 0.03)	**0.025**
Age,47–53 years	-0.0003(-0.005, 0.005)	0.901	Age,47–53 years	0.01(-0.01, 0.02)	0.27
Age,54–65 years	0.002(-0.006, 0.009)	0.643	Age,54–65 years	0.01(-0.01, 0.03)	0.165
Smoker	0.001(-0.003, 0.004)	0.744	Smoker	0.01(-0.001, 0.02)	0.08
PVD	-0.002(-0.005, 0.002)	0.342	PVD	-0.02(-0.03, -0.01)	**< 0.001**
Baseline life expectancy	-0.0004(-0.002, 0.002)	0.681	Baseline life expectancy	0.01(0.01, 0.02)	0.001
Baseline SBP	0.00002(-0.0001, 0.0001)	0.702	Baseline SBP	-0.00001(-0.0003,0.0003)	0.971
Baseline HR	-0.0001(-0.0002, 0.0001)	0.231	Baseline HR	0.00004(-0.0004,0.0004)	0.827
IHD			**Blindness**		
CSII	0	-	CSII	0	-
CSII-MP	-0.01(-0.03, 0.002)	0.104	CSII-MP	0.01(-0.01, 0.02)	0.345
CSII-S	-0.01(-0.02, 0.004)	0.174	CSII-S	0.01(-0.01, 0.02)	0.353
Sex, female	-0.01(-0.02, 0.01)	0.305	Sex, female	-0.001(-0.01, 0.01)	0.924
Age,29–40 years	0	-	Age,29–40 years	0	-
Age,41–46 years	0.01(-0.01, 0.02)	0.493	Age,41–46 years	0.01(-0.003, 0.02)	0.125
Age,47–53 years	0.02(0.0004, 0.04)	**0.045**	Age,47–53 years	0.002(-0.01, 0.02)	0.748

Variables	Partial regression coefficient(95%CI)	P-value	Variables	Partial regression coefficient(95%CI)	P-value
Age,54–65 years	0.04(0.01, 0.07)	**0.012**	Age,54–65 years	0.01(-0.01, 0.03)	0.316
Smoker	0.01(-0.01, 0.02)	0.367	Smoker	0.01(0.001, 0.03)	**0.031**
PVD	-0.01(-0.02, 0.01)	0.387	PVD	0.01(-0.001, 0.02)	**0.073**
Baseline life expectancy	0.004(-0.004, 0.01)	0.342	Baseline life expectancy	0.01(0.01, 0.02)	< 0.001
Baseline SBP	-0.0003(-0.001, 0.0001)	0.117	Baseline SBP	-0.0002(-0.001, 0.0002)	0.307
Baseline HR	0.0003(-0.0003, 0.001)	0.317	Baseline HR	-0.001(-0.001,-0.0001)	0.016
MI			**Amputation**		
CSII	0	-	CSII	0	-
CSII-MP	-0.02(-0.07, 0.02)	0.324	CSII-MP	0.01(-0.03 ,0.05)	0.617
CSII-S	-0.01(-0.06, 0.03)	0.598	CSII-S	0.002(-0.04, 0.05)	0.923
Sex, female	0.05(-0.002, 0.11)	0.060	Sex, female	0.08(0.03, 0.13)	**0.002**
Age,29–40 years	0	-	Age,29–40 years	0	-
Age,41–46 years	0.06(0.01, 0.11)	**0.031**	Age,41–46 years	0.07(0.02, 0.12)	**0.004**
Age,47–53 years	0.10(0.04, 0.16)	**0.001**	Age,47–53 years	0.05(-0.01, 0.11)	0.078
Age,54–65 years	0.23(0.14, 0.33)	**< 0.001**	Age,54–65 years	0.09(0.01, 0.18)	**0.034**
Smoker	0.03(-0.01, 0.08)	0.156	Smoker	0.02(-0.02, 0.07)	0.284
PVD	-0.01(-0.06,0.03)	0.514	PVD	-0.10(-0.14, -0.06)	**< 0.001**
Baseline life expectancy	0.09(0.06,0.11)	< 0.001	Baseline life expectancy	0.02(-0.01, 0.04)	0.135
Baseline SBP	-0.0002(-0.002, 0.001)	0.766	Baseline SBP	-0.001(-0.002, 0.0001)	0.069
Baseline HR	-0.0001(-0.002, 0.002)	0.900	Baseline HR	-0.002(-0.004,-0.0001)	0.035

CI, confidence interval.

CSII, continuous subcutaneous insulin infusion monotherapy group; CSII-MP, continuous subcutaneous insulin infusion plus metformin and pioglitazone group; CSII-S, continuous subcutaneous insulin infusion plus sitagliptin group.

PVD, peripheral vascular disease; Total QALE: total quality-adjusted life expectancy; SBP, systolic blood pressure; HR, heart rate.

MI, myocardial infarction; IHD, ischaemic heart disease; HF, heart failure; RF, renal failure.

Discussion

Previous studies indicate that short-term CSII treatment of newly diagnosed T2DM patients improved beta-cell function and glycaemic control with long-term drug-free remission [3, 4]. In addition, glycaemic remission after therapy was associated with lower red blood cell distribution width at baseline [19], higher decrement of total daily insulin dose during CSII therapy [20], lower fasting plasma glucose [21] and elevated 1,5-anhydroglucitol [22]. However, long-term health benefits from such short-term CSII therapy have not been well-characterized. Therefore, our investigation provides new information to fill the information gap.

From our clinical trial, all three CSII therapeutic protocols generated similar long-term health benefits to the T2DM patients, with no significant differences among them. This indicates that addition of the three oral anti-hyperglycaemic medicines to CSII therapy did not enhance efficacy compared to CSII monotherapy. Analyses of effects for all patients indicate that their life expectancy and total QALE were significantly extended. In addition, the cumulative risks of all-causes of death and diabetic vascular complications: MI, stroke, amputation, blindness, and ulcer, were reduced significantly. In support of our observations, patients achieved glycaemic control and beta-cell function in less time, and longer glycaemic remission rates using intensive insulin therapy compared to oral therapies [3]. Other reports indicate that certain antidiabetic effects of CSII therapy were still effective 3 months after termination of the therapy [5, 6].

Our data indicate efficacy of the CSII therapy (either alone or in combination with the oral medications). However, the therapy did not generate equal efficacy among the monitored complications of diabetes. The therapy was highly effective in both absolute risk reduction and ratio of risk reduction

for amputation, MI and all-causes of death. Changes in the absolute risks for stroke, blindness and ulcer were small, due to the small cumulative risks at baseline. It was a pleasant observation that the therapy was estimated to prevent half of the patients from suffering each disease. On the other hand, the therapy had limited effects on preventing IHD and HF. Although changes in their risk were statistically significant, both the absolute reduction and the ratio of risk reduction were too small to be clinically relevant. Therefore, from the perspective of population benefits, the CSII therapy generated significant benefits to T2DM patients in MI and amputation, followed by stroke. Although ulcer and blindness had high rates of changes, their risks were low. Furthermore, the therapy generated little to no benefits to IHD, HF, and RF.

From 3 months after the therapy, changes in the variations of core parameters (HbA1c, HDL-c, LDL-c, etc.) were observed, but there were no statistically significant changes among the parameters and health indicators, as well as among the three therapy groups. A similar observation indicates diminutions of beta-cell functions which were improved via intensive insulin treatment, whether the patients were in the sitagliptin or placebo groups [23]. Furthermore, protective effects of sitagliptin on beta-cell functions were not noticeable [23]. Other reports, however, indicate some benefits from intensive insulin therapy with oral anti-hyperglycaemic agents: less hypoglycaemia [10, 12, 13], lower glycaemic variability [8, 14], and less usage of daily insulin [8–12]. For these reasons, adding oral agents to CSII monotherapy may still be useful, even though our monitored end points did not show additional long-term health benefits.

Our results also show that patients who were younger achieved more long-term health benefits than the elders from the three therapeutic protocols, although there was no significant difference among them. Our observations are supported by a report on longer drug-free glycaemic remission after short-term CSII [5]. Other important associations were identified by our study: the cumulative risks for ulcer, amputation and all-causes of death were reduced more in patients with pre-treatment PVD, while that of stroke in the same patients was on the contrary. Female patients received fewer benefits in amputation and ulcer. Obviously, all observed associations have practical values in improving the management of patients' health. Further refinement of our observations may contribute to achieving personalized health management. For example, better algorithms for classification of personal needs should identify more precisely the roles of various influences and factors on health benefits.

Despite our effort to conduct this clinical trial vigorously, there are limitations in this study. First, the long-term health benefits were simulated based on the UKPDS_OM2 program. Despite our effort to adjust ethnicity effects (using Asian-Indians as representatives), there are still potential bias as shown in a report using a German population for estimating risks for death, MI and stroke [17]. Nevertheless, our risk estimation was a conservative one and the estimation is still useful for China because such an effort has not been performed in China previously. Therefore, our results should stimulate additional investigations in China and around the world. Second, out of the 262 recruited subjects, our investigation included only 134 who had completed the 12-month monitoring activities. However, the characteristics of the 134 individuals were similar to those of excluded subjects. It was our decision that inclusion of the excluded subjects who had incomplete data would certainly compromise our estimation of health benefits.

Conclusions

CSII therapy alone generated positive and significant long-term health benefits to T2DM patients. Based on our estimation criteria, addition of other anti-diabetic medication to CSII did not generate more health benefits. The health benefits were influenced by age, sex, smoking status, PVD, baseline HR and baseline SBP. Our data have meaningful and practical values for improving health of T2DM patients, especially in China, and can stimulate further investigations around the world.

Abbreviations

BMI, body-mass index; CSII, continuous-subcutaneous insulin injection; CSII-MP, CSII plus metformin and pioglitazone; CSII-S, CSII plus sitagliptin; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-c, high-density lipoprotein cholesterol; HF, heart failure; IHD, ischaemic heart disease; LDL-c, low-density lipoprotein cholesterol; MI, myocardial infarction; PVD, peripheral vascular disease; QALE, quality-adjusted life expectancy; RF, renal failure; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; UKPDS_OM2, United Kingdom Prospective Diabetes Study Outcomes Model II.

Declarations

Ethics approval and consent to participate

Research Ethics Board of the First Affiliated Hospital of Sun Yat-sen University approved the original trial, and all patients had signed informed consent forms before they participated in the trial.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Authorship

All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' Contributions

Wanjun Zhang contributed to the study by designing and writing the manuscript. Weijian Ke collected the original data and provided expert advice on results interpretation. Qiao Bian, Huijie Guo and Dantong Zheng defined the analytic strategy and analysed the data. Qun He, Liehua Liu supported data collection, statistical modelling, and data analysis. Yanbing Li and Yinghua Xia provided expert advice about study design, data analysis and results interpretation.

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Disclosure

All named authors declare that they have no conflict of interest.

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