Weekly Versus Daily Dipeptidyl Peptidase 4 Inhibitor Therapy for Type 2 Diabetes: Systematic Review and Meta-analysis

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Once-weekly dipeptidyl peptidase 4 inhibitors (weekly DPP-4is) were recently developed in addition to the once-daily agents (1), and weekly DPP-4is may improve compliance by reducing the burden of medication. Omarigliptin and trelagliptin are the weekly DPP-4is currently available in Japan. We performed a meta-analysis to assess the efficacy and safety of weekly DPP-4is compared with daily DPP-4is and placebo for type 2 diabetes.

This research was carried out according to a predetermined protocol (CRD42017069004) and followed the standard guidelines for conduct and reporting of systematic reviews and meta-analyses (Supplementary Appendices 1 and 2). We searched MEDLINE, EMBASE, and the Cochrane Library up to 16 September 2017. Prospective randomized double-blind trials of weekly DPP-4is performed in adults with type 2 diabetes using an intervention period of at least 12 weeks were identified. Studies were excluded if other aspects of treatment were targeted, if not double-blind (e.g., open-label or crossover), or if the follow-up period was <12 weeks. Studies of children and observational studies were also ineligible. We checked the reference lists of the original studies, review articles, and meta-analyses identified by our searches to find other eligible trials. There were no language restrictions. Two reviewers independently assessed the studies and extracted data. Bias was analyzed with the Cochrane Collaboration tool. Meta-analysis was performed by a frequentist-based approach with a random-effects model (weekly DPP-4is at the highest dose in each study vs. daily DPP-4is at the highest dose in each study or placebo). Heterogeneity was assessed by using the I^2 statistic. Publication bias was estimated visually by drawing funnel plots and by performing the Begg test and Egger weighted regression test (Supplementary Appendix 9). The arm-specific difference of the mean value from baseline and the odds ratio (OR) were used as measures of effect for continuous and dichotomous variables, respectively. All statistical analyses were done with Stata V.14.0 software, and $P < 0.05$ was considered to indicate significance.

Among 2,399 candidate studies identified in the electronic databases and other sources, seven randomized trials (2,920 patients) satisfied the inclusion criteria (2–8) (Supplementary Appendices 3–7). The weekly DPP-4i was omarigliptin in five studies and trelagliptin in two studies. The treatment period for the primary end points ranged between 12 (N = 2) and 24 (N = 5) weeks. The mean age, fasting plasma glucose, hemoglobin A_{1c} (HbA_{1c}), and BMI were 55–65 years, 8.7–9.5 mmol/L [157–171 mg/dL], 7.5–8.3% [58–67 mmol/mol], and 25–32 kg/m^2, respectively. These factors were balanced between the groups. Risk of bias was low in these studies, except for sponsorship bias (Supplementary Appendix 7).

Meta-analysis revealed that weekly DPP-4is significantly reduced HbA_{1c} by 0.66% (95% CI 0.52, 0.8; $P < 0.001$; I^2 = 64%), fasting plasma glucose by 0.72 mmol/L (0.34, 1.1) [13 mg/dL (6, 20)], and 2-h postprandial glucose by 1.82 mmol/L (0.99, 2.65) [33 mg/dL (18, 48)] compared with placebo. Weekly DPP-4is also increased body weight by 0.59 kg (0.34, 0.84). There was no significant increase of pancreatitis, diarrhea, hypoglycemia, or severe hypoglycemia relative to placebo (Supplementary Appendix 8).

Compared with daily DPP-4is, there were no significant differences in the reduction of HbA_{1c}, fasting plasma glucose, 2-h postprandial glucose, the rate of achieving HbA_{1c} <7.0%, weight gain, and the incidence of pancreatitis, diarrhea, hypoglycemia, and severe hypoglycemia in patients using weekly DPP-4is (Fig. 1). Heterogeneity among studies was not significant, except for fasting plasma glucose. Publication bias was not significant (Supplementary Appendix 8).

The present meta-analysis failed to show any additional clinical benefit of weekly DPP-4is compared with daily

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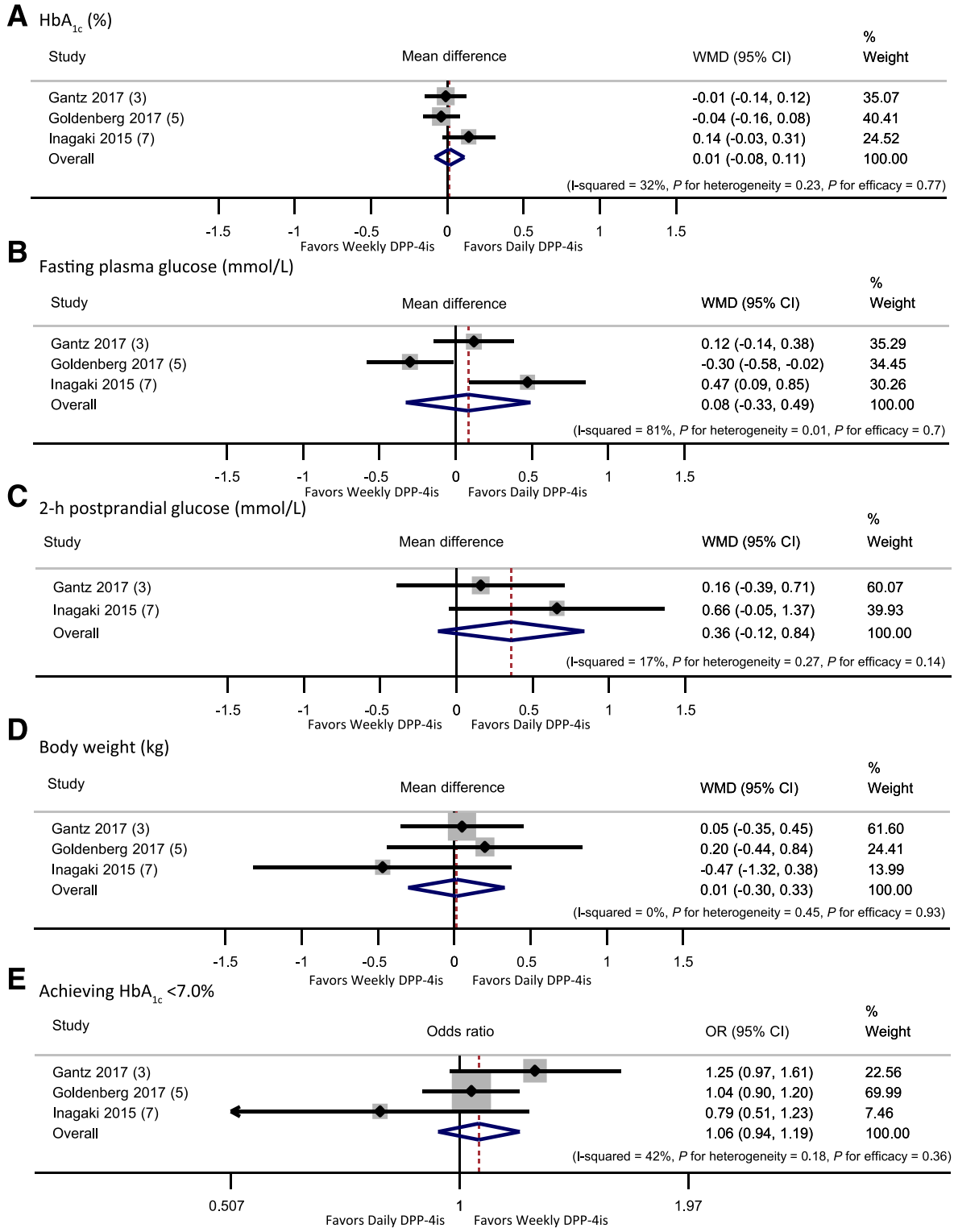

Figure 1—Meta-analysis of seven articles (refs. 2–8) comparing weekly DPP-4is with daily DPP-4is for type 2 diabetes. OR was used as a measure of effect for dichotomous variables. When performing meta-analysis, we added 0.5 as the correction factor if no events were reported in the treatment group of a study. *A*: HbA_{1c} (%). *B*: Fasting plasma glucose (mmol/L). *C*: Two-hour postprandial glucose (mmol/L). *D*: Body weight (kg). *E*: Achieving HbA_{1c} <7.0%. *F*: Diarrhea. *G*: Pancreatitis. *H*: Severe hypoglycemia. *I*: Hypoglycemia. WMD, weighted mean difference.

DPP-4is. However, none of the included studies assessed patient satisfaction with therapy or quality of life. Although large randomized clinical trials have already assessed important outcomes (effects on macrovascular and microvascular disease) with daily DPP-4is (9,10), this has not been done with weekly DPP-4is.

Do weekly DPP-4is fill an unmet need? Scheen (11) reported that most patients with type 2 diabetes use several drugs to achieve glycemic control and to treat

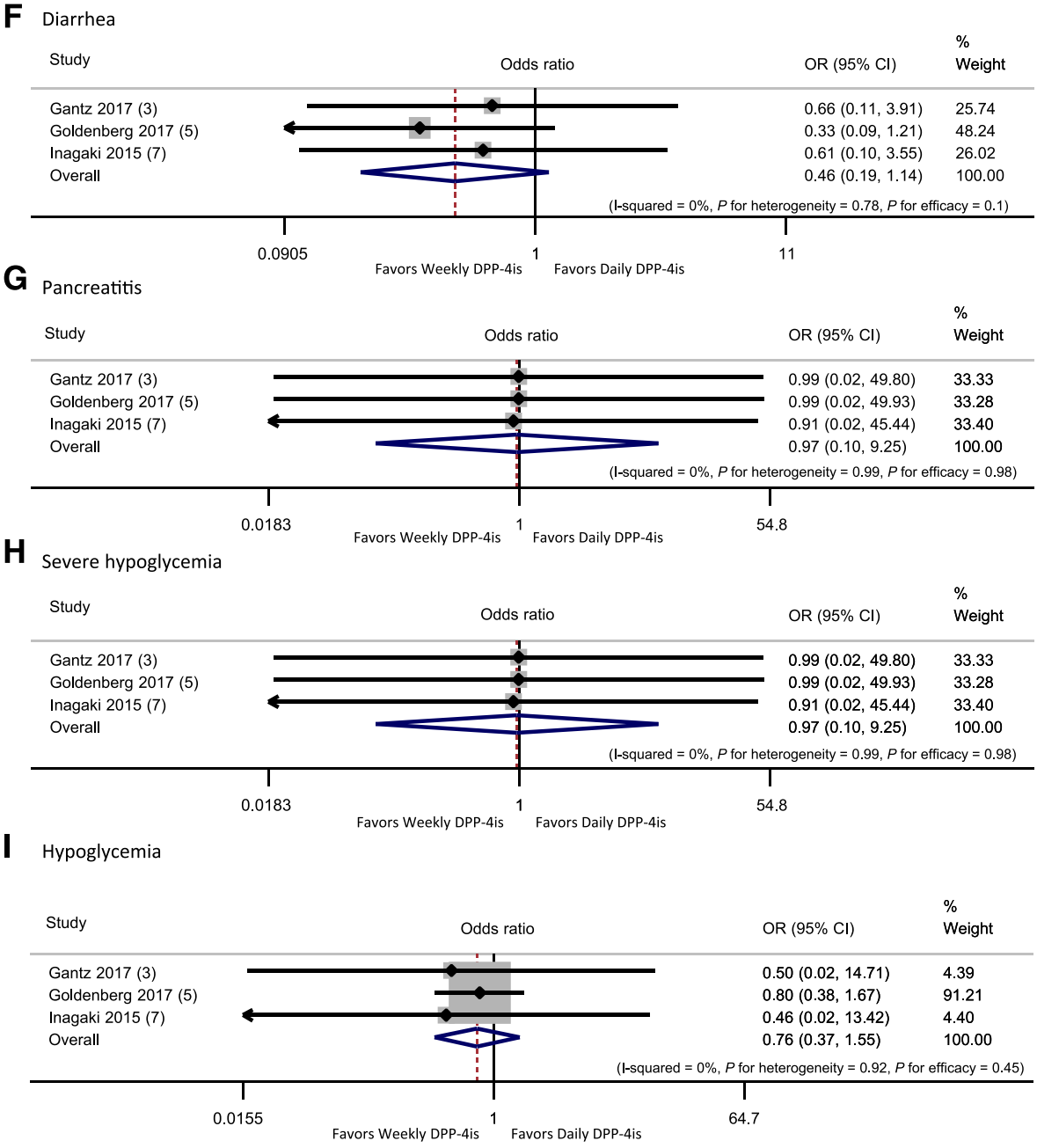

Figure 1—*Continued*.

hypertension, dyslipidemia, and other comorbidities. It may be easier for patients to keep track of several drugs on the same dosing schedule rather than mixing weekly and daily administration. Accordingly, further studies are needed to determine whether weekly DPP-4is actually improve patient satisfaction, compliance, and quality of life, leading to better long-term control of type 2 diabetes.

If medications for other diseases, including antihypertension drugs, lipid-lowering agents, and antiplatelet agents, are developed as once-weekly preparations that become widely available in the future, medication compliance might be improved by such once-weekly agents and patient quality of life might be enhanced. From this perspective, once-weekly DPP-4is might be viewed as having reached the market too early but could be an attractive option in the future.

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