

## sTable 1

### Inclusion criteria

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Subjects were considered eligible for inclusion if they were 45 years old or older but younger than 70 years old at study entry, had type 2 diabetes and met both “(1) and (2)” or both “(1) and (3)” described below.

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(1) Glycemic control: those with HbA1c  $\geq 6.9\%$  (52 mmol/mol) or greater despite treatment with any of the 3 regimens given below:

- a) diet and exercise therapy alone
  - b) diet and exercise therapy plus 1 oral anti-diabetic drug,
  - c) diet and exercise therapy plus alpha-GI and another oral anti-diabetic drug
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(2) Blood pressure control: those with the following casual BP level as measured on an outpatient basis:

- a) systolic BP  $\geq 140$  mm Hg or diastolic BP  $\geq 90$  mm Hg while not taking an antihypertensive drug
- b) systolic BP  $\geq 130$  mm Hg or diastolic BP  $\geq 80$  mmHg while taking 1 or 2 ARB, ACEI, or long-acting CCB

Those receiving antihypertensive drugs other than these 3 drugs were not eligible for study entry, with the exception of those who were receiving these drugs for purposes other than blood pressure lowering

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(3) Lipid control: those with the following fasting lipid levels not taking a lipid-lowering drug or taking a lipid-lowering drug:

- a) LDL-cholesterol  $\geq 120$  mg/dL (as estimated by using the Friedewald formula)
  - b) triglycerides  $\geq 150$  mg/dL
  - c) HDL-cholesterol  $< 40$  mg/dL
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## sTable 2

### Exclusion criteria

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- (1) those with poorly controlled hypertension despite pharmacological therapy (systolic BP  $\geq$ 200 mm Hg or diastolic BP  $\geq$ 120 mm Hg)
  - (2) those receiving insulin therapy
  - (3) those with non-diabetic renal disease
  - (4) those in whom type 1 diabetes, due to pathogenic mechanisms other than those associated with type 2 diabetes, is strongly suspected
  - (5) those who tested anti-GAD antibody-positive
  - (6) those with LDL-cholesterol  $\geq$ 200 mg/dL
  - (7) those suspected of having secondary hypertension other than renal parenchymal hypertension
  - (8) those suspected of having hereditary lipid disorder with a strong family history of lipid metabolic disorder
  - (9) those who were receiving antihypertensive drugs other than ARB, ACEI, or long-acting CCB, except where they were receiving these drugs for purposes other than blood pressure lowering
  - (10) those who were receiving 3 or more antihypertensive drugs (i.e., ARB, ACEI, and long-acting CCB), except where they were receiving these drugs for purposes other than blood pressure lowering
  - (11) those with more serious retinopathy than proliferative retinopathy
  - (12) renal failure (serum Cr:  $\geq$ 2.0 mg/dL in men;  $\geq$ 1.5 mg/dL in women)
  - (13) those with a history of cardiac failure or those with cardiac failure
  - (14) those who were pregnant or potentially pregnant
  - (15) those who met any of the following criteria and who had BNP  $\geq$ 100 pg/mL, myocardial infarction, angina pectoris (or a history of disease), history of coronary artery bypass graft (CABG), history of percutaneous coronary angioplasty (PTCA), other cardiac disease, ECG findings of left ventricular hyperplasia, or abnormal ECG findings (excluding isolated extrasystole or right bundle branch block [RBBB])
  - (16) those judged by the physician in charge to be ineligible for study entry
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**sTable 3**

## Management goals and interventions for lifestyle modification

	CTG	ITG
Weight control	Target BMI, $\leq 24$ Provided with diaries to record their body weight	Target BMI, $\leq 22$ Provided with diaries to record their body weight
Diet therapy	Total energy intake, 25-35 kcal/kg according to daily activity; salt intake, $\leq 6$ g/day with comorbid hypertension, $\leq 9$ g/day in male without hypertension, $\leq 7.5$ g/day in female without hypertension (in accordance with the guideline <sup>19</sup> )	Total energy intake, $\leq 25$ kcal/kg in those with BMI $\geq 25$ , $\leq 27$ kcal/kg in those with BMI $< 25$ Lipid intake, $\leq 25\%$ of total energy intake Cholesterol intake, $\leq 300$ mg/day Salt intake, $\leq 6$ g/day Between-meal and bedtime snacks, prohibited Alcohol (equivalent to 180 mL of sake or less) abstinence to be rigorously adhered to, and obliged to report on alcohol intake Thirty-minute or longer guidance on nutrition by designated national registered dietitians at the start of the study, 1, 3, 6, and 12 months after the start of the study, and every 6 months in the 2nd year afterwards
Exercise therapy	Two or more 15- to 30-minute walks on a daily basis (in accordance with the guideline <sup>19</sup> ) Provided with an accelerometer	Two or more 15- to 30-minute walks on a daily basis Provided with an accelerometer, and should report on the calories consumed as well as the number of steps taken every day
Smoking cessation		Instructed to persevere in their smoking cessation practice and to report at their regular hospital visits on the number of cigarettes smoked Provided with smoking-cessation aids, if necessary
Education		A core program and a post-core program intended to improve lifestyle habits are to be implemented to ensure lifestyle factors are improved

## sTable 4

### Definitions of the events

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#### Myocardial infarction:

the presence of typical symptoms (e.g., lasting severe chest pain), echocardiographic changes, abnormal laboratory findings (e.g., elevation of the cardiac enzyme troponin T), or findings of clinical imaging (e.g., coronary angiography, cardiac scintigraphy, multidetector row computed tomography) which were diagnosed as such by a physician.

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#### Stroke:

the presence of a newly onset focal symptom lasting more than 24 hours which was diagnosed as such by a physician (preferably with the culprit lesion identified/confirmed on CT or MRI/MRA).

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#### Occurrence of onset or progression of nephropathy:

an event when either of the following occurs:

- a. progression from normoalbuminuria (urinary albumin  $<30$  mg/g•Cr) to microalbuminuria (urinary albumin  $\geq 30$  mg/g•Cr,  $<300$  mg/g•Cr), or from normoalbuminuria to macroalbuminuria (urinary albumin  $\geq 300$  mg/g•Cr)
- b. progression from microalbuminuria to macroalbuminuria
- c. serum creatinine levels elevated 2-fold or more compared to that at study entry
- d. endstage renal failure (permanent dialysis initiated or renal transplant performed)

If a. or b. occurs in a particular subject and the measured urinary albumin value is shown to be 30% higher than that at study entry, the subject is to be re-examined (with a morning urine sample), and if the measured value is 30% higher than that at study entry, this is to be construed as the occurrence of an event.

In the event of c., the subject is also to be re-examined within 3 months of the event.

In a., b., or c., the event is to be evaluated in the first occurrence.

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#### Occurrence of onset or progression of retinopathy

an event when either of the following occurs:

- a. progression from absence of retinopathy to nonproliferative retinopathy or proliferative retinopathy
  - b. progression from nonproliferative to proliferative retinopathy
  - c. loss of vision likely due to retinopathy
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**sTable 5**

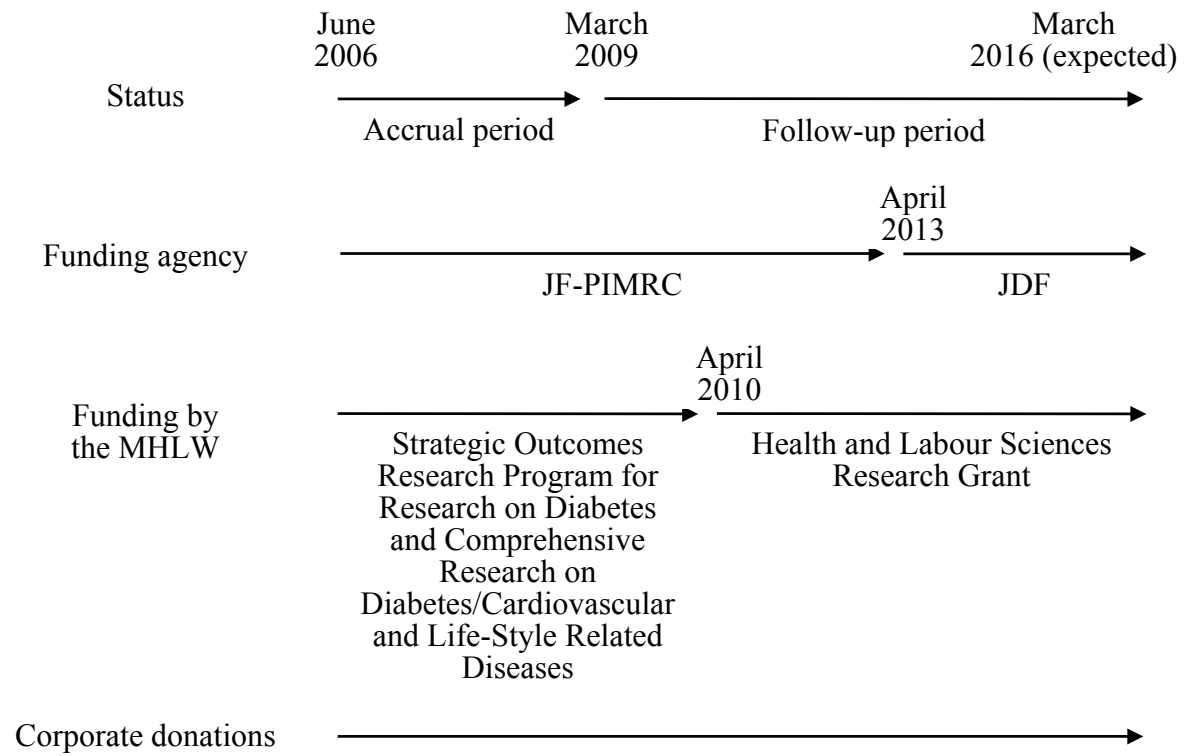
## Baseline medication

	CTG ( <i>n</i> = 1271)	ITG ( <i>n</i> = 1271)	p value
Use of any antidiabetic (%)	77.2	74.6	0.138
SU	40.7	40.1	0.808
Glinides	8.1	7.6	0.658
BG	14.8	14.2	0.736
Pioglitazone	6.7	6.5	0.936
$\alpha$ -GI	28.2	29.0	0.693
Use of any antihypertensive (%)	40.6	41.7	0.600
ARB	28.1	28.4	0.895
ACEI	4.3	5.1	0.400
Long-acting CCB	23.5	22.4	0.540
Use of any antilipemic (%)	34.2	32.0	0.255
Atorvastatin, pitavastatin, or rosuvastatin	18.8	17.9	0.609
Other statins	11.3	9.9	0.274
Anion-exchange resin	0.0	0.2	0.500
EPA	1.0	1.3	0.710
Fibrates	2.8	2.4	0.616

\* *p* values were calculated with the use of Fisher's exact test.

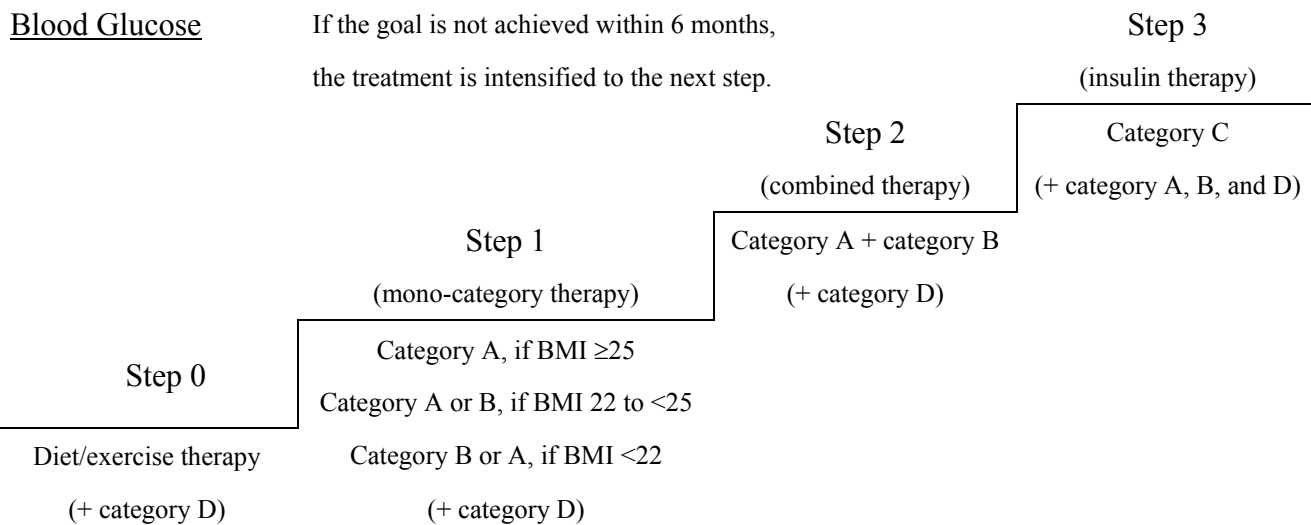
**sFigure 1**

Funding for J-DOIT3



**sFigure 2**

**Multifactorial step-wise treatment in the ITG**



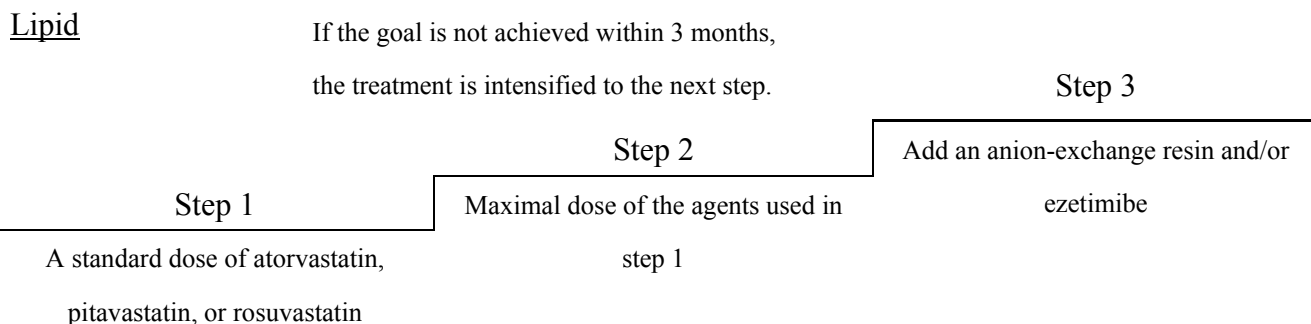
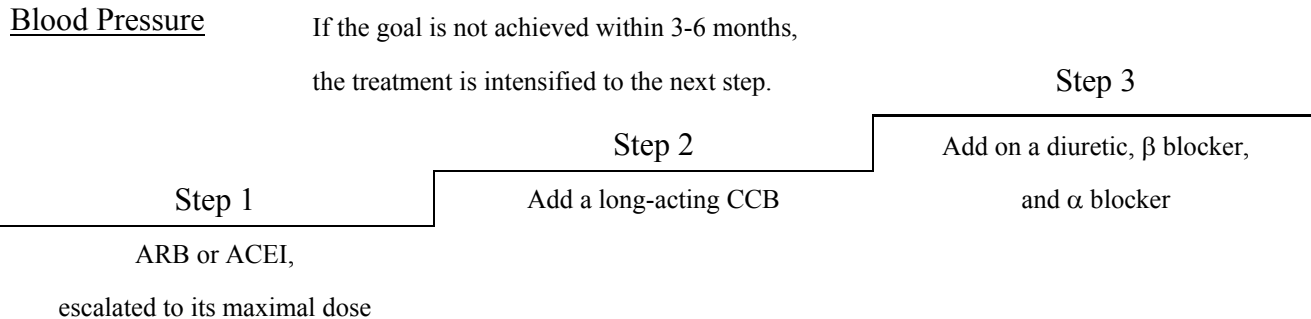
Category A: pioglitazone, BG, GLP-1 receptor agonists

Category C: Insulin

Category B: SU and glinides

Category D:  $\alpha$ GI, DPP-4 inhibitors, SGLT2 inhibitors

\* Pioglitazone is to be chosen whenever possible



\* The omega-3 fatty acids are to be given if the goal for TG has not been achieved.

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