

# Impacts of tight multifactorial intervention in patients with type 2 diabetes: Implications from the Japan Diabetes Outcome Intervention Trial 3

The major aim of the treatment of diabetes is to prevent the occurrence and progression of micro- and macrovascular complications, and finally, to maintain patients' quality of life and to prolong their lives just as in healthy people. It is now clear that tight glycemic control benefits the prevention of microvascular complications<sup>1,2</sup>. However, the benefit is not yet clear for macrovascular complications. In contrast, the benefits of lowering low-density lipoprotein cholesterol (LDL-C)<sup>3</sup> and blood pressure<sup>4</sup> for preventing macrovascular complications are well recognized. Because patients with type 2 diabetes often also have dyslipidemia and/or hypertension, multifactorial intervention is commonly carried out in these patients. In the Steno-2 study, the benefit of intensive multifactorial intervention for the prevention of cardiovascular complications was shown in patients with type 2 diabetes and microalbuminuria<sup>5</sup>.

Recently, Ueki *et al.*<sup>6,7</sup> reported the effect of intensive multifactorial intervention on the prevention of cardiovascular complications and mortality in Japanese patients with type 2 diabetes. In this multicenter, open-label, randomized study, named Japan Diabetes Outcome Intervention Trial 3 (J-DOIT3), 2,542 patients aged 45–69 years who also had dyslipidemia and/or hypertension were randomly assigned (1:1) to conventional therapy group or intensive therapy group. Of these patients, 11% had a previous history of cardiovascular disease.

The glycated hemoglobin (HbA1c) targets were <6.9 and <6.2%, blood pressure were 130/80 and 120/75 mmHg, and LDL-C were 120 and 80 mg/dL in the conventional therapy and intensive therapy groups, respectively. The primary outcome was the occurrence of any of a composite of myocardial infarction, cerebrovascular diseases, revascularization and all-cause mortality. Secondary outcomes included onset or progression of nephropathy and of retinopathy.

The patients were followed up for a mean of 8.5 years. During the intervention period, the mean HbA1c, systolic blood pressure, diastolic blood pressure and LDL-C were significantly more improved in the intensive therapy group than in the conventional therapy group (6.8% vs 7.2% [−0.4%], 123 mmHg vs 129 mmHg [−6 mmHg], 71 mmHg vs 74 mmHg [−3 mmHg] and 85 mg/dL vs 104 mg/dL [−19 mg/dL], respectively). The primary outcome showed a trend of reduction (−19%,  $P = 0.094$ ) in the intensive therapy group, which did not reach statistical significance. In the post-hoc analysis of cardiovascular outcome, cerebrovascular events were significantly reduced by 58% ( $P = 0.044$ ) in the intensive treatment group. Among the secondary outcomes, the onset or progression of nephropathy and of retinopathy were reduced by 32% ( $P < 0.0001$ ) and 14% ( $P = 0.046$ ), respectively (Figure 1)<sup>8</sup>.

With regard to the adverse events, probably as a result of the intensive therapy for diabetes and increased use of pioglitazone, non-severe hypoglycemia (41% vs 22%) and edema (15% vs 10%) were more frequent in the intensive therapy group. However, the frequencies of severe hypoglycemia, as well as major

adverse events, were comparable between the groups. Raised creatine kinase was slightly, but significantly, more frequent in the intensive treatment group (7% vs 4%), probably because of the increased use of statins.

Compared with the results of the Steno-2 study in which the cardiovascular events occurred in 24% and 44% in the intensive and conventional treatment groups, respectively, during 7.8 years of the mean follow-up period, the frequencies of the events were much less in this J-DOIT3, and were 8.6% and 10.5% in the intensive and conventional treatment groups, respectively, during 8.5 years of the mean follow-up period. This could be explained by ethnic differences of the patients studied, and also by the better control of glycemia, blood pressure and lipids in the J-DOIT3 compared with those in the Steno-2 study.

In addition to the improvements of HbA1c, blood pressure and lipids, the body mass index of the intensive therapy group was initially decreased and was maintained comparable thereafter with that of the conventional therapy group. Compared with the baseline values, body mass index was not increased and remained at 24.8 kg/m<sup>2</sup> in each group<sup>7</sup>. This is of note, as some of the intensive intervention in other clinical studies, especially in those using sulfonylurea, insulin or pioglitazone, showed a greater increase of bodyweight compared with a placebo or the conventional intervention. Although the target of body mass index in the intensive intervention group was 22 kg/m<sup>2</sup>, which was not achieved at the end of the study, intensive intervention for lifestyle might have contributed to the results.

\*Corresponding author. Eiichi Araki

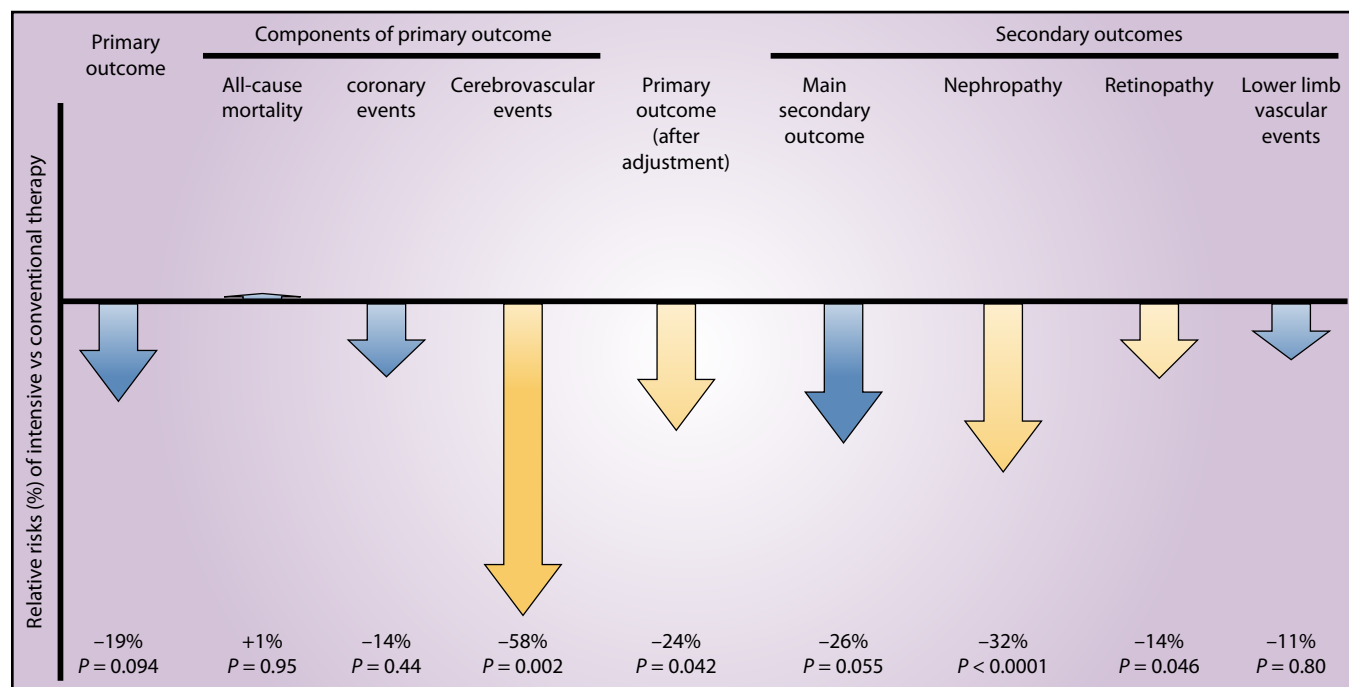
Tel: +81-96-373-5169

Fax: +81-96-366-8397

E-mail address: earaki@gpo.kumamoto-u.ac.jp

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**Figure 1** | Effects of intensive versus conventional therapy on the primary and secondary outcomes in the Japan Diabetes Outcome Intervention Trial 3. Relative risks (%) of intensive therapy on the primary outcome, components of the primary outcome and secondary outcomes compared with conventional therapy reported in the Japan Diabetes Outcome Intervention Trial 3 are shown. Red arrows and blue arrows show the statistically significant ( $P < 0.05$ ) and not significant changes, respectively. This figure was adapted from the #59 slide on the website ([www.jdioint3.jp/jdioint3\\_result\\_medical.html](http://www.jdioint3.jp/jdioint3_result_medical.html)), and translated from Japanese to English.

In J-DOIT3, intensive therapy did not significantly reduce the occurrence of the primary outcome. However, there was a significant reduction in the primary outcome after adjustment for prespecified stratification factors and other important prognostic factors, possibly at least partly because smoking status at baseline was imbalanced between the treatment groups. In addition, intensive therapy was associated with a significant reduction in cerebrovascular events. Furthermore, microvascular complications, such as the onset or progression of nephropathy and of retinopathy, were also reduced by intensive therapy (Figure 1). Therefore, although we have to be alert to hypoglycemia and other drug-related adverse events, it would be recommended patients with type 2 diabetes be treated with intensive therapy, as performed in J-DOIT3, especially when patients are relatively young and have multiple risk factors, including hypertension and dyslipidemia.

It is also necessary to discuss the treatment targets of HbA1c, blood pressure and lipids. Recent treatment targets of those in Japan are HbA1c  $<7.0\%$ , blood pressure  $<130/80$  mmHg and LDL-C  $<120$  mg/dL ( $<70$  mg/dL in patients with a previous history of cardiovascular disease)<sup>9</sup>. With regard to the prevention of microvascular complications, lower HbA1c might be necessary, and for the prevention of cerebrovascular events, lower blood pressure might be the aim. In addition to these values, target values of high-density lipoprotein cholesterol and triglyceride should also be investigated, as there was a small, but significant, increase of high-density lipoprotein cholesterol in the intensive intervention group. The triglyceride data was not described in the initial report<sup>7</sup>, and this should also be mentioned in future. Therefore, the detailed analysis of these parameters in J-DOIT3 and/or a longer period of follow up of J-DOIT3 should be very interesting.

Recently, treatment of patients with type 2 diabetes and a previous history of cardiovascular diseases with sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists has been reported to improve the cardiovascular outcome<sup>10,11</sup>. As the numbers of patients treated with these drugs are small ( $<5\%$  in both groups) and are comparable between groups in J-DOIT3, the effect of these drugs on cardiovascular outcome could be neglected at this time in J-DOIT3. In addition, dipeptidyl peptidase-4 inhibitor has started to be used in  $>50\%$  of patients in each group during the 8.5 years of the study period. Because the follow-up study of J-DOIT3 has just started, the impacts of longer time of intensive intervention, as well as those of the newly developed antidiabetic drugs, will be of great interest.

**DISCLOSURE**

EA is a member of the J-DOIT3 Study Group and a member of the Advisory

Committee, and therefore is a co-author of the manuscript<sup>4</sup>. EA reports receiving personal fees from Kowa during the study; and grants from Astellas Pharma, AstraZeneca, Ono Pharmaceutical, Kowa Pharmaceutical, Sanofi, Daiichi Sankyo, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer Japan, Nippon Boehringer Ingelheim, Novo Nordisk Pharma and Novartis Pharma; and personal fees from MSD, Astellas Pharma, AstraZeneca, Ono Pharmaceutical, Kowa Pharmaceutical, Sanofi, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novartis Pharma, Novo Nordisk Pharma and Eli Lilly. NF and TS declare no conflict of interest.

Eiichi Araki<sup>1\*</sup> , Takafumi Senokuchi<sup>1</sup>,  
Noboru Furukawa<sup>2</sup>

<sup>1</sup>Department of Metabolic Medicine, and

<sup>2</sup>Center for Medical Education and Research, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

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